NDA 209353 Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	NDA 209353/ IND 126753
Priority or Standard	Standard
Submit Date(s)	October 23, 2017
Received Date(s)	October 27, 2017
PDUFA Goal Date	August 27, 2018
Division/Office	Division of Dermatology and Dental Products
Review Completion Date	July 18, 2018
Established Name	Tretinoin
(Proposed) Trade Name	ALTRENO
Pharmacologic Class	Retinoid
Code name	IDP-121
Applicant	Dow Pharmaceutical Sciences Inc c/o Valeant Pharmaceuticals North America LLC
Formulation(s)	Lotion
Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of acne vulgaris
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	ALTRENO is indicated for the treatment of acne vulgaris in patients age 9 years and older

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Reviewers Team and Signature Approval Section

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Product Quality Team Lead	Yichun Sun, PhD	Branch V/ Division of New Drug Products II	Sections: 4.2	**Select one:** ✓ Authored ___ Acknowledged ✓ Approved
	Signature: Yichun Sun -S Digitally signed by Yichun Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yichun Sun -S, 0.9.2342.19200300.100.1.1=1300393310 Date: 2018.08.22 00:22:03 -04'00'			
Nonclinical Reviewer	Jill Merrill, PhD	ODE III/DDDP	Sections: 5, 13.3	**Select one:** ✓ Authored ___ Acknowledged ___ Approved
	Signature: Jill C. Merrill -S Digitally signed by Jill C. Merrill -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300224781, cn=Jill C. Merrill -S Date: 2018.08.21 20:41:46 -04'00'			
Nonclinical Supervisor	Barbara A. Hill, PhD	ODE III/DDDP	Sections: 5, 13.3	**Select one:** ___ Authored ___ Acknowledged ✓ Approved
	Signature: Barbara A. Hill -S Digitally signed by Barbara A. Hill -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300098991, cn=Barbara A. Hill -S Date: 2018.08.22 06:55:49 -04'00'			
Clinical Pharmacology Reviewer	Jihye Ahn, PhD	OCP-DCP III	Sections: 6	**Select one:** ✓ Authored ___ Acknowledged ___ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
	Signature: Jihye Ahn -S (Affiliate)	Digitally signed by Jihye Ahn -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001814798, cn=Jihye Ahn -S (Affiliate) Date: 2018.08.22 12:25:37 -04'00'		
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP-DCP III	Section: 6	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
	Signature: Chinmay Shukla -S	Digitally signed by Chinmay Shukla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chinmay Shukla -S, 0.9.2342.19200300.100.1.1=2000377244 Date: 2018.08.22 12:50:47 -04'00'		
Biostatistics Reviewer	Kathleen Fritsch	OTS/OB/DBIII	Sections: 7.1.2, 7.2, 7.4, 7.5	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
	Signature: Kathleen S. Fritsch -S	Digitally signed by Kathleen S. Fritsch -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300162288, cn=Kathleen S. Fritsch -S Date: 2018.08.23 07:34:12 -04'00'		
Biostatistics Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 7.1.2, 7.2, 7.4, 7.5	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
	Signature: Mohamed A. Alosh -S	Dig tally signed by Mohamed A Alosh S DN:c US o U S Government ou HHS ou FDA ou People 0.9.2342 19200300 100 1 1 1300089441 cn Mohamed A Alosh S Date: 2018 08 23 07 50:47 04 00		
OB Division Director (DBIII)	Laura Lee Johnson, PhD	OTS/OB/DBIII	Sections: 7.1.2, 7.2, 7.4, 7.5	**Select one:** ____ Authored ____ Acknowledged ✓ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2018.08.23 08:53:53 -04'00'			
Clinical Reviewer	Melinda McCord, MD	ODE III/DDDP	Sections: 1.1, 1.2, 1.3, 2, 3, 4.1,7.1.1, 7.3, 7.5, 8, 9, 10, 11, 12, 13.1, 13.2, 13.4	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
	Signature: Melinda Mccord -S Digitally signed by Melinda Mccord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Melinda Mccord -S, 0.9.2342.19200300.100.1.1=2000345639 Date: 2018.08.22 13:50:37 -04'00'			
Clinical Team Leader	Gordana Diglisic, MD	ODE III/DDDP	Sections: 1.1, 1.2, 1.3, 2, 3, 4.1,7.1.1, 7.3, 7.5, 8, 9, 10, 11, 12, 13.1, 13.2, 13.4	**Select one:** ✓ Authored ____ Acknowledged ✓ Approved
	Signature: Gordana Diglisic -S Digitally signed by Gordana Diglisic -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300397194, cn=Gordana Diglisic -S Date: 2018.08.22 14:11:33 -04'00'			
Signatory	Jill Lindstrom, MD	ODE III/DDDP	All Section	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
	Signature: See electronic page			

Additional Reviewers of Application

Office/Division	Reviewer/Team Leader	Review Location
ODE III/DDDP – ADL	Nancy Xu, MD	Review not required
ODE III/DDDP – PM/CPMS	Angela Brown, MPH/ Barbara Gould, MBAHCM	Review not required
ODE IV/DPMH	Catherine Roca, MD/ Miriam Dinatale, DO, LCDR	Review not required
OPDP/DMPP	Morgan Walker, PharmD, MBA, CPH/ LaShawn Griffith, MSHS-pH, BSN, RN	DARRTS
OPDP/DAPR2	Laurie Buonaccorsi, PharmD/ Walter Falter, PharmD	DARRTS
OPQ/DND API	Jeffrey Medwid, PhD/ Donna F. Christner, PhD	Integrated Quality Assessment (IQA)/ Panorama
OPQ/DNDP II	Zhengfang Ge, PhD/ Moo-Jhong Rhee, PhD	IQA/Panorama
OPQ/DPA III	Zhao Wang, PhD/ Yubing Tang, PhD	IQA/Panorama
OPQ/DMA	Daniel Schu, PhD/ John W. Metcalf, PhD	IQA/Panorama
OPQ/DB	Sandra Suarez Sharp, PhD/ Vidula Kolhatkar, PhD	IQA/Panorama
OPQ/DRBM	Bamidele (Florence) Aisida/	IQA/Panorama
OPQ/DNDP	Yichun Sun, PhD/ Moo Jhong Rhee, PhD	IQA/Panorama
OSE/DMEPA	Madhuri R. Patel, PharmD/ Sarah K. Vee, PharmD	DARRTS
OSE/DPV-I	Carmen Cheng, PharmD/ Vicky Chan, PharmD	DARRTS
OSE/PMS	Tri Bui-Nguyen PhD/ Sue Kang, MS	Review not required
OSI/DCCE	Bei Yu, PhD/ Janice Pohlman, MD, MPH	DARRTS

ADL = Associate Director of Labeling
DAPR2 = Division of Advertising and Promotion Review 2
DB=Division of Biopharmaceutics
DB III = Division of Biometrics III
DBRR I = Division of Biotechnology Research and Review 1
DCP 3 = Division of Clinical Pharmacology 3
DDDP = Division of Dermatology and Dental Products

DDS = Deputy Director for Safety
DEPI = Division of Epidemiology
DMA=Division of Microbiology Assessment
DMPP = Division of Medical Policy
DND API= Division of New Drug API
DNDP II=Division of New Drug Products II
DPA III=Division of Process Assessment III
DPM = Division of Pharmacometrics
DPA=
DPMH = Division of Pediatrics and Maternal Health
DARRTS = Document Archiving, Reporting, and Regulatory Tracking System
DRBM=
OB = Office of Biostatistics
OBP = Office of Biotechnology Products
OCP = Office of Clinical Pharmacology
ODE III = Office of Drug Evaluation III
ODE IV = Office of Drug Evaluation IV
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
RBPMBI = Regulatory and Business Process Management Branch I
SRPM = Safety Regulatory Project Manager

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCC	*Burkholderia cepacia* complex
BCOP	bovine corneal opacity and permeability
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CPK	creatine phosphokinase; creatine kinase (CK)
CRF	case report form
EGSS	Evaluator's Global Severity Score
FDA	Food and Drug Administration
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ITT	intent to treat
IVIS	in vitro irritancy score
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
MRHD	maximum recommended human dose
NDA	New Drug Application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PI	prescribing information
PK	pharmacokinetics
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
RAR	retinoic acid receptor
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SOC	system organ class
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

ALTRENO™ (tretinoin) Lotion, 0.05% is a topical drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the treatment of acne vulgaris. This application is for a new dosage form of tretinoin. The active ingredient is tretinoin, all-trans-retinoic acid, which is a member of the retinoid class of compounds and a metabolite of Vitamin A. It is currently marketed in the United States (U.S.) in various dosage forms (cream, gel, solution and capsule). The proposed indication is the topical treatment of acne vulgaris. The proposed dose and administration is a thin layer applied to the affected areas once daily.

The Agency concluded that the proposed proprietary name, ALTRENO, was acceptable from both a promotional and safety perspective under NDA 209353 [Proprietary Name Review by Sherly Abraham, R.Ph., Division of Medication Error Prevention and Analysis dated 1/26/2018.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted data from two adequate and well-controlled trials (V01-121A-301 and V01-121A-302) which provided evidence of the effectiveness of tretinoin lotion 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 co-primary 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* or *almost clear* and at least two-grade reductions from Baseline

Tretinoin lotion was statistically superior to vehicle (p-values ≤ 0.007) on the co-primary endpoints in both trials. The applicant has demonstrated that tretinoin lotion 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.

Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dow Pharmaceutical Sciences submitted a New Drug Application (NDA) 209353 for ALTRENO (tretinoin) Lotion, 0.05% for the treatment of acne vulgaris under the 505(b)(1) regulatory pathway. Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. ALTRENO is a new dosage form of tretinoin and the safety profile of the moiety is well characterized. The applicant relies on data from other tretinoin product applications (right of reference for NDA 22070 (ATRALIN Gel, 0.05%), NDA 17522 (RETIN-A Cream, 0.05%), NDA 19963 (RENOVA 0.05%), NDA 20475 (RETIN-A MICRO), NDA 21108 (RENOVA 0.02%), to support the systemic (nonclinical and clinical)) and long-term safety of their product.

In two, multicenter, randomized, double-blind clinical trials enrolling 1640 subjects age 9 years and older with acne vulgaris, tretinoin lotion was statistically superior to vehicle for the treatment of acne vulgaris. The co-primary efficacy endpoints were success on the EGSS, absolute change in noninflammatory lesion count, and absolute change in inflammatory lesion count at Week 12. Success on the EGSS was defined as at least a 2-grade improvement from Baseline and an EGSS score of clear (0) or almost clear (1).

The safety profile for tretinoin lotion was adequately characterized during the drug development program. Treatment with tretinoin lotion was not associated with an increased risk of mortality or serious adverse events. There were no deaths or drug- related, serious adverse events (SAEs) in the Phase 3 trials, Study V01-121A-301 and Study V01-121A-302 (referred to as Study 301 and Study 302). In the pooled safety analysis set, SAEs occurred in 0.9% subjects in the tretinoin lotion group and 0.5% subjects in the vehicle group. Review of the data supports including the potential for skin irritation and effects of ultraviolet light and environmental exposure 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, hypopigmentation, itching, burning, and stinging) at a post Baseline visits was greater in the tretinoin lotion group than the vehicle group. The most common adverse reactions occurred at the application site: dryness (4%), pain (3%), erythema (2%), irritation (1%), and exfoliation (1%).

In summary, acne vulgaris is a chronic disease which may be associated with substantial impairment of quality of life. Tretinoin lotion provides an additional treatment option. The available evidence of safety and efficacy supports the approval of ALTRENO (tretinoin) Lotion, 0.05% 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 2 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 substantial impairment of quality of life.	Acne is a common chronic disorder with a range of disease severities which may significantly 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. There is a need for additional retinoid formulations that promote compliance by addressing patient preferences.
Benefit	• Data from 2 adequate and well controlled trials (Study 301 and 302), provided substantial evidence of the effectiveness of tretinoin lotion for the treatment of acne vulgaris. These trials enrolled 1640 subjects age 9 years and older with moderate to severe acne vulgaris. Tretinoin lotion was superior to vehicle in both trials for the co-primary efficacy endpoints of absolute change in non-inflammatory lesion count, absolute change in inflammatory lesion count and EGSS success. • Review of the safety data from clinical trials identified no new safety signals with this new dosage form of tretinoin. Tretinoin lotion was well tolerated in all evaluated subgroups.	Tretinoin lotion 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
Abbreviations: FDA = Food and Drug Administration

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The primary safety database (Study 301 and 302) included 1550 subjects who received tretinoin lotion once daily for 12 weeks. There were no deaths or serious adverse events related to the study product. The most common adverse reactions occurring in ≥1% of subjects and greater than vehicle was localized to the application site: dryness, pain, erythema, irritation and exfoliation. Active assessment of local adverse reactions indicated that some reactions were severe.	The risks associated with the use of tretinoin lotion are similar to other tretinoin products. Local effects such as irritation and pigmentary changes may occur during treatment and may be severe.
Risk Management	• Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and identified during product development. • No issues require further assessment with a post marketing requirement or post marketing commitment. • A risk evaluation and mitigation strategy (REMS) is not recommended.	Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the risks of the product.

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 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.

[2] Bhate K, Williams HC. Epidemiology of acne vulgaris. BJD. 2013 168, pp474–485.
[3] UpToDate. Thiboutot, D et al. Accessed May 9, 2018.
[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

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, 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.

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[1]	Tetracycline, Doxycycline, Minocycline
Retinoids Isotretinoin	Isotretinoin
Hormonal therapies[2]	Various oral contraceptives

Source: Modified from NDA 209269, Clinical Review by Patricia Brown, MD
*Over-the counter monograph approved products

[7] Lasek RJ et al. Acne Vulgaris and the Quality of Life of Adult Dermatology Patients. Arch Dernmatol.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:

1 Azithromycin/ Erythromycin, Ampicillin/amoxicillin used off- label
2 Spironolactone, flutamide, corticosteroids used off- label

Table 2: Representative Examples of FDA Approved Topical Products

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information from labeling	Important Safety and Tolerability Issues
Antimicrobials				
ACZONE (dapsone) Gel, 7.5%, NDA 207154 (2016)	topical treatment of acne vulgaris in patients 12 years of age and older	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 1.GAAS: 30% vs 21% Inflam: 56% vs 49% Noninflm: 45% vs 39% -2.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	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: 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 1.IGA: 29% vs 16% Inflam: 58% vs 45% Noninflm: 55% vs 33% Total: 56% vs 39%	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
			-2.IGA: 28% vs 13% Inflam: 57% vs 41% Noninflam: 46% vs 41% Total: 56% vs 43%	
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 1.IGA: 26% vs 17% Inflam: 55% vs 40% Noninflm: 50% vs 36% Total: 52% vs 37% -2.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
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.	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 1.EGSS: 0/1: 29% vs 14% 2 grade: 33% vs 19% Inflam: 55% vs 35% Noninflm: 45% vs 29% 2.EGSS: 0/1: 28% vs 11% 2 grade: 37% vs 14% Inflam: 54% vs 23% Noninflm: 41% vs 19%	AR: application site pain, exfoliation, irritation W&P: Colitis, UV light exposure
EPIDUO® FORTE (adapalene and benzoyl peroxide)	topical treatment of acne vulgaris	Apply a thin layer of EPIDUO FORTE gel to	A 12-week R, DB, VC trial subjects 12 years and older	AR: skin irritation, eczema, atopic dermatitis, and skin

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information from labeling	Important Safety and Tolerability Issues
gel, 0.3%/2.5% NDA 207917 (2015)		affected areas of the face and/or trunk once daily after washing	with moderate to severe acne vulgaris Active vs vehicle IGA: 33.7% vs 11.0% Inflam:27.8% vs 13.2% Noninfl:40.5% vs19.7%	burning sensation. W&P: UV light exposure, local cutaneous reactions

Source: Reviewer Table from "Drugs at FDA," and "DAILYMED" accessed June 14, 2018.
Abbreviations: GAAS = Global Acne Assessment Score, AR = adverse reaction, W&P = Warnings and Precautions, R = randomized, DB = double-blind, IGSA = Investigator Global Static Assessment, VC = vehicle controlled, IGA = Investigator Global Assessment, EGSS = Evaluator's Global Severity Score, Inflam = inflammatory, Noninfl = non-inflammatory

Table 3: Examples of Systemic Acne Products

Generic Name	Brand Name	Formulations	Applicant	Indication
Oral Antibiotics				
Minocycline Hydrochloride	SOLODYN	Extended release tablets 55mg, 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 & 120mg Delayed release tablets, 75, 100, 150, 200mg	Mayne pharma	In severe acne may be useful adjunctive therapy
Doxycycline Monohydrate	Monodox	Capsule; 50 mg,75 mg, 100mg	Aqua Pharms	
Tetracycline Hydrochloride	Tetracycline hydrochloride	Capsule; 250 mg, 500 mg	Heritage Pharms Inc	
Isotretinoin	ABSORICA	Capsules; 10, 20, 25, 30, 35, 40 mg	Ranabxy	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

Generic Name	Brand Name	Formulations	Applicant	Indication
Norgestimate 0.180, 0.215, 0.250 mg/ ethinyl estradiol .035 mg Norgestimate 0.250 mg/ethinyl estradiol .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: Adapted from Table 1, NDA 209269

2.3. Patient Experience Data

The applicant conducted patient reported outcome (PRO) assessments during the Phase 3 trials which included an evaluation of oiliness/shininess of the face and three questionnaires, the exploratory Subject Self-Assessment scale (SSA), the Patient Satisfaction Survey, and the Acne-Specific Quality of Life Questionnaire. The applicant summarized the results using descriptive statistics and used the data to identify trends between treatment groups. However, the protocol did not include prespecified endpoints based on these instruments. As the endpoints related to the patient reported outcomes were not prespecified or controlled for multiplicity, the data will not be included in labeling or discussed in this review.

Table 4: Patient Experience Data Relevant to this Application

	The patient experience data that was submitted as part of the application includes:	Section where discussed, if applicable
	□ Clinical outcome assessment data, such as	
	X Patient reported outcome	
	□ Observer reported outcome	
	X Clinician reported outcome	Section 7.2.1
	□ Performance outcome	
	□ 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 was not submitted as part of this application.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The proposed product, ALTRENO (tretinoin) Lotion, 0.05%, 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

The applicant developed tretinoin lotion for treatment of acne vulgaris under the 505(b)(1) regulatory pathway with reliance on data from other tretinoin products. The applicant owns ATRALIN Gel, 0.05% (NDA 022070) and provided a right of reference to approved products owned by its parent company, Valeant Pharmaceuticals (RETIN-A Cream, 0.05% (NDA 017522), RETIN-A MICRO (NDA 020475), RENOVA Cream, 0.05% (NDA 019963), and RENOVA Cream, 0.02% (NDA 021108).

The applicant interacted with the Agency during two milestone meetings: End-of-Phase 2 Meeting (EOP2) held on May 6, 2015 and Pre-NDA meeting scheduled for June 21, 2017. During the EOP2 meeting (under Investigational New Drug 063067), the applicant proposed to develop a new formulation of tretinoin, tretinoin lotion 0.05% under the 505(b)(1) regulatory pathway. The applicant proposed to reference NDA 022070 and NDA 020475 to support the nonclinical and clinical safety and effectiveness of tretinoin for the treatment of acne. In addition, the applicant intended to reference NDA 019963 and NDA 021108 to support the long-term safety of the proposed product. The Agency recommended providing a Right of Reference for each referenced NDA. The referenced products are tabulated in Table 5 below.

Table 5: Approved Products for Reference

Product Approval Date	NDA	Approved Indication	Reason for Reference	NDA Owner
ATRALIN Gel, 0.05% 7/26/2007*	022070	Treatment of acne vulgaris	Supportive nonclinical safety & clinical efficacy and safety of tretinoin	DPS
RETIN-A Cream, 0.05% 7/19/1974	017522	Treatment of acne vulgaris	Supportive clinical efficacy and safety of tretinoin	Valeant Pharm
RETIN-A Micro Gel microsphere, 0.04%, 0.08%, and 0.1% 2/7/1997	020475	Treatment of acne vulgaris	Supportive nonclinical safety & clinical efficacy and safety of tretinoin	Valeant Pharm

Product Approval Date	NDA	Approved Indication	Reason for Reference	NDA Owner
RENOVA (tretinoin cream) 0.05% 12/29/1995	019963	Mitigation (palliation) of fine facial wrinkles	Supportive long-term safety of tretinoin	Valeant Pharm
RENOVA (tretinoin cream) 0.02% 8/31/2000	021108	Mitigation (palliation) of fine facial wrinkles	Supportive long-term safety of tretinoin	Valeant Pharm

Source: Pre-NDA Meeting Package IND 126753; Drugs @FDA accessed 4/5/2018.
Abbreviations: Valeant Pharm = Valeant Pharmaceuticals North America LLC Full rights of reference per 21CFR 314.3, DPS = Dow Pharmaceutical Sciences *505(b)(2) to NDA 020475

The EOP2 Meeting focused on the late development program including the trial design, endpoints, study population, safety monitoring, and planned statistical analyses. The applicant inquired about the need to conduct assessments of long-term safety and dermal safety studies. The Agency agreed that waivers for dermal safety studies (photo allergy/phototoxicity and irritation/ sensitization), long term safety trial, and assessments of the pediatric population from a 0 to 8 years and 11 months were reasonable. (Meeting Minutes dated 5/8/2015).

The applicant developed tretinoin lotion under Investigational New Drug application (IND) 126753 which was submitted on July 24, 2015. The initial IND submission included one of 2 identically designed Phase 3 protocols (V01-121A-301) and an initial pediatric study plan (iPSP). There was no request for review of the Phase 3 protocol under a Special Protocol Assessment. In alignment with Agency comments, the applicant proposed to evaluate the safety and efficacy of tretinoin (IDP-121) lotion in approximately 800 subjects 9 years of age and older with moderate to severe acne vulgaris (core of 3 or 4 on the EGSS). The protocol included modifications to the EGSS (to a 5-point scale) and safety monitoring (pregnancy testing and adverse event assessments).

For the Phase 3 protocols, the Agency provided comments (Advice Letter dated 9/10/2015) regarding the safety monitoring (addition of periodic laboratory evaluations and assessment of pigmentary changes with the local safety assessment), patient-reported outcome instruments, informed consent to include the potential for hypersensitivity reactions from fish proteins, secondary endpoints to be limited in number and statistical issues (control of multiplicity, imputation procedures, and estimates of treatment effect used to power the trial). The applicant submitted an amended protocol on October 19, 2015 which addressed these comments.

For the maximal use Pharmacokinetic (PK) trial (V01-121A-501 (Study 501)), the Agency recommended that the study population include subjects age 9 to 16 years and 11 months with moderate to severe acne with involvement of both the face and trunk (Advice Letter 7/1/2016).

The Pre-NDA meeting, scheduled on June 21, 2017, was cancelled by applicant upon receipt of the Preliminary Meeting Comments. The Agency provided general guidance regarding the data requirements to support filing.

See Section 7.3.8Pediatrics and Assessment of Effects on Growth for a discussion of the pediatric development plan for tretinoin lotion.

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 sites which were selected for inspection by Office of Scientific Investigations had high site efficacy effect, high enrollment numbers, and absence of prior inspections. The Clinical Inspection Summary (Table 6) included the following results (Review by Bei Yu, Ph.D. dated 5/25/2018):

Table 6: Site Inspection Results

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification	Inspection Dates
Site #202: Eichenfield, Lawrence Pediatric & Adolescent Dermatology, 8010 Frost Street #600 San Diego, CA 92123	V01-121A-302	28	NAI*	4/16/2018-4/19/2018
Site #115: Jazayeri, Sadra 4045 East Bell Road, Suite 125 Phoenix, AZ 85032	V01-121A-301	28	NAI**	4/30/2018-5/3/2018

Source: Reviewer's Table.
Key to Compliance Classifications: *final compliance classification **preliminary compliance classification
Abbreviations: NAI = no deviation from regulations, VAI = deviation(s) from regulations, OAI = significant deviations from regulations, data unreliable, pending = preliminary classification based on information in 483 or preliminary communication with the field; Establishment Inspection Report (EIR) has not been received from the field, and complete review of EIR is pending; final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Based on the results of the inspections, Dr. Yu concluded that the conduct of the trials appears to be adequate and the data generated by these sites appears to be acceptable to support the use of this product for the proposed indication. Refer to the Clinical Inspection Summary by Bei Yu, Ph.D. dated May 25, 2018, for a brief review of the data to support this conclusion.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient chemistry, manufacturing, and controls information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility (OPF) has issued an "Acceptable" recommendation for the facilities involved in this application.

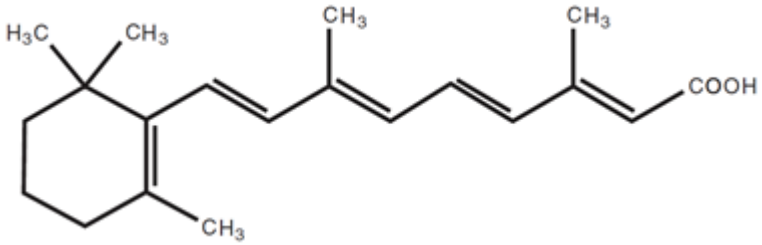
From a product quality standpoint, this NDA is approvable provided labeling comments are adequately addressed by the applicant.

Summary of Quality Assessments

Drug Substance

The active pharmaceutical ingredient in ALTRENOL Lotion, 0.05% is tretinoin, which is a retinoid.

The chemical name for tretinoin is all-trans (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. The chemical structure of tretinoin is:



It has a molecular formula of $C_{20}H_{28}O_2$ and a molecular weight of 300.44 g/mol.

(b) (4)

The drug substance is manufactured by (b) (4)
Detailed chemistry, manufacturing, and controls information of tretinoin drug substance for this NDA is referred to DMF (b) (4) DMF (b) (4) was reviewed by Dr. Jeffrey B. Medwid on March 20, 2018 and found adequate in supporting the approval of this NDA.

Drug Product

The drug product, ALTRENO Lotion, is a topical lotion, which contains 0.05% (by weight) tretinoin. The inactive ingredients used in the drug product include: benzyl alcohol, butylated hydroxytoluene, carbomer copolymer type B (Pemulen TR-1), carbomer homopolymer type A (Carbopol 981), glycerin, methylparaben, mineral oil, (b) (4) octoxynol-9, purified water, sodium hyaluronate, soluble collagen and trolamine. The compendial excipients comply with their respective current United States Pharmacopeia (USP) monographs with additional control of residual solvents to comply with the current USP <467>. The non-compendial excipients (sodium hyaluronate and (b) (4) collagen) are used in the applicant's approved ATRALIN Gel and are controlled to the same quality standards as in the approved drug product. The non-compendial-grade

octoxynol 9 is purchased, but tested to ensure conformance with the current USP monograph except for the (b) (4) content test. The drug product is packaged as nominal 3 g and 45 g fill sizes in a (b) (4) The tubes with 3 g filling are the proposed physician samples. The applicant provided sufficient information to demonstrate the safe use of the container/closure system.

The revised final specification for ALTRENO Lotion is deemed adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. The long-term (25°C/60%RH) stability data up to 18 months, intermediate (at 30°C/65%RH) stability data for 12 months and accelerated (40°C/75%RH) stability data for 6 months are provided for the three registration batches of the drug product (packaged in 3 g and 45 g package sizes) produced a (b) (4) scale in the NDA submission. The stability data submitted are sufficient to support the proposed expiration dating period of 24 months when stored at room temperature. The results of in-use studies support that the product can be continuously used over the course of 12 weeks with no undesirable trends to physical and chemical characteristics. The drug product can withstand repeated freezing and thawing, and cold-warm cycling stressed conditions. The estimated expected introduction concentration for the drug substance is well below one part per billion. The claim of categorical exclusion is acceptable per 21 CFR 25.31(b).

Labeling and Labels

Pending labeling negation with applicant.

Drug Product Manufacturing Process

The bulk drug product is prepared by (b) (4) (b) (4) The active ingredient, tretinoin, i (b) (4) in the lotion. The batch formula, manufacturing process parameters, and in-process controls are deemed adequate to ensure the robustness of the drug product manufacturing process. The proposed manufacturing process, batch size ((b) (4)), and facility for intended commercial batches are the same as those used for manufacturing the registration batches of the drug product.

Biopharmaceutics

The active pharmacological ingredient, tretinoin, is (b) (4) Particle size distribution of the active pharmacological ingredient is deemed critical for the in vitro and in vivo performance of the drug product. Particle size distribution test is included in both the bulk and finished drug product specifications.

The applicant did not include in vitro release test in the drug product specification. Nevertheless, the Applicant was advised during the review cycle to consider the development and validation of a robust and reproducible in vitro release test method.

In the amendment dated December 21, 2017, the applicant stated that they would (b) (4) .

The manufacturing site for the clinical and commercial product is the same, which is Valeant Pharmaceuticals International, in Quebec, Canada. The assurance of the quality of the drug product relies on drug product specifications (other than in vitro release testing) and in process controls characteristic of topical lotion formulation.

Quality Microbiology

The drug product is a non-sterile lotion containing 0.05% tretinoin. (b) (4) (b) (4) methylparaben and benzyl alcohol, are included in the drug product formulation.

The antimicrobial effectiveness testing per USP <51> was performed with drug product lots formulated with both preservatives at 50%, 75%, 80%, and 100% of the label claim. Method suitability testing was performed with modified Tryptic Soy Broth. Log reduction data for the drug product lots formulated with both preservatives at all four concentrations were provided and met USP <51> acceptance criteria for Category 2 products. All challenge bacteria demonstrated a greater than 4.1 log reduction at 14 days and no increase at 28 days. All samples inoculated with *C. albicans* and *A. brasiliensis* demonstrated no increase at 14 and 28 days.

Microbial testing for Total Aerobic Microbial Count, Total Combined Yeast/Mold Count, Absence of *S. aureus* and *P. aeruginosa*, and Absence of *Burkholderia cepacia* complex (BCC) is included in the drug product specification. Method suitability testing was performed for microbial enumeration per USP <61> and specified microorganisms (i.e., *S. aureus* and *P. aeruginosa*) per USP <62> with acceptable results. The results of validation study for the method used for routine evaluation for the absence of BCC were provided in the submission. Routine testing for BCC will require 24 to 48-hour incubation at 30 to 35ºC for enrichment broth (TSB-M (modified Tryptic Soy Broth)) and 48 to 72-hour incubation at 30 - 35ºC for the subsequent subculture onto BCC selective agar plates.

Assays of methylparaben and benzyl alcohol are included in the drug product specification. Antimicrobial effectiveness testing was performed at initial and 6 months for stability samples stored at 40ºC/75%RH and at initial and 12 months for stability samples stored at 25ºC/60%RH and 30ºC/65%RH. Samples at all test conditions and time points passed antimicrobial effectiveness testing requirements. Microbiological testing (i.e., total aerobic microbial count, total yeast/mold count, absence of *S. aureus*, *P. aeruginosa*, and *BCC*) is included in the post-approval stability protocol per Agency's request.

Facilities

The status of the facilities related to the **drug substance** manufacture and testing is summarized in the following table:

Table 7: Status of Facilities Related to Drug Substance Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b) (4)		Drug Substance Manufacture and Testing Profile Code: **CSN**	Approve based on profile
		Alternate testing of Drug Substance Profile Code: **LCP**	Approve based on profile

Abbreviation: FEI = FDA establishment number.

The status of the facilities related to the **drug product** manufacture and testing is summarized in the following table:

Table 8: Status of the Facilities Related to the Drug Product Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
Valeant Pharmaceuticals International, Inc. 2150 St. Elzear Boulevard West Laval, Quebec, Canada H7L 4A8	3002807186	Manufacturing, packaging, labeling, release and stability testing Profile Code: **OIN**	Approve base on file review
Dow Pharmaceutical Sciences 1330 Redwood Way Petaluma, California 94954	1000135370	Alternate release and stability testing facility Profile Code: **LCP**	Approve based on Profile
(b) (4)		Alternate microbiological testing facility Profile Code: **LMN**	Approve based on Profile
		Emulsion droplet size for drug product and particle size testing for drug substance Profile Code: **LCP**	Approve based on Profile
		Alternate compendial testing for excipients and drug substance (particle size) Profile Code: **LCP**	Approve based on Profile
		Alternate compendial testing for excipients and drug substance Profile Code: **LCP**	Approve based on Profile
		Alternate compendial testing for excipients and drug substance Profile Code: **LCP**	Approve based on Profile
		Alternate compendial testing for excipients Profile Code: **LCP**	No Further Evaluation (NFE)

Abbreviation: FEI number = FDA establishment number.

4.3. Clinical Microbiology

Not applicable. Refer to Section 4.2 *Quality Microbiology* for summary information regarding the microbial properties and testing of the drug product.

4.4. Devices and Companion Diagnostic Issues

Not applicable. The drug product is packaged in an (b) (4) (b) (4) The applicant proposed no other device for drug delivery. Refer to Section 4.2 *Drug Product* for information regarding the container/ closure system.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant has filed a 505(b)(1) NDA for ALTRENO (tretinoin) Lotion, 0.05%. The applicant owns ATRALIN (tretinoin) Gel, 0.05% (NDA 22070) and considers the nonclinical data in NDA for ATRALINGel essential to their 505(b)(1) filing of NDA 209353. Since ATRALIN Gel was a 505(b)(2) NDA with Retin-A Micro (tretinoin) Gel, 0.1% (NDA 20475) as the listed drug, the applicant has provided the right of reference letters authorizing FDA to refer to the relevant data for both ATRALIN Gel (NDA 22070) and Retin-A Micro Gel (NDA 20475), in addition to Renova (tretinoin) Cream, 0.02% (NDA 21108); Retin-A (tretinoin) Cream, 0.05% (NDA 17522); and Renova (tretinoin) Cream, 0.05% (NDA 19963).

No pivotal nonclinical studies were included in this NDA. The applicant is referencing the nonclinical studies conducted in support of their previously approved drug product, ATRALIN Gel (NDA 22070, approved 7-26-2007).

When tested in a gel formulation, mild skin irritation was noted in a 13-week dermal toxicity study in minipigs exposed to increasing doses of tretinoin (0.015, 0.045, or 0.075 mg/kg/day at a maximum tretinoin concentration of 0.05%). Due to the absence of significant toxicity in any of the dosed groups, the high-dose of 0.075 mg/kg/day tretinoin was considered to be the no observed adverse effect level. The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test, an in vitro chromosomal aberration assay in human lymphocytes, and an in vivo rat micronucleus assay. All tests were negative. In reproductive and developmental toxicity studies, tretinoin had potent effects on reproductive function when administered orally, particularly with respect to cranial malformations. Topical tretinoin has generated equivocal results in reproductive and developmental toxicity studies.

ALTRENO Lotion, 0.05% is approvable from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

IND 63067, IND 126753, NDA 17522, NDA 20475, NDA 21108, NDA 22070, NDA 19963

The applicant has provided a right of reference letter authorizing FDA to refer to the relevant data for the above-listed NDAs to support the current NDA.

5.3. Pharmacology

Primary pharmacology
Tretinoin is a metabolite of Vitamin A that binds with high affinity to specific retinoic acid receptors (RARs) located in both the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiological concentrations occur following application of a tretinoin-containing topical drug product.

Although tretinoin activates three members of the RARs-RARα, RARβ, and RARγ, which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of RARs, other mechanisms, or both.

Secondary Pharmacology
Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

Safety Pharmacology
No specific safety pharmacology studies have been conducted with ALTRENO Lotion, 0.05%. Topical tretinoin has been in clinical use for many years and no toxicologically important safety pharmacology issues have been identified.

5.4. ALTRENO Lotion ADME/PK

Table 9: ALTRENO Lotion ADME/PK

Type of Study	Major Findings
A 3-month dermal toxicity study of Col-RA™ (tretinoin gel 0.05%) in Hanford minipigs (3551.6)	Minipig Plasma tretinoin levels were either near or below the level of detection for the assay method.

Abbreviations: ADME = absorption, distribution, metabolism, excretion; PK = pharmacokinetics

5.5. Toxicology

5.5.1. General Toxicology

A 13-week topical toxicity study was conducted in Hanford minipigs with a tretinoin gel, 0.05%. Groups of four males and four females received nominal tretinoin dose levels of 0.015, 0.045, or 0.075 mg/kg/day. Heparinized blood samples for toxicokinetic analyses were collected on day 85 (males) and day 86 (females) at 0.5, 1, 2, 4, 8, and 24 hours post-dosing. Plasma samples

were analyzed by LC-MS-MS-equipped with a high performance liquid chromatography column for tretinoin (lower limit of quantification = 1.00 ng/mL). The results indicate that the plasma levels of tretinoin were relatively low and not appreciably different between the treatment groups or sexes. Mild dermal irritation was observed in tretinoin-treated animals. Due to the absence of significant toxicity in any of the dosed groups, the high-dose of 0.15 mL/kg/day of tretinoin gel, 0.05% (*i.e.*, 0.075 mg/kg/day tretinoin) was considered to be the no observable adverse effect level.

5.5.2. Genetic Toxicology

The applicant has obtained the right of reference to the genetic toxicology studies conducted to support ATRALIN Gel (NDA 22070). The following information appears in the Mutagenesis Section of the labeling for ATRALIN Gel.

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test, an in vitro chromosomal aberration assay in human lymphocytes, and an in vivo rat micronucleus assay. All tests were negative.

5.5.3. Carcinogenicity

The applicant has obtained the right of reference to the carcinogenicity studies conducted to support ATRALIN Gel (NDA 22070). The following information appears in the Carcinogenicity Section of the labeling for ATRALIN Gel.

A 2-year dermal mouse carcinogenicity study was initiated with topical administration of 0.005%, 0.025% and 0.05% ATRALIN Gel. Although no drug-related tumors were observed in surviving animals, the irritating nature of the drug product precluded daily dosing, confounding data interpretation, and reducing the biological significance of these results.

Studies in hairless albino mice with a different formulation suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of ultraviolet B (UVB) and ultraviolet A (UVA) light from a solar simulator. This effect was confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should be advised to minimize exposure to sunlight or artificial ultraviolet irradiation sources.

5.5.4. Reproductive and Developmental Toxicology

The applicant has obtained the right of reference to the fertility and embryofetal development studies conducted to support ATRALIN Gel (NDA 22070). The following information appears in the corresponding sections of the labeling for ATRALIN Gel.

Fertility and Early Embryonic Development

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (3 mg/m^2, approximately four times the clinical dose based on body surface area comparison. Slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (1.5 mg/cm^2, approximately two times the clinical dose based on body surface area comparison), were observed.

Embryo-Fetal Development

ATRALIN Gel at doses of 0.1, 0.3, and 1 g/kg/day was tested for maternal and developmental toxicity in pregnant Sprague-Dawley rats by dermal application. The dose of 1 g/kg/day was approximately four times the clinical dose assuming 100% absorption and based on body surface area comparison. Possible tretinoin-associated teratogenic effects (craniofacial abnormalities (hydrocephaly), asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were noted in the fetuses of ATRALIN Gel-treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the ATRALIN Gel-treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the clinical dose is defined as 2 g of ATRALIN Gel applied daily to a 50-kg person.
Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters and nonhuman primates. Tretinoin was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (approximately eight times the clinical dose based on body surface area comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day, but none were observed at 5 mg/kg/day (approximately 80 times the clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in a different formulation has generated equivocal results in animal teratogenicity tests. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (approximately eight times the clinical dose assuming 100% absorption and based on body surface area comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 160 times the clinical dose assuming 100% absorption and based on body surface areas comparison) was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 20 times the clinical dose based on body surface area comparison. Topical tretinoin has been shown to be

fetotoxic in rabbits when administered in doses eight times the clinical dose based on body surface area comparison.
Given that the maximum recommended human dose (MRHD) for ATRALIN Gel was 2 g/day for 50 kg person and the MRHD for ALTRENO Lotion, 0.05% is 4 g/day for 60 kg person, the multiples of exposure referenced in the ALTRENO Lotion, 0.05% labeling will decrease accordingly.

Study title/ number: Bovine corneal opacity and permeability test (V01-121A-602)
The applicant has conducted an ex vivo bovine corneal opacity and permeability assay to determine the ocular irritation potential of tretinoin lotion, 0.05% and the corresponding vehicle. Following exposure, opacity measurements were made, sodium fluorescein permeability was determined, and the in vitro irritancy score (IVIS) was calculated as shown below:
IVIS = corrected mean opacity score + (15 x mean optical density score)

Based on an IVIS of -1.0, tretinoin lotion, 0.05% is not considered to be a severe ocular irritant causing serious eye damage (see table 10, taken directly from the Study report). The IVIS for the positive control, 100% ethanol, met the acceptance criterion, validating assay sensitivity.

Table 10: Bovine Corneal Opacity and Permeability Results of the Test Articles and the Positive Control

Assay Date	IIVS Test Article Number	Sponsor's Designation	Conc.	Exposure Time	Opacity Value	OD_{490} Value	*In Vitro* Score	pH
19 May 2016	16AB21	IDP-121 Lotion	Neat	10 minutes	-1.0	0.002	-1.0	5.0
	16AB22	IDP-121 Vehicle	Neat	10 minutes	-0.3	0.001	-0.3	5.0
	Positive Control	Ethanol	NA	10 minutes	35.7	0.808	47.8	NA

NA – Not Applicable

Study title/ number: Phototoxicity Assay with Preliminary Screening Assay using the Epiderm Skin Model (V01-121A-601)
To evaluate the potential phototoxicity of ALTRENO Lotion, 0.05%, the reconstructed EpiDerm™ Skin Model was used and viability of the treated tissues was determined with and without UVA light. The test articles were ALTRENO Lotion and Vehicle. To increase confidence in the predictive potential of this alternative assay the test was run with ATRALIN Gel as a benchmark control. Epiderm™ tissues were treated with each test article (n=6) and the positive control (0.02% chlorpromazine; n=4) for an exposure time of 4 ±0.5 hours. After the exposure time, half

of the tissues in each treatment group were subjected to UVA light for 60 minutes (6 J/cm^2), while the other half were held at room temperature in the dark. The tissues were returned to the incubator for a post-exposure incubation of 21±1.0 hours. Viability was determined using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) conversion assay, which measures the NAD(P)H-dependent microsomal enzyme reduction of MTT (and to a lesser extent, the succinate dehydrogenase reduction of MTT) to a blue formazan precipitate. Phototoxicity was then determined for the test articles and positive control by comparing tissue viability between UVA-exposed and dark-exposed groups. Based on the results of this test ALTRENO Lotion is not phototoxic.
Table 11 (taken directly from the study report) summarizes the results for the test articles and the positive control. The positive control met the acceptance criterion, validating the sensitivity of the assay.

Table 11: Summary Results of the EpiDerm™ Definitive Phototoxicity Assay

IIVS Test Article Number	Sponsor's Designation	Conc. (mg/mL)	Exposure Time	% Viable		% Difference between +UVA and -UVA	Phototoxic Response?*	pH
				w/ UVA	w/o UVA			
16AB21	IDP-121 Lotion	Neat	4 hours	49.7 ± 3.2	53.5 ± 5.7	3.8	NO	NCC
16AB22	IDP-121 Vehicle	Neat	4 hours	50.6 ± 3.9	61.3 ± 6.8	10.7	NO	NCC
16AB23	Atralin® (tretinoin) gel 0.05%	Neat	4 hours	56.3 ± 14.8	58.6 ± 18.2	2.3	NO	NCC
Positive Control	Chlorpromazine	0.02%	24 hours	33.7 ± 2.4	98.8 ± 0.3	65.1	YES	7.0
R&D	Chlorpromazine	0.02%	4 hours	39.5 ± 3.9	108.7 ± 5.6	69.2	YES	7.0

** - A test article was predicted to be phototoxic if it induced at least a 30% decrease in viability of UVA exposed tissues compared without UVA*
NCC – No color change; a pH value was not determined

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology program consisted of a Phase 1b pharmacokinetic (PK)study where PK of tretinoin lotion was assessed in subjects with moderate or severe acne vulgaris under maximal use conditions [V01-121A-501 (Study 501)]. Relative bioavailability was not assessed as the applicant followed a 505(b)(1) regulatory pathway. The key review findings with specific recommendations and comments are summarized in Table 12.

Table 12: Summary of Clinical Pharmacology Review.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy was not evaluated in the Phase 1b PK study. See section 7 for further information on evidence of effectiveness for tretinoin lotion.
General dosing instruction	The proposed dosing regimen (apply once daily) is acceptable and supported primarily by the data from two Phase 3 trials.
Pharmacokinetics	PK of tretinoin and two metabolites, isotretinoin and 4-oxo-isotretinoin was assessed under maximal use conditions following application of tretinoin Lotion for 14 days. Tretinoin, isotretinoin and 4-oxo-isotretinoin are endogenous substances and hence the Baseline levels were assessed prior to dosing. Baseline corrected PK parameters are reported for tretinoin lotion Baseline.
Pediatric Subjects	Maximal use PK study enrolled only pediatric subjects aged 10 to <17 years.
Formulation used in Clinical Trials	The to-be-marketed formulation was used in two Phase 3 trials and in the maximal use PK study. Hence, PK bridge between to-be-marketed and clinical formulations is not necessary for approval of this NDA.

Abbreviations: PK = pharmacokinetics, NDA = New Drug Application

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable provided labeling comments are adequately addressed by the applicant.

6.1.2. Post-Marketing Requirements and Commitment(s)

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The PK results of tretinoin, and its two metabolites (isotretinoin, and 4-oxo-isotretinoin) from the maximal use study are summarized in Table 13.

Table 13: Summary of Pharmacokinetics of Tretinoin, Isotretinoin, and 4-Oxo-Isotretinoin

<table>
<tr><th>Review Issues</th><th>Conclusion/Comments</th></tr>
<tr><td>Baseline Levels</td><td>Plasma concentrations of tretinoin and its metabolites (isotretinoin and 4-oxo-isotretinoin) were measurable in most subjects at Baseline. The mean Baseline concentrations of tretinoin, isotretinoin, and 4-oxo-isotretinoin were 1.25, 1.27, and 2.06 ng/mL, respectively.</td></tr>
<tr><td>Systemic Exposure</td><td>The table below presents the Baseline-corrected and Baseline-uncorrected PK parameters of tretinoin and its two metabolites following topical administration of tretinoin lotion for 14 days.
<table>
<tr><th></th><th colspan="2">Baseline-Corrected</th><th colspan="2">Baseline-Uncorrected (Raw Concentrations)</th></tr>
<tr><th></th><th>C_{max} (SD) (ng/mL)</th><th>AUC_{0-t} (SD) (h*ng/mL)</th><th>C_{max} (SD) (ng/mL)</th><th>AUC_{0-t} (SD) (h*ng/mL)</th></tr>
<tr><td>Tretinoin</td><td>0.33 (0.33)</td><td>6.46 (5.15)</td><td>1.58 (0.18)</td><td>29.12 (7.47)</td></tr>
<tr><td>Isotretinoin</td><td>0.49 (0.66)</td><td>9.3 (9.95)</td><td>1.76 (0.6)</td><td>34.65 (8.25)</td></tr>
<tr><td>4-oxo-isotretinoin</td><td>0.57 (0.82)</td><td>14.51 (18.28)</td><td>2.63 (0.86)</td><td>55.38 (19.42)</td></tr>
</table>
The tretinoin lotion C_{max} levels (based on raw concentrations) for tretinoin and its metabolites slightly increased compared to the respective observed Baseline levels; however, high inter-subject variability was observed. The mean tretinoin lotion accumulation ratios between Day 14 and Day 1 based on Baseline corrected AUC for tretinoin, isotretinoin, and 4-oxo-isotretinoin was approximately 1.5, 4.5 and 7.3, respectively.</td></tr>
<tr><td>Terminal Half-life</td><td>Terminal half-life ($T_{1/2}$) of tretinoin was 11 hours based on the data from only two subjects. In most subjects $T_{1/2}$ could not be determined due to not enough quantifiable timepoints in the elimination phase. The $T_{1/2}$ determination is not considered reliable.</td></tr>
<tr><td>Pediatric Subjects</td><td>The PK study was performed only in pediatric subjects (10 to <17 year). Although the applicant is seeking indication down to 9-year old, it is noted that there were no 9-year old subjects studied. However, there were four subjects (20%) between the ages 10-11 years which are considered reasonable to represent lowest age range. Furthermore, physiologically a 9-year old patient is not very different compared to a 10-year old and drug disposition is expected to be very similar. In addition, the disease manifestation of acne vulgaris is similar between a 9-year old subject and 10 to11-year-old subject. Hence, from a clinical pharmacology perspective, the lack of 9-year old subject in the maximal use PK study would not impact approvability of this product down to 9 years of age.</td></tr>
<tr><td>Drug-Drug Interaction</td><td>Evaluation of drug-drug interaction was not performed as this in not a new molecular entity and this applicant owns and markets other dosage forms of tretinoin at the same strength.</td></tr>
</table>

Bioanalytical Method	Full validation report was submitted and bioanalytical method was adequately validated.

Abbreviations: AUC = area under the curve, SD = standard deviation, PK = pharmacokinetics

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant has proposed a dosing regimen of application of a thin layer of tretinoin lotion, once-daily to affected areas. This dosing regimen is similar to other approved topical tretinoin formulations and is supported by safety from the maximal use study and efficacy and safety data from the two Phase 3 trials. Refer to Section 7 of this review for efficacy and safety findings from the Phase 3 trials.

Therapeutic Individualization

Therapeutic individualization was not evaluated.

Outstanding Issues

There are no outstanding issues that would preclude the approval of tretinoin lotion, 0.05% from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The design of the maximal use study is described in Table 12-Table 13. Demographics of enrolled subjects were presented in Table 14.

Table 14: Subject Disposition and Demographic Characteristics

Safety Population, n (%)		20 (100%)
Number of Subjects Completing, n (%)		20 (100%)
Age (years)	Mean (SD)	14.0 (2.1)
	Median	15.0
	Minimum, Maximum	10,16
Sex, n (%)	Male	13 (65.0)
	Female	7 (35.0)
Race, n (%)	White	16 (80.0)
	Black or African American	4 (20.0)
Ethnicity, n (%)	Hispanic or Latino	4 (20.0)
	Not Hispanic or Latino	16 (80.0)

Abbreviation: SD = standard deviation

Tretinoin lotion, 0.05% was administered once daily in the morning for 14 days on the entire face (excluding eyes and lips), neck, upper chest, upper back, and shoulders. Information on the

extent of non-facial involvement in each subject was not provided. The mean study drug usage during the study (14 days) by each subject was 48.9 g (median 54.2 g). Therefore, the mean daily dose was approximately 3.5 g.

Plasma concentrations of tretinoin, isotretinoin and 4-oxo-isotretinoin were determined using validated high-performance liquid chromatographic methods with tandem mass spectrometric detection (LC-MS/MS). The lower limits of quantification (LLOQs) for tretinoin, isotretinoin, and 4-oxotretinoin were 1.19 ng/mL, 0.833 ng/mL, and 0.706 ng/mL, respectively. Plasma concentrations of tretinoin, isotretinoin, and 4-oxoisotretinoin for PK analysis were collected at following time points:

- Days 1-2: Pre-dose (-2 to -1 hour, -1 to 0 hour), 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose
- Day 12: A pre-dose sample prior to application of study drug (in the morning)
- Days 14-15: Pre-dose (-1 to 0 hour), 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose

PK Results

Baseline Levels of Tretinoin, Isotretinoin and 4-Oxo-Isotretinoin: Tretinoin is an endogenous substance. Diurnal characteristics of tretinoin and its metabolites are unknown and were not explored by this applicant. Baseline of tretinoin and its metabolites was assessed by obtaining pre-dose plasma levels on Day 1 at two windows (-2 to -1 hour and -1 to 0 hour). Results are summarized in Table 15. It is noted the mean Baseline level of tretinoin at -2 to -1 h time point (1.21 ng/mL) was close to the LLOQ (1.19 ng/mL) of the bioanalytical method. Baseline values were calculated as the mean of the two pre-dose measurements (-2 to -1 hours and -1 to 0 hour) on Day 1.

Table 15: Pre-Dose (Day 1) Concentration of Tretinoin, Isotretinoin, and 4-Oxo-Isotretinoin

Time Point		Tretinoin N=20	Isotretinoin N=20	4-oxo-isotretinoin N=20
Day 1 Visit				
-2 to -1 h Pre-Dose	N	20	20	20
	N_{quant}	15	20	20
	Arithmetic Mean	1.21	1.29	2.05
	Geometric Mean	1.13	1.26	1.97
	SD	0.40	0.29	0.55
	CV	33.04	22.49	26.80
	Minimum, Maximum	0.6, 1.9	0.9, 1.8	1.1, 3.0
-1 to 0 h Pre-Dose	N	20	20	20
	N_{quant}	17	18	20
	Arithmetic Mean	1.30	1.25	2.08
	Geometric Mean	1.24	1.17	1.99
	SD	0.34	0.41	0.65
	CV	26.51	32.52	31.00
	Minimum, Maximum	0.6, 1.9	0.4, 1.8	1.2, 3.0

BLQ = Below Limit of Quantitation (<1.19 ng/mL Tretinoin, <0.833 ng/mL Isotretinoin, <0.706 ng/mL 4-oxo-isotretinoin); N_{quant} = number of samples in the N population with quantifiable levels of analyte; SD = Standard Deviation
Concentrations below the limit of quantitation are reported as 1/2 of LLOQ for calculating summary statistics.

Baseline-Corrected PK Parameters: Baseline corrected pharmacokinetic parameters for each analyte are presented in Table 16-Table 18. Baseline corrected concentration values were calculated as the raw concentration minus the Baseline value. Measurements below the level of quantitation were set to 1/2 the LLOQ of the analyte. Negative concentration values were set to 0 in calculation of area under the curve (AUC) AUC_{0-t} and AUC_{0-24h}.

Tretinoin: On Days 14-15, the mean C_{max} standard deviation (SD) was 0.33 (0.33) ng/mL with median T_{max} of 7 hours. The mean AUC_{0-t} (SD) was 6.46 (5.15) ng*h/mL. The mean accumulation ratios for C_{max} and AUC_{0-t} were 0.93, and 1.51, respectively.

Table 16: Summary of Baseline Corrected PK Parameters of Tretinoin

		C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (h)	$R(C_{max})$	$R(AUC_{0-t})$	$R(AUC_{0-24})$
Day 1-2	N	20	20	20	12	0	0	N/A	N/A	N/A
	Arithmetic Mean	0.42	-0.48	9.45	7.06	--	--	N/A	N/A	N/A
	Geometric Mean	0.28	--	6.71	3.85	--	--	N/A	N/A	N/A
	Median	0.25	-0.51	4.00	3.62	--	--	N/A	N/A	N/A
	SD	0.39	0.38	10.11	6.59	--	--	N/A	N/A	N/A
	CV (%)	91.71	-78.48	107.01	93.35	--	--	N/A	N/A	N/A
	Minimum, Maximum	0.1, 1.2	-1.3, 0.0	0.0, 24.0	0.4, 17.3	--	--	N/A	N/A	N/A
Day 14-15	N	20	20	20	12	0	0	20	9	0
	Arithmetic Mean	0.33	-0.46	11.00	6.46	--	--	0.93	1.51	--
	Geometric Mean	--	--	9.04	4.78	--	--	--	1.09	--
	Median	0.22	-0.51	7.00	5.16	--	--	0.82	0.87	--
	SD	0.33	0.45	9.30	5.15	--	--	0.86	1.49	--
	CV (%)	100.55	-98.95	84.56	79.67	--	--	91.93	99.01	--
	Minimum, Maximum	-0.1, 1.1	-1.3, 0.6	0.0, 24.0	1.2, 18.1	--	--	-1.0, 2.6	0.4, 4.9	--

Note: Baseline corrected plasma concentration = post-baseline conc. – baseline conc. Baseline conc. = Mean of two pre-dose concentrations (-2 to -1 hours pre-dose and -1 to 0 hour pre-dose) on Day 1.
$R(C_{max})$ is accumulation ratio, calculated as C_{max} on Day 14 divided by C_{max} on Day 1.
$R(AUC_{0-t})$ is accumulation ratio, calculated as AUC_{0-t} on Day 14 divided by AUC_{0-t} on Day 1.
$R(AUC_{0-24})$ is accumulation ratio, calculated as AUC_{0-24} on Day 14 divided by AUC_{0-24} on Day 1.

Isotretinoin: On Days 14-15, the mean C_{max} (SD) was 0.49 (0.66) ng/mL with median T_{max} of 6 hours. The mean AUC_{0-t} (SD) was 9.3 (9.95) ng*h/mL. The mean accumulation ratios for C_{max} and AUC_{0-t} were 13.13, and 4.5, respectively.

Table 17: Summary of Baseline Corrected PK parameters of Isotretinoin

		C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (h)	$R(C_{max})$	$R(AUC_{0-t})$	$R(AUC_{0-24})$
Day 1-2	N	20	20	20	11	0	0	N/A	N/A	N/A
	Arithmetic Mean	0.24	-0.28	8.20	3.47	--	--	N/A	N/A	N/A
	Geometric Mean	0.15	--	9.16	3.10	--	--	N/A	N/A	N/A
	Median	0.25	-0.23	8.00	2.54	--	--	N/A	N/A	N/A
	SD	0.18	0.20	8.31	2.03	--	--	N/A	N/A	N/A
	CV (%)	73.08	-71.95	101.31	58.56	--	--	N/A	N/A	N/A
	Minimum, Maximum	0.0, 0.6	-0.7, -0.1	0.0, 24.0	1.7, 8.7	--	--	N/A	N/A	N/A
Day 14-15	N	20	20	20	11	1	1	20	6	0
	Arithmetic Mean	0.49	-0.15	9.05	9.30	0.72	1.22	13.13	4.50	--
	Geometric Mean	--	--	7.08	4.77	0.72	1.22	--	2.24	--
	Median	0.28	-0.18	6.00	3.81	0.72	1.22	1.66	3.52	--
	SD	0.66	0.44	8.79	9.95	--	--	48.09	4.14	--
	CV (%)	133.02	-303.08	97.09	107.00	--	--	366.42	92.07	--
	Minimum, Maximum	-0.1, 2.3	-0.9, 1.0	0.0, 24.0	0.7, 31.6	0.7, 0.7	1.2, 1.2	-1.5, 217.0	0.1, 10.6	--

4-oxo-isotretinoin: On Days 14-15, the mean C_{max} (SD) was 0.57 (0.82) ng/mL with median T_{max} of 6 hours. The mean AUC_{0-t} (SD) was 14.51 (18.28) ng*h/mL. The mean accumulation ratios for C_{max} and AUC_{0-t} were 3.19, and 7.27, respectively.

Table 18: Summary of Baseline Corrected PK Parameters of 4-Oxo-Isotretinoin

		C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (h)	$R(C_{max})$	$R(AUC_{0-t})$	$R(AUC_{0-24})$
Day 1-2	N	20	20	20	9	1	1	N/A	N/A	N/A
	Arithmetic Mean	0.21	-0.35	6.35	2.30	0.92	10.59	N/A	N/A	N/A
	Geometric Mean	0.16	--	6.21	1.50	0.92	10.59	N/A	N/A	N/A
	Median	0.16	-0.28	2.00	1.80	0.92	10.59	N/A	N/A	N/A
	SD	0.16	0.21	8.46	2.21	--	--	N/A	N/A	N/A
	CV (%)	78.06	-61.10	133.16	95.89	--	--	N/A	N/A	N/A
	Minimum, Maximum	0.0, 0.6	-0.9, -0.1	0.0, 24.0	0.2, 7.6	0.9, 0.9	10.6, 10.6	N/A	N/A	N/A
Day 14-15	N	20	20	20	12	2	2	20	6	0
	Arithmetic Mean	0.57	-0.06	9.40	14.51	22.51	87.00	3.19	7.27	--
	Geometric Mean	--	--	6.25	7.75	17.31	29.43	--	6.37	--
	Median	0.40	-0.08	6.00	9.15	22.51	87.00	1.57	7.79	--
	SD	0.82	0.71	9.38	18.28	20.35	115.78	6.92	3.63	--
	CV (%)	143.29	-1260.18	99.76	126.03	90.40	133.08	217.14	49.98	--
	Minimum, Maximum	-0.5, 3.1	-1.3, 1.9	0.0, 24.0	1.2, 63.5	8.1, 36.9	5.1, 168.9	-10.5, 21.5	2.3, 12.9	--

It was noted that many of Baseline corrected concentrations were negative values. The negative concentration values were set to 0 in the applicant's calculation of AUC_{0-t} and AUC_{0-24h}. Therefore, the reported AUCs (Baseline-corrected) only account positive concentrations.

Following 14 days of treatment, it is noted that the Baseline corrected C_{max} were less than 1 ng/mL for all analytes. The mean C_{max} of the two metabolites appear to increase from Day 1 to Day 14, which may be indicative of accumulation of the metabolites in the system. However, the interpretation should be made with caution as Baseline-corrected PK parameters are highly variable.

Baseline-Uncorrected PK Parameters: Baseline uncorrected PK parameters were calculated based on the raw concentrations of each analyte and are summarized in Table 19-Table 21.

Tretinoin: On Days 14-15, the mean C_{max} (SD) was 1.58 (0.18) ng/mL and was observed at a median T_{max} of 7 hours. The mean AUC_{0-t} (SD) was 29.12 (7.47) ng*h/mL. The mean accumulation ratios for C_{max} and AUC_{0-t} were 0.95, and 1.02, respectively.

Table 19: Summary of Pharmacokinetics Parameters for Tretinoin

		C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (1/h)	$R(C_{max})$	$R(AUC_{0-t})$	$R(AUC_{0-24})$
Days 1- 2	N	20	20	20	19	2	2	N/A	N/A	N/A
	Arithmetic Mean	1.67	0.77	--	29.53	22.30	10.85	N/A	N/A	N/A
	Geometric Mean	1.66	0.72	--	28.53	22.30	10.85	N/A	N/A	N/A
	Median	1.60	0.60	4.00	31.61	22.30	10.85	N/A	N/A	N/A
	SD	0.20	0.31	--	6.92	0.17	0.03	N/A	N/A	N/A
	CV (%)	12.19	40.74	--	23.44	0.75	0.26	N/A	N/A	N/A
	Minimum, Maximum	1.4, 2.1	0.6, 1.4	--	13.4, 37.1	22.2, 22.4	10.8, 10.9	N/A	N/A	N/A
Days 14- 15	N	20	20	20	17	0	0	20	16	0
	Arithmetic Mean	1.58	0.79		29.12	--	--	0.95	1.02	--
	Geometric Mean	1.57	0.74		27.96	--	--	0.94	0.93	--
	Median	1.52	0.60	7.00	30.30	--	--	0.98	0.95	--
	SD	0.18	0.32		7.47	--	--	0.13	0.44	--
	CV (%)	11.17	39.80		25.65	--	--	13.50	43.70	--
	Minimum, Maximum	1.4, 2.0	0.6, 1.4		12.0, 40.5	--	--	0.7, 1.1	0.3, 2.2	--

Isotretinoin: On Days 14-15, the mean C_{max} (SD) was 1.76 (0.60) ng/mL and was observed at a median T_{max} of 6.0 hours. The mean AUC_{0-t} (SD) was 34.65 (8.25) ng*h/mL. The mean accumulation ratios for C_{max} and AUC_{0-t} were 1.2 and 1.16, respectively.

Table 20: Summary of Pharmacokinetics Parameters for Isotretinoin

		C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (h)	$R(C_{max})$	$R(AUC_{0-t})$	$R(AUC_{0-24})$
Day 1-2	N	20	20	20	18	0	0	N/A	N/A	N/A
	Arithmetic Mean	1.51	0.99	8.20	31.43	--	--	N/A	N/A	N/A
	Geometric Mean	1.47	0.90	9.16	30.33	--	--	N/A	N/A	N/A
	Median	1.57	1.09	8.00	32.10	--	--	N/A	N/A	N/A
	SD	0.34	0.37	8.31	7.41	--	--	N/A	N/A	N/A
	CV (%)	22.49	37.26	101.31	23.57	--	--	N/A	N/A	N/A
	Minimum, Maximum	0.9, 2.1	0.4, 1.5	0.0, 24.0	12.1, 41.0	--	--	N/A	N/A	N/A
Day 14-15	N	20	20	20	19	0	0	20	17	0
	Arithmetic Mean	1.76	1.12	9.05	34.65	--	--	1.20	1.16	--
	Geometric Mean	1.68	1.04	7.08	33.79	--	--	1.14	1.10	--
	Median	1.66	1.13	6.00	32.61	--	--	1.03	1.00	--
	SD	0.60	0.40	8.79	8.25	--	--	0.46	0.47	--
	CV (%)	34.14	35.76	97.09	23.81	--	--	38.17	40.03	--
	Minimum, Maximum	0.9, 3.4	0.4, 2.0	0.0, 24.0	20.7, 57.2	--	--	0.7, 2.2	0.8, 2.6	--

Abbreviations: SD = standard deviation, AUC = area under curve, CV = coefficient of variation

4-oxo-Isotretinoin: On Days 14-15, the mean the C_{max} (SD) was 2.63 (0.86) ng/mL and was observed at a median T_{max} of 6 hours. The mean AUC_{0-t}(SD) was 55.38 (19.42) ng*h/mL and the mean AUC_{0-24} (SD) was 63.48 (20.74) ng*h/mL. The median $t_{1/2}$ of 4-oxo-isotretinoin was 59.8

hours based on 4 subjects. The mean accumulation ratios for C_{max} and AUC_{0-t} were 1.19, and 1.19, respectively.

The reported half-life of tretinoin and the metabolites should be interpreted with caution because this data is based on small number of subjects (2 subjects for tretinoin and 4 subjects for 4-Oxo-Isotretinoin).

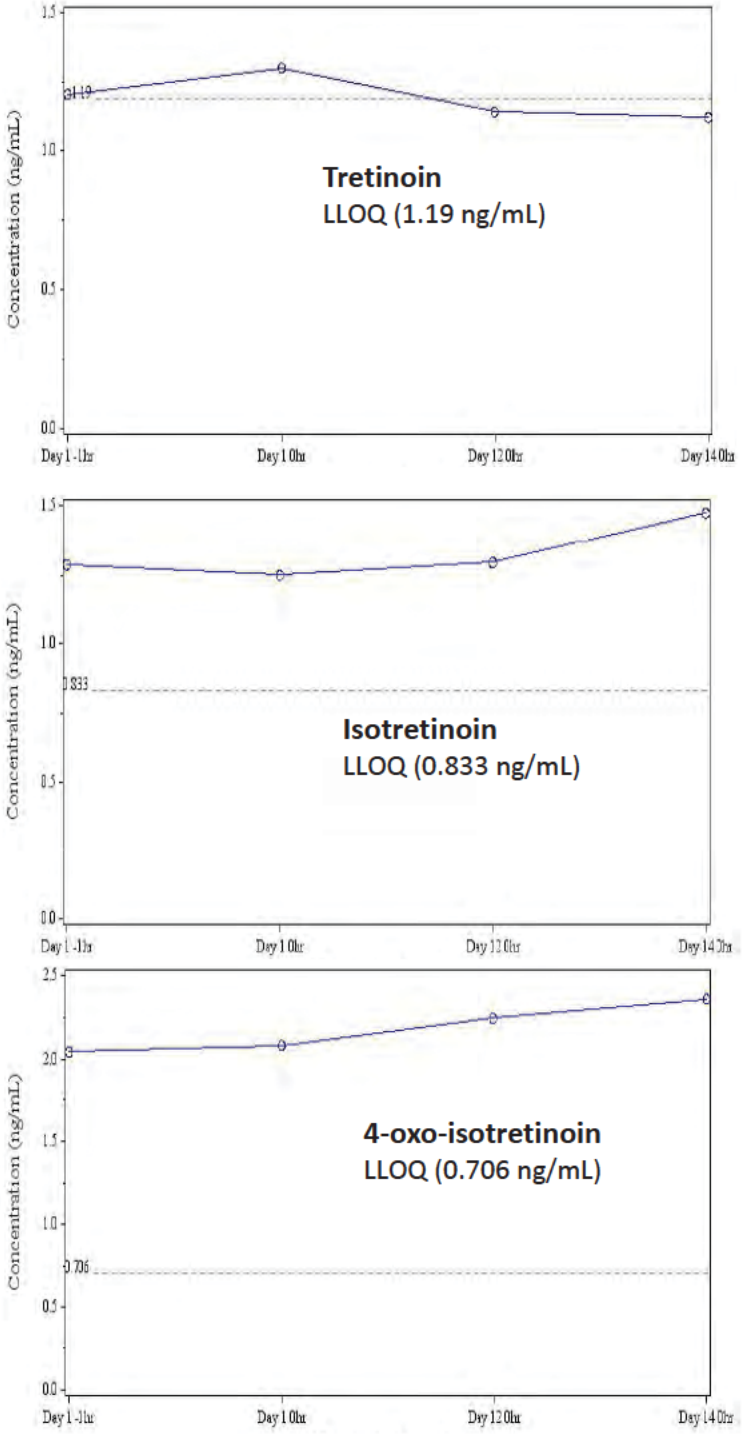
Table 21: Summary of Pharmacokinetics Parameters for 4-Oxo-Isotretinoin

		C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (1/h)	$R(C_{max})$	$R(AUC_{0-t})$	$R(AUC_{0-24})$
Days 1- 2	N	20	20	20	20	4	4	N/A	N/A	N/A
	Arithmetic Mean	2.27	1.72		47.51	45.33	49.38	N/A	N/A	N/A
	Geometric Mean	2.19	1.65		45.70	44.13	47.97	N/A	N/A	N/A
	Median	2.30	1.65	2.00	47.86	46.57	52.89	N/A	N/A	N/A
	SD	0.63	0.48		13.30	11.61	12.52	N/A	N/A	N/A
	CV (%)	27.54	28.11		28.00	25.61	25.36	N/A	N/A	N/A
	Minimum, Maximum	1.4, 3.3	1.1, 2.6		27.7, 68.0	30.9, 57.3	31.4, 60.3	N/A	N/A	N/A
Days 14- 15	N	20	20	20	20	4	4	20	20	2
	Arithmetic Mean	2.63	2.01		55.38	63.48	154.35	1.19	1.19	1.60
	Geometric Mean	2.51	1.90		52.43	61.30	81.69	1.15	1.15	1.58
	Median	2.58	1.94	6.00	54.58	55.60	59.80	1.06	1.07	1.60
	SD	0.86	0.72		19.42	20.74	211.94	0.33	0.34	0.32
	CV (%)	32.83	36.08		35.06	32.68	137.31	27.46	28.75	20.00
	Minimum, Maximum	1.3, 5.0	0.9, 3.7		26.9, 107.9	48.6, 94.1	26.4, 471.4	0.8, 2.0	0.8, 2.1	1.4, 1.8

Pre-dose Mean Plasma Concentrations

The linear plots of mean pre-dose concentration of tretinoin, isotretinoin, and 4-oxo-isotretinoin on Day 1 (-2 to -1h and -1 to 0 h), 12, and 14 are shown in Figure 1.

Figure 1 - Pre-dose Mean Plasma Concentration of Tretinoin, Isotretinoin, and 4-Oxo-Isotretinoin on Days 1, 12, and 14



Following 14 days of administration of tretinoin lotion, the mean pre-dose concentration of tretinoin does not appear to change from its Baseline levels (Figure 1). The mean pre-dose

concentrations of isotretinoin and 4-oxo-isotretinoin increased slightly from their Baseline levels.

Pediatric Assessment
As described above, the maximal use PK study did not have any 9-year old subject and had enrolled subjects ages 10 to <17 years. However, the 2 Phase 3 trials included pediatric subjects who are at least 9 years of ages. The applicant has asked for a waiver in subjects below the age of 9 years and this is reasonable form a clinical pharmacology standpoint.

Evaluation of Safety

See Section 7 for safety assessment.

Bioanalytical Method Validation and Performance

Tretinoin, isotretinoin, and 4-oxo-isotretinoin in human plasma was quantified using a validated LC-MS/MS method for the study (protocol V01-121A-501). Bioanalytic method validation report for tretinoin, isotretinoin, and 4-oxo-isotretinoin are summarized in Table 22. The endogenous levels of tretinoin, isotretinoin, and 4-oxo-isotretinoin were determined to be 1.19 ng/mL, 0.833 ng/mL, and 0.706 ng/mL, respectively from blank samples of pooled plasma that were used to set up calibration standards and quality controls. The method is based on analysis of 0.150 mL of plasma and linear over the range of 0.00-50.0 ng/mL on top of endogenous levels for all three analytes.

Table 22: Summary of Method Validation Results

Validation Report **Bioanalytical Report**	VVALN1600P1 BVALN1600P1		
Relevant Clinical Trial	V01-121A-501		
Matrix	Human plasma		
Analytes	**Tretinoin**	**Isotretinoin**	**4-oxo-Isotretinoin**
Linearity	1.19 to 51.2 ng/mL	0.833 to 50.8 ng/mL	0.706 to 50.7 ng/mL
LLOQ	1.19 ng/Ml	0.833 ng/mL	0.706 ng/mL
Precision (% CV)			
Intra-assay	1.8 to 2.8% (LLOQ); 1.4 to 3.6% (>LLOQ)	4.5 to 8.2% (LLOQ); 0.8 to 5.4% (>LLOQ)	2.9 to 5.2% (LLOQ); 0.9 to 4.5% (>LLOQ)
Inter-assay	2.6% (LLOQ); 1.6 to 2.8% (>LLOQ)	6.5% (LLOQ); 1.8 to 5.2% (>LLOQ)	5.1% (LLOQ); 1.8 to 3.4% (>LLOQ)
Accuracy (% Bias)			
Intra-assay	-0.9 to 2.3% (LLOQ); -3.8 to 2.1% (>LLOQ)	-4.2 to -0.4% (LLOQ); -4.0 to 3.4% (>LLOQ)	-5.2 to 1.8% (LLOQ); -3.4 to 0.1% (>LLOQ)
Inter-assay	0.3% (LLOQ); -2.7 to 0.9% (>LLOQ)	-2.8% (LLOQ); -3.2 to -0.3% (>LLOQ)	-0.9% (LLOQ); -2.7 to -0.9% (>LLOQ)
Solution Stability	▪ Stable for 104 days in 0.2% ammonium hydroxide in 50/50 ACN/20 mM ammonium acetate, pH 5.8 (-20 ºC) glass		

	▪ Stable for 21.00 hr in 0.2% ammonium hydroxide in 50/50 ACN/20 mM ammonium acetate, pH 5.8 (RT) glass		
Freeze-thaw Stability	▪ Stable 4 cycles at Freeze/Thaw (-70 °C/ Ice- Water) ▪ Stable 4 cycles at Freeze/Thaw (-20 °C/ Ice- Water)		
Bench-top Stability	Stable for 6 hrs in: ▪ Ice water ▪ Ice-Water with 29-hour room temperature ascorbic acid ▪ Ice-Water With 115-day old ascorbic acid		
Long Term Storage Stability	Stable for 168 days at -70 °C and -20 °C		
Selectivity	Complies following acceptance criteria ▪ Interferences at ≤ 5% mean IS (at least 5 of 6 screened) ▪ % CV for IS normalized MF must be ≤ 15% over all 6 lots out of 6 spiked matrix lots		
Incurred sample reanalysis (ISR)	Approximately 10% of the samples are re-analyzed. These include samples approximating the C_{max}, provided they did not require dilution, as well as samples near the elimination phase.		
Number of samples	41	42	
Total % ISR samples Pass	95%	98%	90%

Abbreviations: LLOQ = lower limit of quantification, ACN = acetonitrile, hr = hour, CV = coefficient of variation, IS = internal standard, MF = matrix factor

The applicant notes that a total of 399 samples were analyzed between 07 Jun 2016 and 20 Oct 2016. The maximum possible period of storage between first sample collection on 09 May 2016 and analysis was 164 days. All samples were analyzed within the long-term stability window (168 days). The linearity range (0 to 50 ng/mL) was adequate as none of the plasma concentrations of three analytes exceeded the upper limit of the concentration range. Approximately 10 % (41 out of 399 samples) were analyzed for incurred sample repeat analysis. Greater than 67% of ISR samples met the criteria of assay reproducibility, which was the percent difference must be within 20% of the mean of the original and repeated values.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy evaluated in the two Phase 3 trials and was not evaluated in the Phase 1 Pharmacokinetic Study (V01-121A-501). See Section 7 of this multi-disciplinary review for efficacy results.

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

Based on the safety results from the maximal use and Phase 3 trails and efficacy results from the 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?

No. A dose adjustment is not necessary based on the available efficacy and safety data in Phase 3 trials. The effect of other intrinsic and extrinsic factors except age (see Section 6.3.1) on the PK of tretinoin lotion, 0.05%was not evaluated.

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 potential was not needed for approval of this product, as the this is a new dosage form at the same strength of already approved and marketed products that are owned by this applicant.

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The development program for tretinoin lotion for the topical treatment of acne vulgaris included 3 trials:

- Phase 3 Trials
  randomized, placebo- controlled trials to evaluate the efficacy and safety of a once daily topical applications of tretinoin (IDP-121) lotion for 12 weeks compared with its vehicle in subjects age 9 years and older with moderate to severe acne vulgaris
  - V01-121A-301 (Study 301)
  - V01-121A-302 (Study 302)

- Phase 1 Trial
  Open- label trial to evaluate the safety and the pharmacokinetics (PK) of tretinoin and its relevant metabolites (isotretinoin and 4-oxo-isotretinoin) in pediatric subjects ages 9 years to 16 years 11 months with moderate to severe acne vulgaris under maximal use conditions for 14 days.
  - V01-121A-501 (Study 501)

The table below provides a summary of all trials pertinent to the evaluation of the efficacy and safety of tretinoin lotion for the topical treatment of acne vulgaris.

Table 23: Clinical Trials in the NDA 209353 Development Program

Trial Identity	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							
V01-121A-301 (Study 301)	Multicenter, randomized, double-blind, parallel group, vehicle- controlled efficacy and safety trial	Tretinoin lotion (IDP-121) applied once daily to the face	Primary efficacy 1. Absolute change in the mean non-inflammatory lesion count from Baseline to Week 12 2.Absolute change in the mean inflammatory lesion count from Baseline to Week 12 3. treatment success in the EGSS defined as percentage of subjects achieving 0 "clear" or 1 "almost clear" and at least a 2- grade reduction from Baseline at Week 12 in the EGSS Safety: AEs, VS, PE local reactions, laboratory tests & pregnancy testing	12 weeks	ITT Total: 820 IDP-121: 406 Vehicle: 414 Age < 18 years: 372 Safety Total: 763 IDP-121: 378 Vehicle: 385	Male and female subjects 9 years of age and older with moderate to severe acne vulgaris (i.e., EGSS of moderate [3] or severe [4] and 20-40 inflammatory lesions, 20-100 noninflammatory lesions & ≤2 nodules	US: 40 El Salvador: 2
V01-121A-302	Multicenter, randomized, double-	Tretinoin lotion (IDP-121)	Primary efficacy 1. Absolute change in	12 weeks	ITT Total: 820:	Male and female subjects with	US: 34 Dominican

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
(Study 302)	blind, parallel group, vehicle- controlled efficacy and safety trial	applied once daily to the face	the mean non-inflammatory lesion count from Baseline to Week 12 2.Absolute change in the mean inflammatory lesion count from Baseline to Week 12 3. treatment success in the EGSS defined as percentage of subjects achieving 0 "clear" or 1 "almost clear" and at least a 2- grade reduction from Baseline at Week 12 in the EGSS Safety: AEs, VS, PE local reactions, laboratory tests & pregnancy testing		IDP-121: 413 Vehicle: 407 Age < 18 years: 357 <u>safety</u> Total: 787 IDP-121: 389 Vehicle: 398	moderate to severe acne vulgaris (i.e., EGSS of moderate [3] or severe [4] and 20-40 inflammatory lesions, 20-100 noninflammatory lesions & ≤2 nodules	Republic: 1 Honduras: 1
Studies to Support Safety							
V01-121A-501 (Study 501)	Open-label, safety and pharmacokinetic (PK) trial conducted under maximal use conditions	4.0 grams tretinoin lotion applied once daily in the morning to the face, neck, upper chest,	<u>PK parameters</u> for tretinoin & metabolites (isotretinoin & 4-oxo-isotretinoin) on Days 1-2, Day 12, and Days 14-15	14 Days	20	Male and female subjects ages 9 to < 17 years with moderate to severe acne vulgaris (i.e., EGSS of moderate [3] or	US: 2

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		upper back, and shoulders	Safety: AEs, VS, PE local reactions, laboratory tests & pregnancy testing Efficacy: EGSS & lesion counts			severe [4] and 20-40 inflammatory lesions, 20-100 noninflammatory lesions & ≤2 nodules	

Abbreviations: ITT = intent to treat, AEs = adverse events, VS = vital signs, US = United States, PE = physical examination, EGSS = Evaluator's Global Severity Score, PK = pharmacokinetics

7.1.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of tretinoin lotion, 0.05% included the applicant's clinical study reports, 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\nda209353\0001\m5\datasets.

Data and Analysis Quality

The original submission included statistical programs for generating multiple imputations for missing data, but did not provide the statistical programs for analyzing the data from the imputed datasets. Without the statistical programs, the statistical reviewer could not precisely replicate the applicant's results, as it appeared that the applicant may have made some adjustments to the models that were not described in the statistical analysis plan, possibly to deal with a lack of convergence in some of the models. Thus, the statistical programs were requested of the applicant. With the additional details provided by the statistical programs, the statistical reviewer was able to replicate the applicant's results. Once the statistical programs were received, the databases for the studies required minimal data management prior to performing analyses.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Studies 301 and 302

Trial Design and Endpoints

Study 301 and Study 302 were identical randomized, double-blind, vehicle-controlled Phase3 trials evaluating tretinoin lotion 0.05% in the treatment of acne. The trials enrolled subjects age 9 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 20-40 facial inflammatory lesions, 20-100 facial non-inflammatory lesions, and 2 or fewer facial nodules.

The trials were designed to randomize approximately 800 subjects in a 1:1 ratio to tretinoin lotion or vehicle lotion at approximately 32-50 investigational centers in North America and Latin America. Subjects applied treatment once daily for 12 weeks. Subjects were evaluated at Screening, Baseline, and Weeks 4, 8, and 12.

Efficacy was assessed using the EGSS and inflammatory and non-inflammatory lesion counts. The EGSS is as follows:

Table 24: Evaluator's Global Severity Score

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic
3	Moderate	Non-inflammatory 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
Abbreviation: EGSS = Evaluator's Global Severity Score

Inflammatory lesion counts (papules and pustules) and non-inflammatory lesion counts (open and closed comedones) were conducted on the subject's face. Nodules were counted separately.

The co-primary efficacy endpoints were:

- The absolute change in inflammatory lesions at Week 12
- The absolute change in non-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 inflammatory lesions at Week 12
- The percent change in non-inflammatory lesions at Week 12

The supportive endpoints were:

- At least 2 grades improvement on the EGSS from Baseline to Week 12
- The percent change in inflammatory lesions at Weeks 8 and 4
- The percent change in non-inflammatory lesions at Weeks 8 and 4

Clear or almost clear on the EGSS with at least 2 grades improvement at Weeks 8 and 4

Statistical Analysis Plan

The absolute changes in lesion counts were to be analyzed with either ANCOVA or ANCOVA on the ranks depending on the results of a skewness test. Specifically, the absolute change values would be analyzed with analysis of covariance (ANCOVA) with terms for treatment, analysis center, and Baseline lesion count as a covariate. If the treatment-by-analysis center interaction is significant at alpha level 0.10, then the effect will be included in the model, otherwise it will be removed. A skewness test will be applied to the residuals of the ANCOVA model using Zar's

test[10]. If the two-sided p-value is significant at 0.01, then the analysis based on ranks will be considered the primary analysis. Missing data was to be handled with Markov Chain Monte Carlo (MCMC) multiple imputation. Imputation is conducted separately for each treatment group. The number of imputations will be 5 × *nmiss* where *nmiss* is the maximum number of missing Week 12 values between the treatment groups. After the lesion count values have been imputed, each imputed dataset will be analyzed with the ANCOVA procedure and combined into a single result.

Success on the EGSS will be analyzed using logistic regression with terms for treatment and analysis center. Missing data will be 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 will be analyzed using repeated measures ANCOVA with terms for treatment analysis center, visit, treatment-by-visit interaction, and Baseline lesion count. A second sensitivity analysis will use model-based multiple imputation using ANCOVA rather than MCMC. For EGSS success, the first sensitivity analysis will be a repeated measures logistic regression model (generalized estimating equations) with terms for treatment, analysis center, visit, and treatment-by-visit interaction. A second sensitivity analysis will use model-based multiple imputation using logistic regression.

The secondary endpoints of percent change in inflammatory and non-inflammatory lesion counts will be analyzed with the same methods as the absolute change in lesion counts. The supportive endpoints will also be analyzed in the same way as the primary endpoints.

All three co-primary endpoints will need to demonstrate statistical significance. The secondary endpoints will be analyzed sequentially: (1) percent change in non-inflammatory lesions and (2) percent change in inflammatory lesions. The supportive endpoints will also be analyzed sequentially in the following order:

Table 25: Supportive Endpoint

Step Number	Supportive Endpoint
1	Percent change in non-inflammatory lesion count from Baseline to Week 8
2	Percent change in inflammatory lesion count from Baseline to Week 8
3	Percent change in non-inflammatory lesion count from Baseline to Week 4
4	Percent change in inflammatory lesion count from Baseline to Week 4
5	Percentage of subjects who have at least a 2-grade reduction at Week 12 from Baseline in the EGSS
6	Percentage of subjects who have at least a 2-grade reduction at Week 8 from Baseline in the EGSS

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

7	Percentage of subjects who have at least a 2-grade reduction at Week 4 from Baseline in the EGSS

Abbreviation: EGSS = Evaluator's Global Severity Score

The intent to treat (ITT) population is defined as all randomized subjects who receive study medication. The per protocol (PP) population is defined as all subjects in the ITT 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 related to study treatment or documented lack of treatment effect), missed both the Week 4 and Week 8 visits, were noncompliant with the dosing regimen, or who were out of window at the Week 12 visit (-3/+5 days).

The study was intended to enroll a minimum of 5 subjects per treatment arm per center. If too few subjects were enrolled at a site, then the subjects from the smallest site were to be combined with the site with the largest enrollment. This pooling procedure would continue with the next smallest and next largest site until all analysis centers had a minimum of 5 subjects per arm.

Protocol Amendments

The development plan for tretinoin lotion, 0.05% was first discussed with the FDA at an End-of-Phase 2 meeting held on 5/6/2015 under IND 63067, which is the applicant's IND for tretinoin gel for the treatment of acne. Because of the formulation, the applicant opened a new IND (IND 126753) to submit their protocols for tretinoin lotion. Protocol 301 was submitted on 7/24/2015 in the initial submission, with a note that Protocol 302 with an identical design was planned.

Protocols 301 and 302 were amended twice before the studies began enrollment. The key change in Amendment 1 (dated 8/20/2015) was to remove the requirement for serum pregnancy testing. Amendment 2 (dated 9/28/2015) was designed to address the comments from FDA's review of the original protocol. The key design modification in Amendment 2 was to reorganize the nine secondary endpoints into two secondary endpoints and seven supportive endpoints. The studies opened enrollment under Amendment 2. Amendment 3 was dated 10/7/2016. The key modification in Amendment 3 was to open enrollment in Latin American sites. No substantive changes were made to the design or analysis.

7.2.2. Study Results

Compliance with Good Clinical Practices

The applicant required that participating principal investigators agree to comply with the internationally recognized code of Good Clinical Practices and all other applicable regulatory requirements.

Financial Disclosure

Refer to Appendix 13.2.

Patient Disposition

Study 301 enrolled 820 subjects (406 on tretinoin and 414 on vehicle) and Study 302 enrolled 820 subjects (413 on tretinoin and 407 on vehicle). Approximately 18% of subjects in Study 301 and 14% of subjects in Study 302 discontinued. The most common reasons for discontinuation were loss to follow-up and subject request. See Table 26. Subjects who withdrew from the study due to subject request, parent/guardian request, or other reasons were to provide a reason for the discontinuation. Some subjects and guardians provided reasons for discontinuation due to lack of efficacy or adverse events. These reasons provided in the case report form (CRF) were classified by the statistical reviewer as either describing withdrawal due to 'lack of efficacy', 'adverse events', or 'other. These reviewer classifications are summarized in Table 26. and the additional detail on the terms used in the CRF are provided in Table 27.

Table 26:Disposition of Subjects in Studies 301 and 302

	Study 301		Study 302	
	Tretinoin Lotion	Vehicle	Tretinoin Lotion	Vehicle
Subjects Randomized	406	414	413	407
Discontinued	68 (16.7%)	77 (18.6%)	71 (17.2%)	43 (10.6%)
Lost to follow-up	36 (8.9%)	40 (9.7%)	40 (9.7%)	18 (4.4%)
Subject request	16 (3.9%)	25 (6.0%)	22 (5.3%)	13 (3.2%)
Withdrawal by parent or guardian	6 (1.5%)	8 (1.9%)	3 (0.7%)	6 (1.5%)
Adverse event	3 (0.7%)	0 (0%)	3 (0.7%)	0 (0%)
Lack of efficacy	0 (0%)	2 (0.5%)	1 (0.2%)	0 (0%)
Pregnancy	2 (0.5%)	0 (0%)	1 (0.2%)	0 (0%)
Protocol violation	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.2%)
Non-compliance with study drug	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Worsening condition	2 (0.5%)	0 (0%)	0 (0%)	2 (0.5%)
Physician decision	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Other	1 (0.2%)	0 (0%)	0 (0%)	1 (0.2%)

Source: pg. 48 of Study Report 301 and pg. 48 of Study Report 302 and reviewer analysis.

Table 27: Specified Reasons for Discontinuation in Studies 301 and 302

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Subject request	16 (3.9%)	25 (6.0%)	22 (5.3%)	13 (3.2%)
Lack of efficacy	*3 (0.7%)*	*7 (1.7%)*	*4 (1.0%)*	*5 (1.2%)*
Other reasons	*13 (3.2%)*	*18 (4.3%)*	*17 (4.1%)*	*8 (2.0%)*
Adverse event			*1 (0.2%)*	
Withdrawal by parent or guardian	6 (1.5%)	8 (1.9%)	3 (0.7%)	6 (1.5%)
Lack of efficacy	*2 (0.5%)*	*2 (0.5%)*	*1 (0.2%)*	*0 (0%)*
Other reasons	*4 (1.0%)*	*6 (1.4%)*	*2 (0.5%)*	*6 (1.5%)*

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Other *Adverse event* *Other reasons*	1 (0.2%) *1 (0.2%)*	0 (0%)	0 (0%)	1 (0.2%) *1 (0.2%)*

Source: reviewer analysis

Protocol Violations/Deviations

Approximately 28% of subjects treated with tretinoin and 30% of subjects treated with vehicle in Study 301 were excluded from the PP population due to protocol violations. Approximately 31% of subjects treated with tretinoin and 21% of subjects treated with vehicle in Study 302 were excluded from the PP population due to protocol violations. Table 28 Table 28presents the reasons for exclusion. The most common reasons for exclusion were no post-Baseline safety evaluations, not attending the Week 12 visit, and Week 12 visit out of window.

Table 28: Per Protocol Analysis Set in Studies 301 and 302

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Subjects included in the PP analysis set	293 (72.2%)	290 (70.0%)	285 (69.0%)	321 (78.9%)
Subjects excluded from the PP analysis set	113 (27.8%)	124 (30.0%)	128 (31.0%)	86 (21.1%)
Reason for exclusion				
No post-Baseline safety evaluation	28 (6.9%)	29 (7.0%)	24 (5.8%)	9 (2.2%)
Violated inclusion/exclusion criteria	2 (0.5%)	1 (0.2%)	0 (0%)	0 (0%)
Used an interfering Con Med	12 (3.0%)	12 (2.9%)	17 (4.1%)	8 (2.0%)
Did not attend the Week 12 visit	27 (6.7%)	43 (10.4%)	34 (8.2%)	27 (6.6%)
Missed both Weeks 4 and 8	0 (0%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Not compliant with dosing regimen	15 (3.7%)	13 (3.1%)	22 (5.3%)	10 (2.5%)
Week 12 visit out of window	29 (7.1%)	24 (5.8%)	28 (6.8%)	31 (7.6%)
Other	0 (0%)	1 (0.2%)	2 (0.5%)	0 (0%)

Source: pg. 49 of Study Report 301 and pg. 49 of Study Report 302 and reviewer analysis.

Table of Demographic Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies, with a few exceptions. In Study 302, a slightly higher proportion of female subjects were randomized to vehicle than tretinoin, while a slightly higher proportion of male subjects were randomized to tretinoin than vehicle and in Study 301, a slightly higher proportion of Hispanic/Latino subjects were randomized to vehicle than tretinoin, while a slightly higher proportion of Not Hispanic/Latino subjects were randomized to tretinoin than vehicle. See

Table 29.

The mean age was 20 years in both studies. Approximately 1.5% of subjects were 9 to 11 years old. Over 70% of subjects were White. Slightly more than half of the subjects in each study were female. Thirty-eight percent of subjects in Study 301 and 55% of subjects in Study 302 were Hispanic/Latino.

Table 29: Demographics in Studies 301 and 302

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Age (years)				
Mean	20.3	20.5	20.5	20.7
Range	9-49	9-52	10-54	11-58
9-11 years	5 (1.2%)	7 (1.7%)	6 (1.5)	6 (1.5%)
12-17 years	180 (44.3%)	180 (43.5%)	177 (42.9%)	168 (41.3%)
18+ years	221 (54.4%)	227 (54.8%)	230 (55.7%)	233 (57.2%)
Gender				
Female	229 (56.4%)	247 (59.7%)	204 (49.4%)	229 (56.3%)
Male	177 (43.6%)	167 (40.3%)	209 (50.6%)	178 (43.7%)
Race				
White	296 (72.9%)	308 (74.4%)	297 (71.9%)	311 (76.4%)
Black or Afric.-Amer.	75 (18.5%)	72 (17.4%)	90 (21.8%)	71 (17.4%)
Am. Ind./ AK Native	4 (1.0%)	0 (0.2%)	0 (0%)	1 (0.2%)
Asian	20 (4.9%)	20 (4.8%)	16 (3.9%)	13 (3.2%)
Native HI/ Pac. Isl.	3 (0.7%)	5 (1.2%)	1 (0.2%)	3 (0.7%)
Other	8 (2.0%)	8 (1.9%)	9 (2.2%)	8 (2.0%)
Ethnicity				
Hispanic or Latino	146 (36.0%)	168 (40.6%)	225 (54.6%)	227 (55.8%)
Not Hispanic or Latino	260 (64.0%)	246 (59.4%)	187 (45.4%)	180 (44.2%)
Not Reported	--	--	1 (0.2%)	--

Source: pg. 51 of Study Report 301 and pg. 51 of Study Report 302 and reviewer analysis.
Abbreviations: AK = Alaska, HI = Hawaii, Am. Ind = American Indian, Afric. Amer. = African American

Other Baseline Characteristics

The Baseline disease characteristics were balanced across treatment arms. In Study 301, subjects had an average of 39 non-inflammatory lesions and 26 inflammatory lesions. In Study 302, subjects had an average of 47 non-inflammatory lesions and 26 inflammatory lesions. About 90% of subjects were classified as moderate on the EGSS in both studies. See Table 30.

Table 30: Baseline Disease Characteristics

	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Non-inflammatory lesions				
Mean (SD)	38.0 (15.67)	39.2 (16.70)	46.1 (19.25)	48.3% (19.91)
Median	34	35	42	44
Range	20-100	200-99	20-99	20-98
Inflammatory lesions				
Mean (SD)	26.1 (5.56)	26.4 (5.63)	26.5 (5.42	26.0 (5.25)

Median Range	25 20-40	25 20-55	25 20-40	25 20-40
EGSS 3 – Moderate 4 – Severe	 369 (89.3%) 44 (10.7%)	 356 (87.5%) 51 (12.5%)	 369 (89.3%) 44 (10.7%)	 356 (87.5%) 51 (12.5%)

Source: pg. 52 of Study Report 301 and pg. 52 of Study Report 302 and reviewer analysis.
Abbreviations: SD = standard deviation, EGSS = Evaluator's Global Severity Scale

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance

The applicant evaluated compliance by documenting the number applications and amounts of study drug used by each subject during the treatment period. In Study V01-121A-301 (301), subjects in both treatment groups achieved greater than 93% compliance; in Study V01-121A-302 (302), subjects in both treatment groups achieved greater than 92% compliance. Refer to Section 7.3.2 for a tabulation of this data.

Concomitant Medications

The Phase 3 protocols excluded the use of topical and systemic concomitant therapies that could interfere with study results. In both trials, the most common concomitant products were facial moisturizers and cleansers. Other common concomitant medications included pain medications, contraceptives, and antihistamines.

Rescue Medication Use

Investigators provided no rescue medications. If the risks of continued participation outweighed the benefits, investigators withdrew subjects from the trial who received the study product for a least 2 weeks and required alternative treatment for their acne.

Efficacy Results – Primary Endpoint

Tretinoin lotion was superior to vehicle in both Study 301 and Study 302 for the three co-primary efficacy endpoints of absolute change in non-inflammatory lesion count, absolute change in inflammatory lesion count and EGSS success. The results are presented in

Table 31.

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 (non-inflammatory 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 significant in two of the models: change in non-inflammatory lesions in Study 301 and change in inflammatory lesions in Study 302, and the interaction terms were retained in these two analyses.

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 non-inflammatory and inflammatory lesions were similar to the p-values for the ranked analyses in both studies (p<0.001).

Table 31: Primary Efficacy Endpoints (Studies 301 and 302)

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Non-inflammatory lesions				
Baseline Mean	38.0	39.2	46.1	48.3
Week 12 Mean (LOCF)	21.5	28.4	25.6	32.8
LSMean Change (MI)	-17.8 (15.2)	-10.6 (16.1)	-21.9 (22.7)	-13.9 (23.3)
p-value	<0.001[a]		<0.001[b]	
Inflammatory lesions				
Baseline Mean	26.1	26.4	26.5	26.0
Week 12 Mean (LOCF)	13.9	16.7	13.0	14.9
LSMean Change (MI)	-13.1 (10.5)	-10.2 (10.9)	-13.9 (12.0)	-10.7 (12.1)
p-value	<0.001[b]		<0.001[a]	
EGSS				
Success (MI)	16.5%	6.9%	19.8%	12.5%
p-value	<0.001		0.007	

[a] Analysis based on ranks. Includes term for treatment-by-analysis center interaction.
[b] Analysis based on ranks. Does not include term for treatment-by-center interaction.
Source: pg. 54 of Study Report 301 and pg. 54 of Study Report 302 and reviewer analysis.
Abbreviations: LOCF = last observation carried forward, EGSS = Evaluator's Global Severity Score, LS = Least Squares, MI =multiple imputation

Treatment-by-Center Interactions

The applicant investigated both treatment-by-investigational site interactions (prior to pooling small centers) and treatment-by-analysis site interactions (after pooling small centers). The results were consistent in each case. The tests for the interaction were conducted using the multiple imputation datasets. Treatment-by- analysis center interactions were significant (p<0.10) for the analysis of change in non-inflammatory lesions in Study 301 and for the change in inflammatory lesions in Study 302. See Table 32.

Table 32: Treatment by Center Interaction P-Values

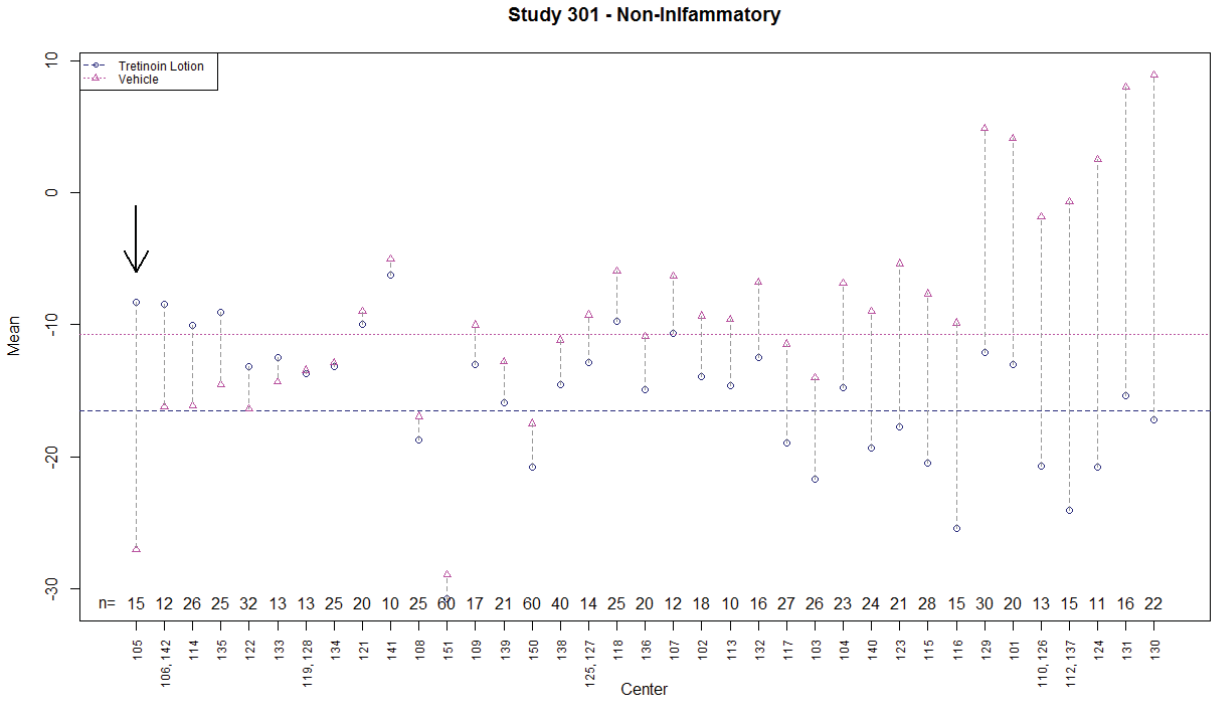
	Study 301		Study 302	
	Investigational site-by-treatment interaction p-value	Analysis center-by-treatment interaction p-value	Investigational site-by-treatment interaction p-value	Analysis center-by-treatment interaction p-value
Change in non-inflammatory lesions	0.927	0.874	0.012	0.013
Change in inflammatory lesions	0.006	0.003	0.166	0.184
EGSS Success	0.992[a]	0.981	0.941[b]	0.928

[a]Two small investigational sites that did not enroll at least 2 subjects in each arm were removed from the model.

[b] Seven small investigational sites that did not enroll at least 3 subjects in each arm were removed from the model.
Source: pg. 131 of Study Report 301 and pg. 131 of Study Report 302.
Abbreviation: EGSS = Evaluator's Global Severity Scale

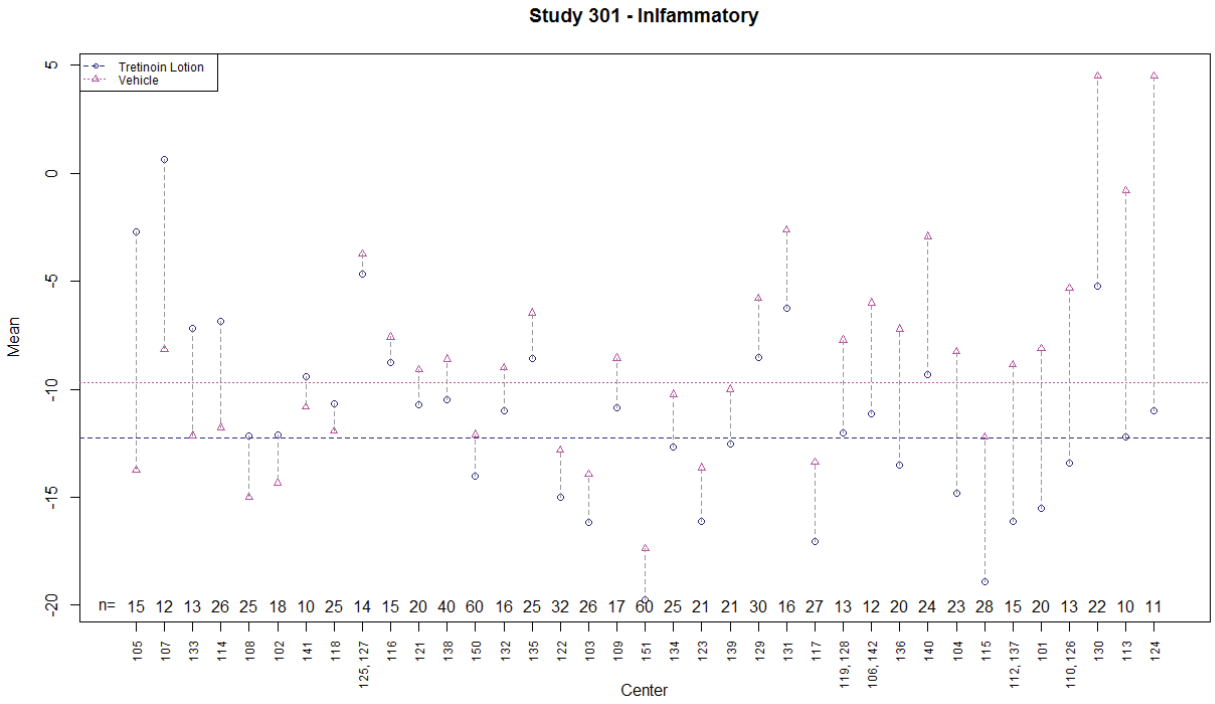
The SAP specified that if the treatment-by-analysis center interaction term was significant in an analysis, then an investigation would be conducted to identify the extreme analysis center or centers that contribute to the statistical significance of the interaction term. First, all subsets created by excluding one analysis center would be created. If one or more subsets resulted in an analysis with the p-value >0.10 for the interaction, then the analysis center excluded from the subset with the largest p-value will be deemed the extreme analysis center. If all p-values are ≤ 0.10 after single analysis center deletion, then the process was repeated deleting all pairs of analysis centers. Using this process, Center 105 was identified as the 'extreme' analysis center in the analysis of change in non-inflammatory lesions in Study 301, and the pair of Centers 202 and 223 were identified as the 'extreme' analysis centers in the analysis of change in inflammatory lesions in Study 302. Center 105 had the largest 'negative' observed treatment effect for the change in non-inflammatory lesions (larger improvement on vehicle than tretinoin at the center), and Centers 202 and 223 had the largest 'positive' observed treatment effects for the change in inflammatory lesions. Figure 2 through Figure 5 present the absolute change in inflammatory and non-inflammatory lesions by analysis center for the two studies. Figure 6 and Figure 7 present the EGSS success rates by analysis center. The analysis centers are ordered by the observed magnitude of treatment effect for each analysis. The analysis centers identified by the applicant as 'extreme' following a significant treatment-by-analysis center interaction are identified with arrows.

Figure 2 – Absolute Change in Non-Inflammatory Lesions by Analysis Center (Study 301)



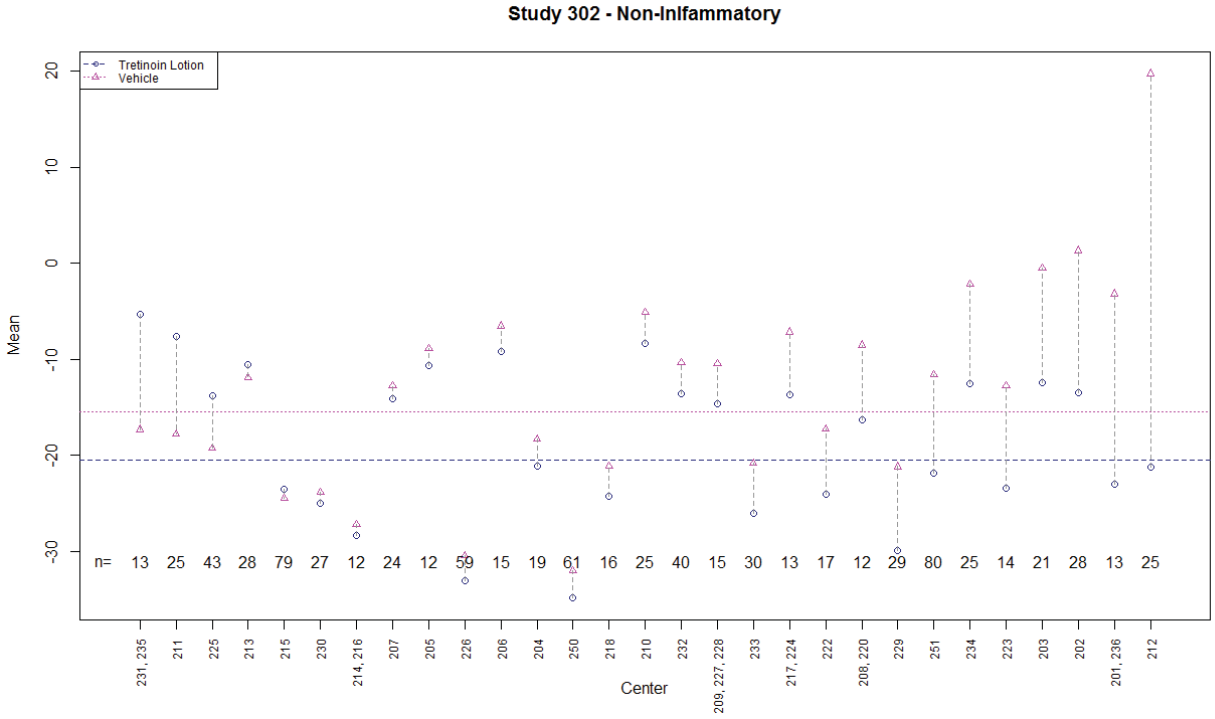
Source: reviewer analysis.

Figure 3 – Absolute Change in Inflammatory Lesions by Analysis Center (Study 301)



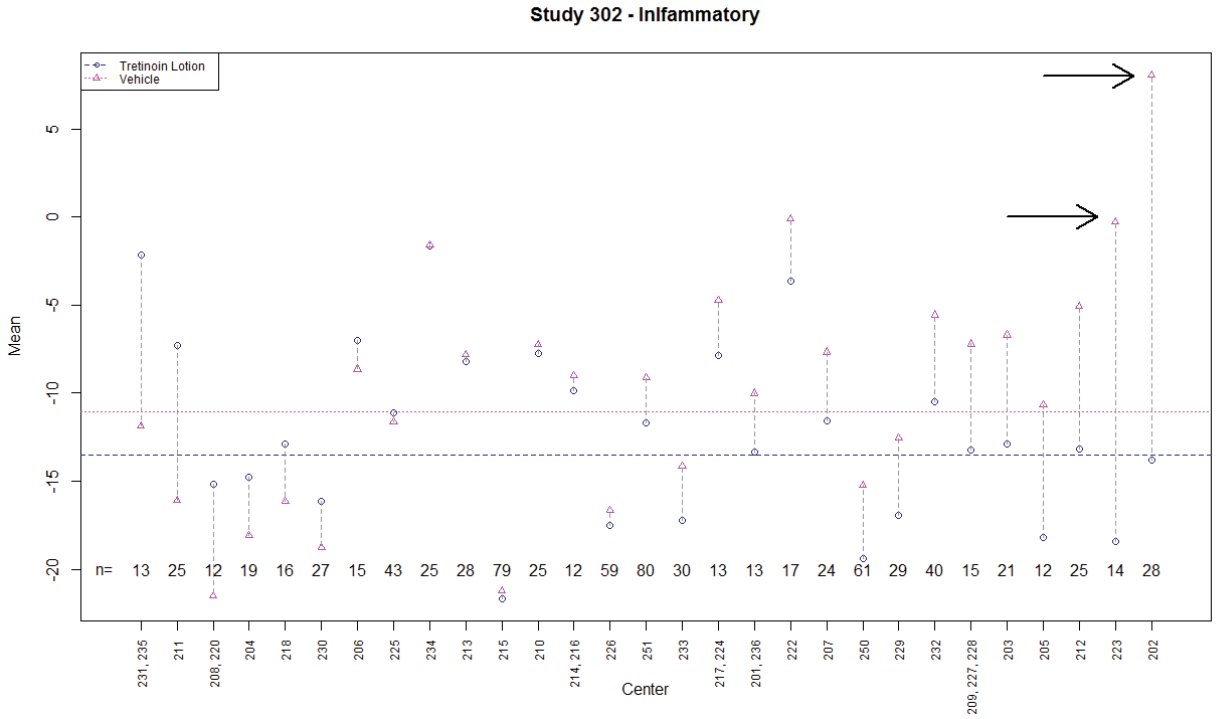
Source: reviewer analysis.

Figure 4 – Absolute Change in Non-Inflammatory Lesions by Analysis Center (Study 302)



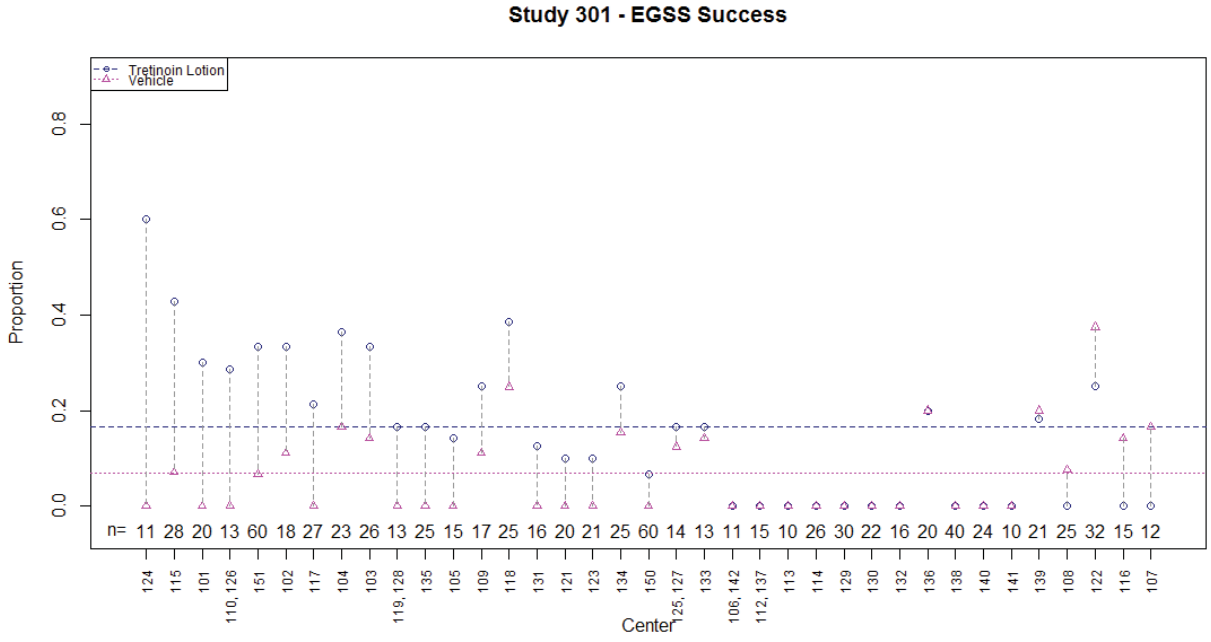
Source: reviewer analysis.

Figure 5 – Absolute Change in Inflammatory Lesions by Analysis Center (Study 302)



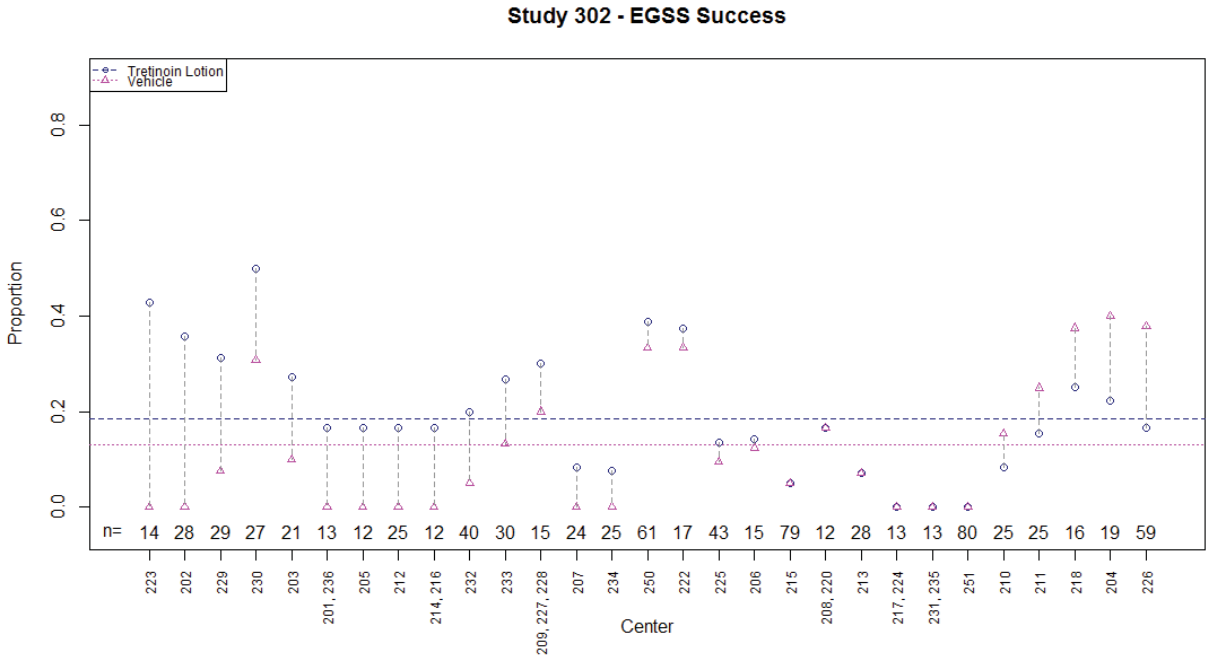
Source: reviewer analysis.

Figure 6 – EGSS Success (Study 301)



Source: reviewer analysis.

Figure 7 – EGSS Success (Study 302)



Source: reviewer analysis.

Missing Data Handling

The primary method of handling missing data was with Markov Chain Monte Carlo (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 and PP analyses produced results similar to the primary analyses. See Table 33.

Table 33: Sensitivity analysis results

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Non-inflammatory lesions				
Repeated Measures	-18.0 (14.3)	-11.4 (14.4)	-22.5 (19.3)	-15.3 (18.6)
Model MI	-17.8 (15.1)	-10.7 (15.6)	-21.7 (23.7)	-13.3 (23.1)
PP (LOCF)	-18.1 (16.7)	-9.8 (16.8)	-21.8 (22.3)	-13.4 (23.2)
Inflammatory lesions				
Repeated Measures	-13.5 (10.2)	-10.5 (10.3)	-14.5 (11.6)	-11.2 (11.3)
Model MI	-13.4 (10.4)	-10.5 (10.6)	-14.1 (12.2)	-10.9 (12.1)
PP (LOCF)	-12.8 (10.8)	-10.5 (10.8)	-13.7 (12.9)	-10.1 (13.6)
EGSS				
Repeated Measures	19.2%	8.2%	21.7%	14.1%

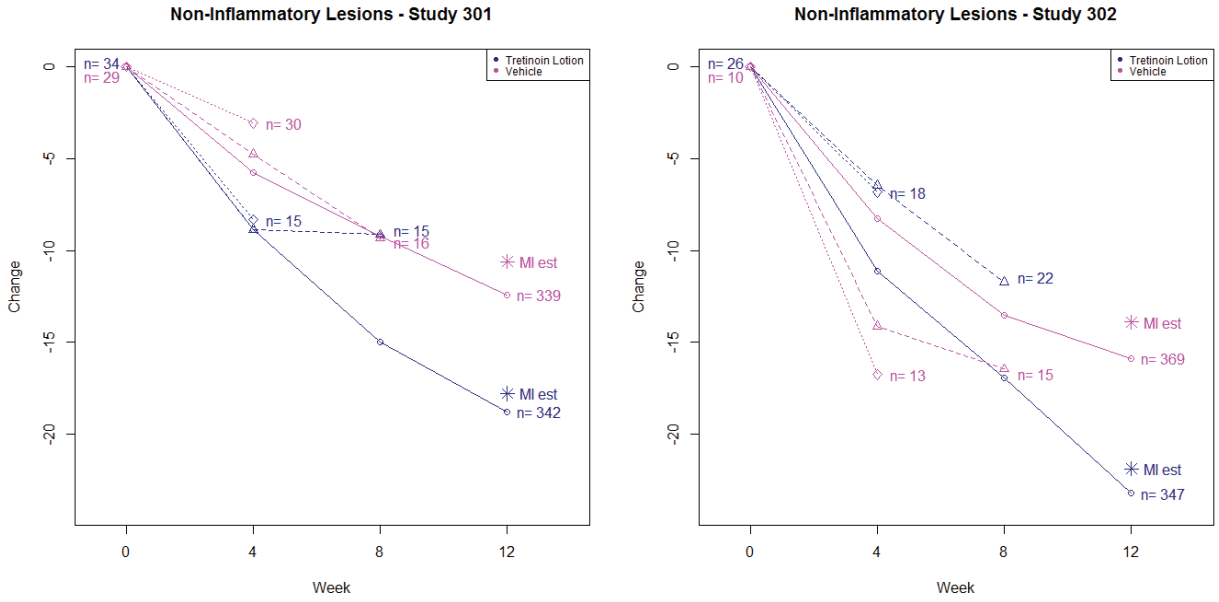
Model MI	17.0%	6.8%	20.7%	13.1%
PP (LOCF)	16.4%	6.7%	18.9%	12.8%

Abbreviations: EGSS= Evaluator's Global Severity Score, PP = per protocol, LOCF = last observation carried forward, MI = Multiple Imputation

Source: pg. 136-139 of Study Report 301 and pg. 136-139 of Study Report 302 and reviewer analysis.

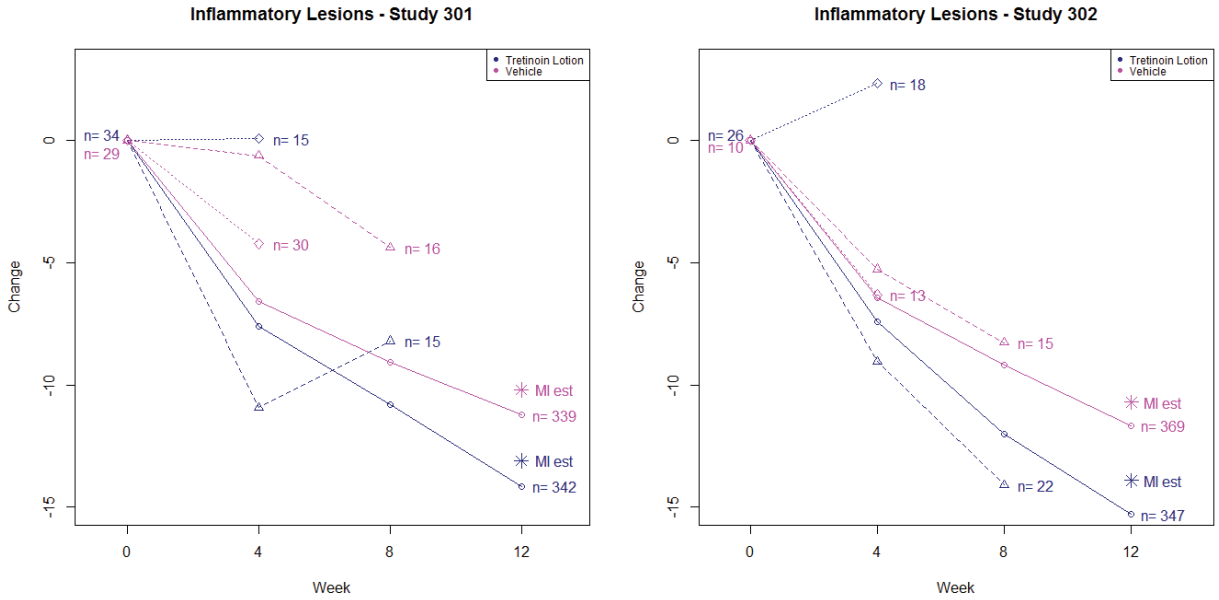
To visualize the impact of missing data on the study estimates, the observed means were plotted over time with subjects grouped according to the last visit at which their efficacy data was assessed (Week 0, 4, 8 or 12). In addition to the by-visit means based on the observed data, the final Week 12 estimates based on the primary analysis using MCMC multiple imputation are presented. The results are presented in Figure 8 through Figure 10. For example, in Study 301, 34 tretinoin subjects and 29 vehicle subjects had only Week 0 efficacy data and thus had no change from Baseline, 15 tretinoin subjects and 30 vehicle subjects had efficacy data through Week 4, 15 tretinoin subjects and 16 vehicle subjects had efficacy data through Week 8, and 342 tretinoin subjects and 339 vehicle subjects had efficacy data through Week 12. In Study 301, on average subjects who discontinued the study early had worse outcomes on the lesion count endpoints on their last visit than subjects who continued in the study. For example, subjects who dropped out after the Week 8 visit had an average reduction of about 10 non-inflammatory lesions at Week 8, while those who continued to Week 12 had an average reduction of about 15 lesions at Week 8. The trend was less apparent in Study 302, with subjects who dropped out sometimes having better reductions on average than those who remained in the trial, and sometimes worse.

Figure 8 – Change in Non-Inflammatory Lesions by Last Available Visit Cohort



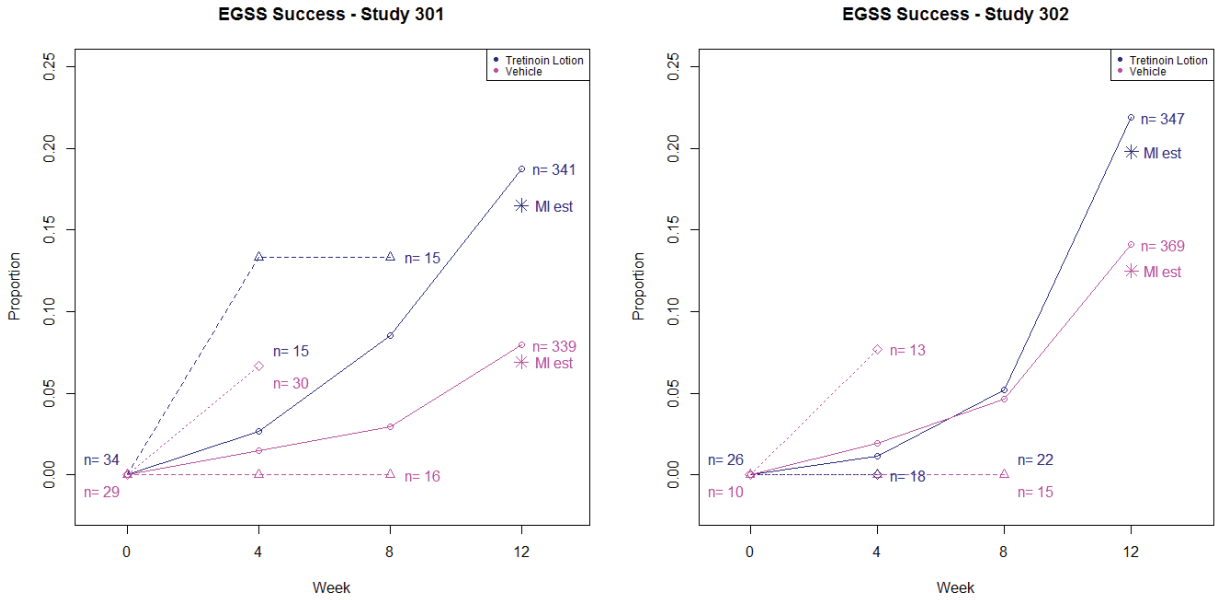
Source: reviewer analysis.

Figure 9 – Change in Inflammatory Lesions by Last Available Visit Cohort



Source: reviewer analysis.

Figure 10 – EGSS Success Rate by Last Available Visit Cohort



Source: reviewer analysis.

Efficacy Results – Secondary and other relevant endpoints

Studies 301 and 302 evaluated two key secondary endpoints. The secondary endpoints were analyzed sequentially: (1) percent change in non-inflammatory lesions at Week 12 and (2) percent change in inflammatory lesions at Week 12. The percent change in lesion count endpoints were analyzed with the same methods as the absolute change in lesion count

endpoints. Both secondary endpoints were statistically significant in each study. The results were consistent with the results for the absolute change in lesion count endpoints. See Table 34.

Table 34: Key Secondary Efficacy Endpoints

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Percent change in non-inflammatory lesions at Week 12	-47.5 (41.9)	-27.3 (44.0)	-45.6 (44.6)	-31.9 (45.8)
p-value	<0.001[a]		<0.001[b]	
Percent change in inflammatory lesions at Week 12	-50.9 (407)	-40.4 (42.3)	-53.4 (45.4)	-41.5 (45.7)
p-value	<0.001[b]		<0.001[a]	

[a] Analysis based on ranks. Includes term for treatment-by-analysis center interaction.
[b] Analysis based on ranks. Does not include term for treatment-by-center interaction.Source: pg. 55 of Study Report 301 and pg. 55 of Study Report 302 and reviewer analysis.

In addition to the two key secondary endpoints, the protocol specified the following supportive endpoints (to be analyzed sequentially in the order listed):

- Percent change in non-inflammatory lesion count from Baseline to Week 8
- Percent change in inflammatory lesion count from Baseline to Week 8
- Percent change in non-inflammatory lesion count from Baseline to Week 4
- Percent change in inflammatory lesion count from Baseline to Week 4
- Percentage of subjects who have at least a two-grade reduction at Week 12 from Baseline in the EGSS
- Percentage of subjects who have at least a two-grade reduction at Week 8 from Baseline in the EGSS
- Percentage of subjects who have at least a two-grade reduction at Week 4 from Baseline in the EGSS

The results for the supportive efficacy endpoints are presented in Table 35. In both Study 301 and Study 302, percent change in inflammatory and non-inflammatory lesions at Week 8 and the percent change in non-inflammatory lesions at Week 4 met the criteria for statistical significance. In both studies, the percent change in inflammatory lesions at Week 4 was not statistically significant, and thus the supportive endpoints based on the EGSS were not formally tested.

Table 35: Supportive Efficacy Endpoints

	Study 301		Study 302	
	Tretinoin Lotion N=406	Vehicle N=414	Tretinoin Lotion N=413	Vehicle N=407
Percent change in non-inflammatory lesions at Week 8	-38.3 (42.5)	-19.1 (44.8)	-32.5 (45.6)	-27.4 (44.7)
p-value	<0.001[a]		0.016[a]	

Percent change in inflammatory lesions at Week 8 p-value	-38.8 (38.0) 0.028[b]	-32.8 (39.2)	-42.9 (44.0) <0.001[b]	-33.8 (43.6)
Percent change in non-inflammatory lesions at Week 4 p-value	-23.4 (35.6) <0.001[a]	-13.2 (35.6)	-22.7 (36.4) 0.041[b]	-18.0 (35.7)
Percent change in inflammatory lesions at Week 4 p-value	-28.5 (37.4) 0.114[b]	-24.3 (38.9)	-27.2 (41.9) 0.129[b]	-25.1 (40.8)
≥ 2 grades reduction in EGSS at Week 12 p-value	17.8% Not tested (<0.001)	8.7%	22.8% Not tested (0.014)	15.7%
≥ 2 grades reduction in EGSS at Week 8 p-value	9.6% Not tested (0.010)	5.1%	7.6% Not tested (0.864)	7.9%
≥ 2 grades reduction in EGSS at Week 4 p-value	4.6% Not tested (0.203)	3.0%	2.8% Not tested (0.136)	4.8%

[a] Analysis based on ranks. Includes term for treatment-by-analysis center interaction. [b] Analysis based on ranks. Does not include term for treatment-by-center interaction. Source: pg. 56-57 of Study Report 301 and pg. 56-57 of Study Report 302 and reviewer analysis. Abbreviation: 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 and geographic region. 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 vs. severe on the EGSS). See Table 36 and Table 37 and Figure 11 through Figure 16.

Table 36: Efficacy Results by Subgroup (Study 301)

	Change in Non-Inflammatory Lesions		Change in Inflammatory Lesions		EGSS Success	
	Tret. Lotion N=406	Vehicle N=414	Tret. Lotion N=406	Vehicle N=414	Tret. Lotion N=406	Vehicle N=414
Age (years)						
9-17 (N=185/187)	-17.6	-11.5	-13.2	-10.1	17.2%	6.4%
18+ (N=221/227)	-19.3	-12.9	-14.4	-11.5	19.5%	9.7%
Gender						
Female (N=229/247)	-18.4	-11.6	-14.0	-11.8	22.5%	10.6%
Male (N=177/167)	-18.7	-13.2	-13.7	-9.6	13.2%	4.7%
Race						
White (N=296/308)	-18.8	-12.9	-13.8	-10.7	19.7%	9.0%
Black /Afr.-Am. (N=75/72)	-17.7	-11.4	-13.9	-12.8	15.5%	7.1%
Am. Ind./ AK Nat. (N=4/1)	-18.8	-12.0	-15.4	-18.0	5.3%	0%

Asian (N=20/20)	-17.1	-5.3	-14.8	-6.8	16.7%	5.6%
Native HI/ Pac. Isl. (N=3/5)	-30.7	-9.0	-19.0	-12.0	33.3%	1.3%
Other (N=8/8)	-16.0	-14.8	-12.9	-9.3	1.8%	0.9%
Ethnicity						
Hispanic or Latino (N=146/168)	-21.0	-15.7	-15.2	-12.8	20.1%	11.2%
Not Hisp or Latino (N=260/246)	-17.1	-9.9	-13.1	-9.6	17.5%	6.2%
Geographic Region						
US (N=346/354)	-17.2	-10.3	-13.3	-10.2	18.1%	9.0%
Outside US (N=60/60)	-26.4	-23.5	-17.3	-14.9	21.6%	3.8%
Baseline Severity						
Moderate (N=368/366)	-18.2	-12.1	-13.7	-11.2	19.1%	9.0%
Severe (N=37/48)	-21.5	-13.1	-15.5	-9.1	12.0%	2.5%

Means are calculated across the multiply imputed datasets.
The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively
Source: pg. 140-148 of Study Report 301 and reviewer analysis.
Abbreviations: Tret. = treatment, EGSS = Evaluator's Global Severity Scale, Am. Ind. = American Indian, Afr. Am. = African American, AK Native = Alaskan Native, Native HI = Native Hawaiian, Pac. Isl. = Pacific Islander

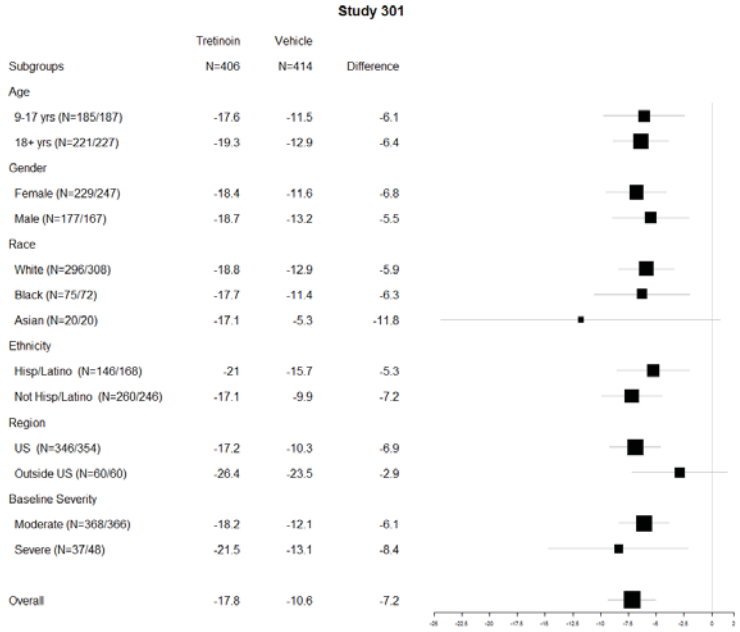
Table 37: Efficacy Results by Subgroup (Study 302)

	Change in Non-Inflammatory Lesions		Change in Inflammatory Lesions		EGSS Success	
	Tret. Lotion N=413	Vehicle N=407	Tret. Lotion N=413	Vehicle N=407	Tret. Lotion N=413	Vehicle N=407
Age (years)						
9-17 (N=183/174)	-21.9	-11.7	-13.6	-8.3	20.0%	10.2%
18+ (N=230/233)	-23.0	-19.1	-16.1	-14.1	22.7%	16.4%
Gender						
Female (N=204/229)	-23.1	-17.5	-15.3	-11.8	24.7%	16.6%
Male (N=209/178)	-21.9	-13.9	-14.8	-11.3	18.4%	10.1%
Race						
White (N=297/311)	-22.5	-15.2	-14.7	-11.4	18.6%	11.6%
Black /Afr.-Am. (N=90/71)	-22.3	-17.4	-15.0	-11.2	25.7%	19.1%
Am. Ind./ AK Nat. (N=0/1)	--	11.0	--	11.0	--	0%
Asian (N=16/13)	-31.7	-19.1	-20.7	-17.1	38.8%	31.8%
Native HI/ Pac. Isl. (N=1/3)	45.0	-25.9	1.0	-16.1	0%	37.8%
Other (N=9/8)	-17.1	-25.4	-16.4	-13.7	47.0%	14.8%
Ethnicity						
Hispanic or Latino (N=225/227)	-24.6	-18.6	-16.2	-13.4	19.2%	13.8%
Not Hisp or Latino (N=187/180)	-20.1	-12.6	-13.5	-9.3	24.3%	13.7%
Geographic Region						
US (N=342/337)	-21.4	-15.0	-15.0	-11.5	22.3%	13.6%
Outside US (N=71/70)	-28.1	-20.4	-15.3	-11.8	17.4%	14.3%
Baseline Severity						
Moderate (N=369/356)	-21.9	-15.4	-15.0	-11.6	22.7%	15.0%
Severe (N=44/51)	-27.5	-19.5	-15.3	-11.2	11.3%	5.0%

Means are calculated across the multiply imputed datasets.
The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively

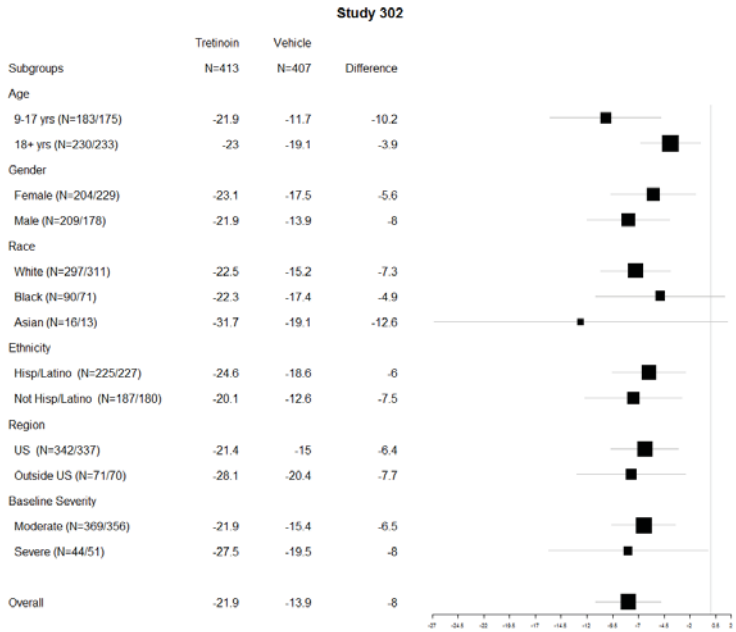
Source: pg. 140-148 of Study Report 302 and reviewer analysis.
Abbreviations: Tret. = treatment, EGSS = Evaluator's Global Severity Score, Am. Ind. = American Indian, AK Nat. = Alaskan Native, Native HI = Native Hawaiian, Pac. Isl. = Pacific Islander

Figure 11 – Change in Non-Inflammatory Lesions by Subgroup (Study 301)



The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively. Only subgroups with ≥ 10 subjects per arm presented.
Source: reviewer analysis.

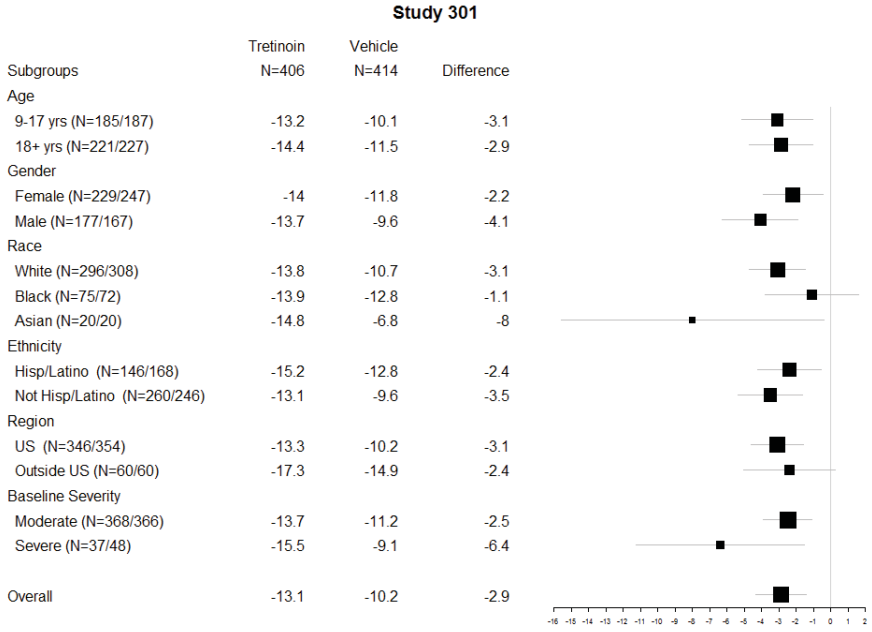
Figure 12 – Change in Non-Inflammatory Lesions by Subgroup (Study 302)



The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively. Only subgroups with ≥ 10 subjects per arm presented.

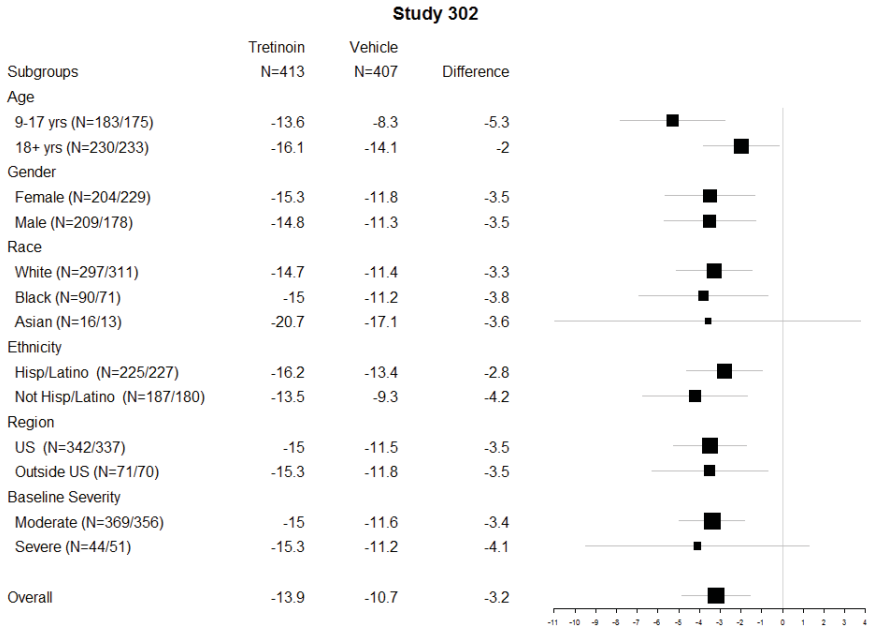
Source: reviewer analysis.

Figure 13 – Change in Inflammatory Lesions by Subgroup (Study 301)



The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively. Only subgroups with ≥ 10 subjects per arm presented.
Source: reviewer analysis.
Abbreviation: US = United States

Figure 14 – Change in Inflammatory Lesions by Subgroup (Study 302)

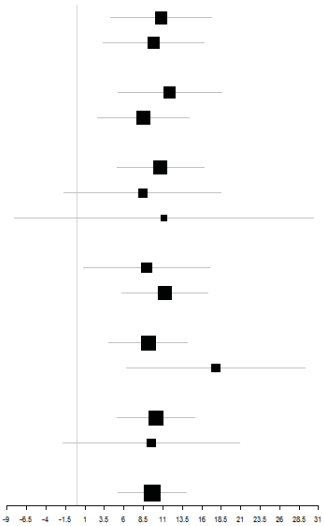


The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively. Only subgroups with ≥ 10 subjects per arm presented.
Source: reviewer analysis.
Abbreviation: US = United States

Figure 15 – EGSS Success by Subgroup (Study 301)

Study 301

Subgroups	Tretinoin N=406	Vehicle N=414	Difference
Age			
9-17 yrs (N=185/187)	17.2	6.4	10.8
18+ yrs (N=221/227)	19.5	9.7	9.8
Gender			
Female (N=229/247)	22.5	10.6	11.9
Male (N=177/167)	13.2	4.7	8.5
Race			
White (N=296/308)	19.7	9	10.7
Black (N=75/72)	15.5	7.1	8.4
Asian (N=20/20)	16.7	5.6	11.1
Ethnicity			
Hisp/Latino (N=146/168)	20.1	11.2	8.9
Not Hisp/Latino (N=260/246)	17.5	6.2	11.3
Region			
US (N=346/354)	18.1	9	9.1
Outside US (N=60/60)	21.6	3.8	17.8
Baseline Severity			
Moderate (N=368/366)	19.1	9	10.1
Severe (N=37/48)	12	2.5	9.5
Overall	16.5	6.9	9.6

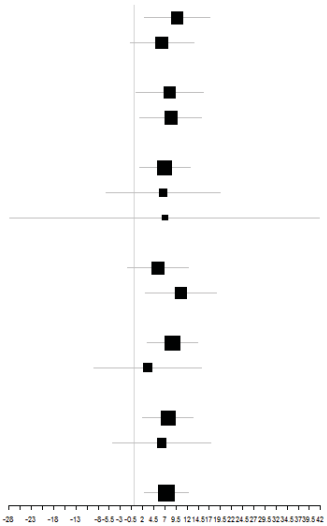


The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively. Only subgroups with ≥ 10 subjects per arm presented.
Source: reviewer analysis.
Abbreviations: EGSS = Evaluator's Global Severity Score

Figure 16 – EGSS Success by Subgroup (Study 302)

Study 302

Subgroups	Tretinoin N=413	Vehicle N=407	Difference
Age			
9-17 yrs (N=183/175)	20	10.2	9.8
18+ yrs (N=230/233)	22.75	16.4	6.35
Gender			
Female (N=204/229)	24.7	16.6	8.1
Male (N=209/178)	18.4	10.1	8.3
Race			
White (N=297/311)	18.6	11.6	7
Black (N=90/71)	25.7	19.1	6.6
Asian (N=16/13)	38.8	31.8	7
Ethnicity			
Hisp/Latino (N=225/227)	19.2	13.8	5.4
Not Hisp/Latino (N=187/180)	24.3	13.7	10.6
Region			
US (N=342/337)	22.3	13.6	8.7
Outside US (N=71/70)	17.4	14.3	3.1
Baseline Severity			
Moderate (N=369/356)	22.7	15	7.7
Severe (N=44/51)	11.3	5	6.3
Overall	19.8	12.5	7.3



The notation N=XXX/YYY indicates the sample size for tretinoin lotion and vehicle, respectively. Only subgroups with ≥ 10 subjects per arm presented.
Source: reviewer analysis.
Abbreviations: EGSS = Evaluator's Global Severity Score, Hisp = Hispanic, US = United States

7.3. Review of Safety

7.3.1. Safety Review Approach

The primary review of the safety of tretinoin lotion, 0.05% for the topical treatment of acne vulgaris focused on pooled data from 2, Phase 3 trials, V01-121A-301 and V01-121A-302. Both trials were multicenter, randomized, double-blind, vehicle-controlled, Phase 3 trials of identical design. The study population included a total of 1640 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 20-40, non-inflammatory lesion count of 20 - 100, and ≤ 2 nodules. In both trials, subjects were randomized in a 1:1 ratio to receive tretinoin 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. Investigators conducted safety and efficacy assessments at screening, Baseline, Week 4, Week 8, and Week 12. The safety population as defined and discussed in the next section of this review included 1550 pediatric and adult subjects.
The applicant submitted additional safety data from Phase 1b Trial V01-121A-501. This was an open- label trial designed to evaluate the safety and the PK of tretinoin and its relevant metabolites (isotretinoin and 4-oxo-isotretinoin) under maximal use conditions. The study population included 20 pediatric subjects ages 9 years to 16 years 11 months with moderate to severe acne vulgaris. Subjects applied approximately 4 grams of tretinoin lotion once daily for 14 days to the face (excluding eyes and lips), neck, upper chest, upper back, and shoulders.

To determine the safety profile of tretinoin lotion, the review team analyzed the following types of pooled data: exposure, demographics, Baseline characteristics, treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory results, vital signs and findings from physical examinations. Per applicant, there were no ongoing trials or supportive safety data to include in a Safety Update Report).

Because safety data is available for other dosage forms of this moiety, the applicant requested waivers for the conduct of the following trials to evaluate tretinoin lotion: long-term safety, thorough QT study, phototoxicity and photo allergy studies. In view of the limited systemic absorption and referenced safety data with tretinoin, the Agency granted waivers for the long-term safety and Thorough QT trials. Refer to the *Summary of Presubmission/Submission Regulatory Activity* for the referenced NDAs. In support of phototoxicity / photo allergenicity waiver, the applicant submitted UVB/UVA/Vis spectra (290 – 700 nm) for tretinoin lotion and ATRALIN (tretinoin) Gel, 0.05% which were similar. As the applicant submitted a right of reference to NDA 22070 (ATRALIN Gel) and the evaluation of phototoxicity and photo allergenicity for ATRALIN Gel showed negative results the Agency granted the proposed waiver of photo-studies. Refer to the *Analysis of Submission Specific Safety Issues* for a discussion of the potential for phototoxicity with this product and associated labeling issues.

7.3.2. Review of the Safety Database

Overall Exposure

The primary analysis dataset for the review of the safety of tretinoin lotion, 0.05% included pooled data from the Phase 3 Trials V01-121A-301 and V01-121A-302. Safety data from subjects enrolled in the maximal use systemic exposure PK trial (Study 501) was not pooled with data from the Phase 3 trials due to differences in the study design (e.g., open-label, 2-week trial compared with randomized, vehicle-controlled, 12-week trial) and dose (sufficient amount to cover face, neck, upper chest, upper back, and shoulders compared with face only).For the Phase 3 Trials V01-121A-301 and V01-121A-302, the safety analysis set included all randomized subjects who were "presumed" to have used the study drug at least once and who provided at least 1 post-Baseline evaluation. All the subjects excluded from the safety population in Phase 3 had no post-Baseline safety evaluation. In contrast, for Phase 1 Trial V01-121A-501, the safety analysis set included all enrolled subjects who received at least 1 confirmed dose of study product.

In the 3 clinical trials, a total of 839 subjects applied at least one dose of tretinoin lotion. Among these subjects, 819 subjects applied the proposed product once daily for up to 12 weeks (pooled Phase 3 Trials V01-121A-301 and V01-121A-302) and 20 subjects applied proposed product once-daily for up to 14 days (Trial V01-121A-501.) The primary analysis populations (pooled Phase 3 Trials V01-121A-301 and V01-121A-302) are presented in the following table:

Table 38: Subject population (Trials V01-121A-301 and Trial V01-121A-302)

Trial	Treatment Group	Number of Subjects	Total Subjects*	Safety** Population	Total Safety Population
V01-121A-301	Tretinoin lotion	406	820	378	763
	Vehicle	414		385	
V01-121A-302	Tretinoin lotion	413	820	389	787
	Vehicle	407		398	
TOTAL	Tretinoin lotion	819	1640	767	1550
	Vehicle	821		783	

Source: Reviewer's table
*Intent to treat population (ITT).
**Subjects excluded from the safety population due to no post-Baseline safety evaluation

In the pooled Phase 3 trials, the applicant evaluated extent of exposure by documenting the weight of the containers before and after product distribution and the number of applications per diary. Subjects in the tretinoin group applied a mean of 50.0 g or 80 applications; subjects in the vehicle group applied a mean of 52.7 g or 81 applications. More than 90% of subjects in each treatment arm were compliant with the dosing regimen. (Per applicant, compliance was defined as applying 80-120% of the expected applications and missing 5 or less consecutive days.) The extent of exposure is summarized in Table 39below.

By comparison, subjects enrolled in the maximal use Trial V01-121A-501 received a mean of 48.9 g ± 13.7 g of tretinoin lotion (range 19.8-62.8 g). All 20 subjects applied 80-100% of the required doses.

Table 39: Phase 3 Studies: Extent of Exposure (Safety Analysis Set)

	Tretinoin Lotion N=767	Vehicle N=783
Total Amount Product Used (g)		
N	685	707
Mean (SD)	50.0 (28.9)	52.7 (29.0)
Median	43.8	48.0
Min/Max	0.1 to 145.7	0.2 to 129.5
Total Number of Days of Exposure		
N	719	740
Mean (SD)	82.5 (11.7)	83.2 (10.6)
Median	84.0	84.0
Min/Max	1 to 112	1 to 162
Total Number of Applications		
N	719	740
Mean (SD)	80.0 (12.5)	81.1 (11.3)
Median	83.0	83.0
Min/Max	1 to 116	1 to 162
Compliant		
Yes	669 (93.0%)	704 (95.1%)
No	50 (7.0%)	36 (4.9%)

Source: Modified from 2.7.4 Summary of Clinical Safety, Table 2
Abbreviations: Min = minimum, Max = maximum, SD = standard deviation

Relevant characteristics of the safety population:

Demographic characteristics of subjects in the safety population are similar to the ITT population. In the pooled Phase 3 trials, the majority of subjects were White (74%), not Hispanic/Latino (54%), female (56%) and 18 years and older (54%). The demographic characteristics of both treatment groups were comparable. Across the 2 Phase 3 trials, no subjects (0/1550) were 65 years of age or older. Most of the subjects enrolled in the Phase 3 trials resided in the United States. Refer to Appendix 13.4 demographic characteristics and disposition of subjects in the safety population.

Adequacy of the safety database:

The total subject exposure to tretinoin lotion applied 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. Therefore, the safety database presented by the applicant is sufficient to characterize the safety profile of tretinoin lotion for the treatment of acne vulgaris.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of

tretinoin lotion, 0.05%. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Categorization of Adverse Events

For both Phase 3 Trials, Study 301 and Study 302, the applicant defined an adverse event as "any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug." AEs included any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a study product that has appeared or worsened during the clinical trial, regardless of causality. Investigators initiated evaluation of subjects for AEs following completion of the consent process and throughout the trials. AEs which occurred prior to administration of tretinoin lotion or vehicle were included in the CSR. TEAEs form the primary basis of the safety review. As such, the applicant defined TEAEs as AEs that occurred after the first application of the study product.

In all clinical trials in the development of tretinoin lotion, AEs were documented by system organ classes and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities, version 18.0. The coding of adverse events in this NDA submission appeared adequate to allow estimates of AE risk. However, some PTs, such as nasopharyngitis and upper respiratory infection, were pooled during analyses to more effectively capture the incidence of the AEs.

Investigators categorized AE for seriousness, intensity, causality, duration, action taken with study drug, corrective treatment and outcome. Per 21 CFR 312.32, the applicant defined a SAE as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life threatening (subject is at risk of death at the time of the event)
- Requires in patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event that may require medical or surgical intervention to prevent death or disability

In addition, the applicant categorized pregnancy and spontaneous abortion as an SAE. PP, SAEs were reported to the medical monitor or applicant within 24 hours of notification. Investigators submitted an expedited report for any SAE that was both unexpected (not documented in the Investigator Brochure) and related. All SAEs were followed until satisfactory resolution or a clinically stable.

Using the following categories, investigators assessed intensity or severity of AEs reported during the Phase 3 trials:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening

Investigators provided an assessment of the relationship of the AE to the study product. In the Phase 3 trials, causality was dichotomized to "related" to the study product or "not related" to the study product per the following definitions:

- Related: There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
- Not Related: There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists

Subjects completed multiple PRO assessments. Subject Self- Assessment (SSA) scale at all post-screening visits and at home at Week 2. Subjects completed the other PRO questionnaires [Patient Satisfaction Survey (PSS), the Acne-Specific Quality of Life (Acne-QoL) questionnaire, and an assessment of the oiliness/shininess of the skin] at Baseline and Week 12. These instruments and findings are discussed in section 7.2.6 of this review.

Routine Clinical Tests

In trials, Study 301 and Study 302 (the pooled safety analysis set), investigators and site staff conducted safety monitoring during clinic visits at Screening, Week 0, 4, 8 and 12. The evaluation of safety included laboratory tests, vital signs, abbreviated physical examinations, concomitant medications, local cutaneous safety assessments and adverse events.

The protocols included clinical laboratory testing at Baseline and Week 12. The assessments included hematology, serum chemistry and urinalysis. Urine pregnancy testing was performed at every visit throughout the trial from Screening through Week 12.

Local safety assessments included an evaluation of signs (scaling, erythema, hypo-pigmentation and hyper-pigmentation) and symptoms (itching, burning and stinging) at the application site. Investigators conducted these assessments at every visit using the following scales:

Table 40: Cutaneous Assessment Scales

Score	Grade	Description
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
Itching:		
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching, somewhat bothersome
3	Severe	Intense itching, may interrupt daily activities +/- sleep
Burning:		
0	None	No burning
1	Mild	Slight burning sensation, not really bothersome
2	Moderate	Definite warm, burning sensation, somewhat bothersome
3	Severe	Hot burning sensation, causes definite discomfort, may interrupt daily activites +/- sleep
Stinging:		
0	None	No stinging
1	Mild	Slight stinging
2	Moderate	Definite
3	Severe	

Source: Tabulated from NDA 209353, Protocol V01-121A-301, Section 11.3.1

7.3.4. Safety Results

Deaths

There were no deaths in the development program for tretinoin lotion, 0.05%.

Serious Adverse Events

In the pooled Phase 3 trials (Studies 301 and 302), 11 subjects experienced serious adverse events (SAEs). A total of 7 subjects (0.9%) in the tretinoin lotion group experienced 8 SAEs and 4 subjects (0.5%) in the vehicle lotion group experienced 7 SAEs. Among the subjects reporting

SAEs, 3 subjects in each treatment group experienced SAEs of severe intensity (3/7 in the tretinoin group and 3/4 in the vehicle group). In the tretinoin lotion group, the severe adverse events were: pregnancy; calculus ureteric; and asthma. In the vehicle lotion group, the severe adverse events were: pancreatitis; alcoholic pancreatitis; and abortion missed. None of the subjects experienced SAEs that were assessed as related to either study product.

Among subjects in the tretinoin lotion group, the serious adverse events included pregnancy (4 subjects), and appendicitis, calculus ureteric, and asthma (1 subject each). Pregnancy was the only event which was defined as serious and reported by more than one subject. The SAEs which resulted in discontinuation from the trial included: asthma and 3 pregnancies.

Table 41: Treatment Emergent Serious Adverse Events

Body System or Organ Class	Preferred Term	Tretinoin Lotion n (%)	Vehicle Lotion n (%)
Subjects reporting SAEs, n (%)		7 (0.91)	4 (0.5)
Number of SAEs		8	7
Gastrointestinal disorders	Alcoholic pancreatitis	0 (0.00)	1 (0.13)
	Pancreatitis	0 (0.00)	1 (0.13)
Infections and infestations	Appendicitis	1 (0.13)	0 (0.00)
Injury, poisoning and procedural complications	Post procedural hemorrhage	0 (0.00)	1 (0.13)
Pregnancy, puerperium and perinatal conditions	Abortion missed	0 (0.00)	1 (0.13)
	Pregnancy	4 (0.52)	2 (0.26)
Psychiatric disorders	Suicidal ideation	0 (0.00)	1 (0.13)
Renal and urinary disorders	Calculus ureteric	1 (0.13)	0 (0.00)
Respiratory, thoracic and mediastinal disorders	Asthma	1 (0.13)	0 (0.00)
	Total subjects	767	783

Source: Reviewer's Table, Safety population, JReview

Among subjects in the vehicle lotion group, the serious adverse events included pregnancy (2 subjects), and abortion missed, alcoholic pancreatitis, pancreatitis, postprocedural hemorrhage, and suicidal ideation (1 subject each). The only events defined as serious which occurred in more than one subject were pregnancy and pancreatitis. One subject experienced 2 serious adverse events: pancreatitis and suicidal ideation. Of the 2 pregnant subjects, one subject experienced 3 serious adverse events: pregnancy, abortion missed and a postprocedural hemorrhage. The other pregnant subject delivered a healthy neonate. None of the SAEs in the vehicle group resulted in subject discontinuation. However, the investigator determined that it was in the best interest of the subject who reported pancreatitis and suicidal ideation to terminate participation in the trial.

Selected narratives

15-year-old male (**Subject** (b) (6) **)** with a history of asthma (since 2001), treated with albuterol and mometasone and formoterol inhalers and multiple food allergies experienced an exacerbation of asthma after 1 application of the study product. The subject presented to the

emergency room (ER) with wheezing, shortness of breath, chest pain with deep breaths, rhinorrhea, nasal congestion, sore throat, and fever of 101.2°F. The subject was admitted to the hospital and improved with continuous nebulizer treatments, oral corticosteroids and pain medication. The subject had a history of status asthmaticus due to viral infections, allergy, or environmental triggers which required hospitalization. The adverse event was assessed as severe, not related and resulted in discontinuation from the trial.

25-year-old white male **(Subject** (b) (6)) with a history of multiple renal calculi since 2013 and treatment with ciprofloxacin, phenazopyridine and tamsulosin experienced nephrolithiasis on Day 19 after initiating the study product. The subject experienced flank pain, nausea and vomiting and presented to the ER on 2 consecutive days. The subject was admitted and improved with IV hydration, antibiotics and pain medication. His evaluation and treatment included cystoscopy, left enteroscopy, left retrograde pyelogram, and placement of stent. The cause of nephrolithiasis was not provided. The adverse event was assessed as severe, not related to the study product and did not result in discontinuation from the trial.

32-year-old white female (**Subject** (b) (6) with a history of smoking and use of morphine experienced appendicitis on Day 10 of treatment with tretinoin lotion. The subject presented to the ER with right lower and periumbilical abdominal pain and nausea and was admitted to the hospital for evaluation and treatment. CT of abdomen and pelvis showed appendicolith at the appendiceal base with dilatation of the more distal appendix suggestive of early acute appendicitis. The subject received IV fluids, hydromorphone hydrochloride and ampicillin and sulbactam, and was treated with appendectomy. The subject had no personal or family history of appendicitis and no known risk factors. The adverse event was assessed as moderate, not related to the study product and did not result in discontinuation from the trial.

Refer to the Human Reproduction and Pregnancy section below for the narratives for subjects who were exposed to tretinoin or vehicle and became pregnant.

Dropouts and/or Discontinuations Due to Adverse Effects

In the pooled Phase 3 trials, 1.6 % (12/767) of subjects who received tretinoin lotion discontinued the study product due to an a TEAE. None (0/783) of the subjects who received vehicle withdrew from the trials or discontinued the study product due to an a TEAE. Among the 12 subjects who discontinued the Phase 3 trials, 4 subjects discontinued the trial due to SAEs (1 subject with asthma and 3 with pregnancy). Per applicant, one subject discontinued the study product due to urticaria but withdrew from the trial by choice (not investigator decision because of the AE.) One subject with application site pain discontinued tretinoin lotion but remained in the trial and another subject who experienced both application site pain and pruritus withdrew consent. This withdrawal was documented as discontinued due to “other” reason. The TEAEs leading to discontinuation are summarized in the following table. The application site reactions leading to discontinuation were assessed as related to the study product while all other adverse events leading to discontinuation (including urticaria) were assessed as unrelated. Refer to Section 7.3.2 of this review for a tabulation of the disposition of

subjects enrolled in the Phase 3 trials.

Table 42: Treatment-Emergent Adverse Events Leading to Discontinuation by Preferred Term

Preferred Term	Tretinoin lotion n (%)	Vehicle lotion n (%)
Subjects discontinued due to TEAE, n (%)	12 (1.56)	0 (0.0)
Application site pain	5 (0.65)	0 (0.0)
Pregnancy	3 (0.39)	0 (0.0)
Application site dermatitis	2 (0.26)	0 (0.0)
Application site pruritus	2 (0.26)	0 (0.0)
Application site erythema	1 (0.13)	0 (0.0)
Application site swelling	1 (0.13)	0 (0.0)
Asthma	1 (0.13)	0 (0.0)
Urticaria	1 (0.13)	0 (0.0)
Total Subjects	767	783

Source: Reviewer's Table: Safety population, JReview

Significant Adverse Events

Human Reproduction and Pregnancy

Requirements for females of childbearing potential who were enrolled in the tretinoin lotion development program included the use of effective forms of contraception, negative serum pregnancy tests at screening and urine pregnancy testing at all study visits. Subjects who became pregnant withdrew from treatment and, where feasible, were followed until delivery.

Among subjects receiving tretinoin lotion in the Phase 3 trials, there were 4 pregnancies. The outcomes included: 2 normal deliveries, 1 elective termination and 1 unknown outcome. Among subjects receiving vehicle, there were 2 pregnancies. The outcomes included a missed abortion and normal delivery. There were no reports of congenital malformations. No pregnancies occurred during Trial V01-121A-501. Refer to Appendix 13.4 for a summary of these events.

Literature Search

Fetal retinoid syndrome is characterized by craniofacial, central nervous system, and cardiovascular system defects.[11] The applicant conducted a literature search to explore the outcomes of maternal exposure to topical tretinoin during pregnancy and lactation (published from 1992 to the 2017.) The applicant provided a summary of the results with limited detail.

Catherine Roca, M.D., the reviewer from Maternal Health Division of Pediatric and Maternal Health (DPMH), conducted a thorough review of the literature regarding the risk of congenital anomalies with the use of topical tretinoin, and provided comments and labeling recommendations for Section 8.1, 8.2, and 17 (Review dated June 2, 2018.) Dr. Roca stated,

"Systemic absorption appears to be limited, and exposure of a fetus would be expected to

[11] Browne h et al. Retinoids and pregnancy: an update. The Obstetrician & Gynecologist 2014; 16:7–11.

be low. Prospective observational studies do not indicate an increased risk of birth defects or other adverse maternal or fetal effects with topical tretinoin exposure. These studies have methodological limitations, including limited sample size and, in some studies, lack of direct examination of the infants by a dysmorphologist. Six cases in the literature report birth defects; however, these case reports do not establish a pattern or association with tretinoin-related embryopathy…

Data on the safety of topical tretinoin use during breastfeeding are not available; however, systemic absorption is low and infant exposure is expected to be minimal. The applicant recommends that women not apply topical tretinoin to the nipple and areola to avoid direct infant exposure, which is a reasonable precaution…

The applicant does not include subsection 8.3 in the proposed labeling. DPMH agrees that since data do not indicate a clear risk for use during pregnancy or infertility, subsection 8.3 is not required in labeling."

Treatment Emergent Adverse Events and Adverse Reactions

Treatment Emergent Adverse Events (TEAE)

There were 364 treatment emergent adverse events (TEAEs) reported in the 180 subjects (24%) in the tretinoin lotion group compared with 233 TEAEs in 151 subjects (19%) in the vehicle lotion group. The most frequent TEAE occurred in the system organ classes of General Disorders and Administration Site Conditions, Infections and infestations, and Investigations. A greater proportion of subjects receiving tretinoin lotion experienced application site reactions (10%) and infections (8%) than subjects receiving vehicle lotion (4% and 6% respectively). In addition, more pregnancies occurred among subjects receiving tretinoin lotion (1% compared with 0%) than vehicle lotion. Refer to the Serious Adverse Events section for discussion of the pregnancies. Selected TEAE are summarized in the following tables by Body System Organ Class (SOC) and Preferred Term (PT).

Table 43: Most Common Treatment Emergent Adverse Events by System Organ Class

Body System or Organ Class	Tretinoin Lotion	Vehicle Lotion
General disorders &administration site conditions	78 (10.17%)	29 (3.70%)
Infections and infestations	58 (7.56%)	47 (6.00%)
Investigations	38 (4.95%)	39 (4.98%)
Gastrointestinal disorders	17 (2.22%)	13 (1.66%)
Nervous system disorders	12 (1.56%)	12 (1.53%)
Injury, poisoning and procedural complications	10 (1.30%)	14 (1.79%)
Renal and urinary disorders	5 (0.65%)	1 (0.13%)
Respiratory, thoracic and mediastinal disorders	5 (0.65%)	5 (0.64%)
Skin and subcutaneous tissue disorders	5 (0.65%)	6 (0.77%)
Pregnancy, puerperium and perinatal conditions	4 (0.52%)	2 (0.26%)
Metabolism and nutrition disorders	4 (0.52%)	5 (0.64%)
Reproductive system and breast disorders	2 (0.26%)	1 (0.13%)
Eye disorders	2 (0.26%)	0 (0.00%)
Immune system disorders	1 (0.13%)	1 (0.13%)
Psychiatric disorders	1 (0.13%)	7 (0.89%)
Ear and labyrinth disorders	1 (0.13%)	3 (0.38%)
Musculoskeletal and connective tissue disorders	1 (0.13%)	8 (1.02%)
Endocrine disorders	0 (0.00%)	1 (0.13%)
Surgical and medical procedures	0 (0.00%)	1 (0.13%)
Blood and lymphatic system disorders	0 (0.00%)	2 (0.26%)
Subjects(filtered)	180 (23.47%)	151 (19.28%)
Total Subjects	767	783

Source: Reviewer's Table, JReview

Table 44: Treatment Emergent Adverse Events by Preferred Term

Preferred Term	Tretinoin Lotion	Vehicle Lotion
Application site dryness	29 (4%)	1 (0%)
Application site pain	25 (4%)	3 (0%)
Blood creatine phosphokinase increased	16 (2%)	12 (2%)
Nasopharyngitis	15 (2%)	20 (3%)
Application site erythema	12 (2%)	1 (0%)
Alanine aminotransferase increased	9 (1%)	4 (1%)
Aspartate aminotransferase increased	8 (1%)	3 (0%)
Application site pruritus	7 (1%)	4 (1%)
Headache	7 (1%)	6 (1%)
Application site photosensitivity reaction	7 (1%)	7 (1%)
Application site irritation	7 (1%)	1 (0%)
Upper respiratory tract infection	6 (1%)	8 (1%)
Application site exfoliation	6 (1%)	3 (0%)
White blood cells urine positive	6 (1%)	4 (1%)
Protein urine present	5 (1%)	1 (0%)
Nausea	5 (1%)	3 (0%)
Red blood cells urine positive	5 (1%)	2 (0%)
Vomiting	5 (1%)	4 (1%)
Gamma-glutamyltransferase increased	4 (1%)	2 (0%)
Sinusitis	4 (1%)	4 (1%)
Influenza	4 (1%)	1 (0%)
Pregnancy	4 (1%)	2 (0%)

Preferred Term	Tretinoin Lotion	Vehicle Lotion
Total Subjects	767	783

Source: Reviewer's Table, JReview

Treatment Emergent Adverse Events by Severity

The majority of TEAEs were mild to moderate in the tretinoin lotion group (172/180, 96%) and the vehicle group (141/151, 93%). A total of 8 subjects experienced 10 SAEs in the tretinoin group and 10 subjects experienced 14 SAEs in the vehicle group. The following table provides a tabulation of the number of subjects with one or more severe TEAEs.

Table 45: Severe Treatment Emergent Adverse Events: Pooled Phase 3 Trials

Preferred Term	Tretinoin lotion N=767; n (%)	Vehicle lotion N=783; n (%)
Subjects Reporting Severe Adverse Events	8 (1.0)	10 (1.3)
Abortion missed	0 (0.0)	1 (0.1)
Alcoholic pancreatitis	0 (0.0)	1 (0.1)
Anxiety	0 (0.0)	1 (0.1)
Application site acne	0 (0.0)	1 (0.1)
Application site dermatitis	1 (0.1)	0 (0.0)
Application site dryness	1 (0.1)	0 (0.0)
Application site pain	1 (0.1)	0 (0.0)
Application site pruritus	1 (0.1)	1 (0.1)
Application site ulcer	1 (0.1)	0 (0.0)
Asthma	1 (0.1)	1 (0.1)
ADD/ADHD	0 (0.0)	1 (0.1)
Creatine Phosphokinase ↑	1 (0.1)	0 (0.0)
Creatinine ↑	1 (0.1)	0 (0.0)
Calculus ureteric	1 (0.1)	0 (0.0)
Depression	0 (0.0)	1 (0.1)
Dizziness	0 (0.0)	1 (0.1)
Headache	0 (0.0)	1 (0.1)
Nausea	0 (0.0)	1 (0.1)
Pancreatitis	0 (0.0)	1 (0.1)
Post procedural hemorrhage	0 (0.0)	1 (0.1)
Pregnancy	1 (0.1)	0 (0.0)
Suicidal ideation	0 (0.0)	1 (0.1)

Abbreviations: ADD = attention deficit disorder, ADHD = attention deficit hyperactivity disorder
Source: Modified from Table 9 Section 2.7.4 Summary of Clinical Safety

Application site reactions comprised half of the severe TEAEs in the tretinoin group.

Adverse Reactions

Per applicant, a total of 62 subjects (8%) in the tretinoin group and 15 subjects in the vehicle group (2%) experienced treatment- related TEAEs, adverse reactions. All adverse reactions (ARs) were local cutaneous reactions at the application site. The majority of AR in both treatment groups were mild to moderate (95% in the tretinoin group and 87% in the vehicle group). In the tretinoin group, 3 subjects experienced severe application site reactions; in the vehicle group, 2 subjects experience severe application site reactions. The application site

reactions which were reported by at least 5 subjects in the tretinoin group included dryness, pain, erythema, irritation, pruritus, and exfoliation.

Table 46: Treatment Emergent Adverse Reactions

Dictionary Derived Term	Tretinoin Lotion	Vehicle Lotion
Application site dryness	28 (3.65%)	1 (0.13%)
Application site pain	24 (3.13%)	3 (0.38%)
Application site erythema	11 (1.43%)	1 (0.13%)
Application site irritation	7 (0.91%)	1 (0.13%)
Application site pruritus	7 (0.91%)	4 (0.51%)
Application site exfoliation	5 (0.65%)	3 (0.38%)
Application site dermatitis	3 (0.39%)	0 (0.00%)
Application site rash	2 (0.26%)	0 (0.00%)
Application site hypersensitivity	2 (0.26%)	0 (0.00%)
Application site swelling	2 (0.26%)	0 (0.00%)
Application site coldness	1 (0.13%)	0 (0.00%)
Application site photosensitivity reaction	1 (0.13%)	2 (0.26%)
Application site acne	0 (0.00%)	2 (0.26%)
Subjects with Ars	62 (8.08%)	15 (1.92%)
Total Subjects	767	783

Source: Reviewer's Table, JReview
*Treatment emergent adverse reactions

There is insufficient data regarding these events to confirm whether the AEs assessed as AR by the applicant are related to the study product. Therefore, the following AEs will be included in Section 6 of ALTRENO labeling:

Adverse reactions reported by ≥1% of subjects treated with ALTRENO in the Pooled Phase 3 Trials and more frequently than vehicle

Adverse Reactions n (%)		
	ALTRENO Lotion N=767	**Vehicle Lotion N=783**
Application site dryness	29 (4)	1 (0)
Application site pain	25 (3)	3 (0)
Application site erythema	12 (2)	1 (0)
Application site irritation	7 (1)	1 (0)
Application site exfoliation	6 (1)	3 (0)

Laboratory Findings

There were no clinically meaningful changes in laboratory parameters such as renal function tests, liver enzymes and creatine phosphokinase (CPK) in subjects exposed to tretinoin lotion. See the Clinical Appendix for a tabulation of the data and discussion of individual parameters.

In the pooled Phase 3 trials, a total of 230 subjects (108/680; 16% in the tretinoin group and 122/699; 17% in the vehicle group) had elevated liver enzymes aspartate transaminase and or alanine transaminase (AST and/or ALT) from 1379 evaluable subjects at Week 12. In the tretinoin group, 54 subjects had normal liver enzymes at Baseline and elevated levels at Week 12; 29 subjects had elevated levels at Baseline which became more elevated at Week 12. In the vehicle group, 59 subjects had normal liver enzymes at Baseline and elevated levels at Week 12; 36 subjects had elevated levels at Baseline which became more elevated at Week 12. Therefore, a total of 83/680 (12%) of subjects in the tretinoin group and 95/699 (14%) in the vehicle group had liver enzymes that became elevated or more elevated from Baseline to Week 12.

In addition, among subjects with normal or elevated hepatic enzymes at Baseline 9/680 (1%) had levels that became more than 3 times the upper limit of normal in the tretinoin group and 5/699 (1%) in the vehicle group.

In the pooled Phase 3 trials, a total of 218 subjects [109 subjects (16%) in each treatment group] had elevated CPK levels from 1379 evaluable subjects at Week 12. In the tretinoin group, 21/680 (3%) subjects with normal CPK at Baseline developed elevated CPK (up to 1.5 times the normal levels) and 28/680 (4%) developed very elevated CPK (≥1.5 times the normal range) at Week 12. In the vehicle group, 32/699 (5%) subjects with normal CPK at Baseline developed elevated CPK levels and 27/699 (4%) developed very elevated levels of CPK at Week 12. In addition, among the subjects with elevated CPK at Week 12, 36 subjects (36/109; 33%) had elevated AST and/ or ALT in the tretinoin group and 35 subjects (35/109; 32%) had elevated AST and/ or ALT in the vehicle group. The literature supports the finding that the CPK elevation alone may result in liver enzyme elevation. [12]In one study of patients with CPK > 1000 units/L 93.1% had elevated AST and 75% had elevated ALT.[13]

Vital Signs

Vital signs including temperature, respiratory rate, hear rate and blood pressure were measured at Baseline and Week 12. Mean values for each parameter were similar across treatment groups. Greater than 89% of all measurements of temperature, respiratory rate and heart rate were within normal limits in both treatment groups. There was more variability in the measurements for systolic and diastolic blood pressure. However, a similar percentage of measurements were out of the normal range in each treatment group and shifted above the normal range at Week 12. Overall, there were no clinically significant changes in vital signs.

Electrocardiograms/QT Wave Study

The applicant did not conduct a thorough QT Study or include cardiac safety monitoring during

[12] Miller ML. Clinical manifestations and diagnosis of rhabdomyolysis. UpToDate. Updated Feb 08, 2018. Accessed June 28, 2018
[13] Nathwani RA, Pais S, Reynolds TB, Kaplowitz N. Serum alanine aminotransferase in skeletal muscle diseases. Hepatology. 2005;41(2):380

the trials in the development program. The moiety is well characterized, systemic absorption is limited and there is no anticipated impact on QT intervals. See Section 7.4.1 Approach to the Safety Review and Section 6 for a review of the systemic exposure data.

Immunogenicity

As the proposed product is not a therapeutic protein, the applicant did not assess the potential immunogenicity.

7.3.5. Analysis of Submission-Specific Safety Issues

Retinoids are a class of compounds which are structural and functional analogues of Vitamin A. These compounds impact many aspects of growth and development primarily by regulating gene transcription. Retinoids are available in both oral and topical formulations. Oral administration of retinoids may be associated with mucocutaneous findings (e.g., xerosis, pruritus, cheilitis), systemic adverse events (e.g., myalgias, depression, headache, hepatitis, pancreatitis, ocular effects such as blepharoconjunctivitis, and fetal retinoid syndrome) and laboratory abnormalities (e.g., elevated liver enzymes, hyperlipidemia, and elevated creatine phosphokinase (CPK)). [14]Although systemic levels following topical administration of tretinoin are substantially lower than following oral administration, the review team considered the potential for systemic toxicity as well as local safety. Selected local and systemic adverse events associated with retinoids are discussed below.

Local Tolerability

The applicant evaluated local tolerability during the 3 trials in their development program at all visits after screening. During the 2-week treatment period, investigators participating in Trial V01-121A-501 (Study 501), graded erythema, scaling, itching, burning, and stinging at the application site using 4-point scales (0 = none, 1 = mild, 2 = moderate, or 3 = severe). During the 12-week treatment period, investigators participating in Study 301 and Study 302 graded the same signs and symptoms with the addition of hypo/hyper-pigmentation using 4-point scales.

In Study 501, none of the 20 subjects who were evaluated for local safety had signs or symptoms of erythema, scaling, itching, burning or stinging, at Baseline. On Day 2 only 1 subject observed mild erythema and itching. By Day 15, after the application of tretinoin lotion under maximal use conditions, 6 (30.0%) subjects experienced mild erythema, 7 (35.0%) subjects experienced mild or moderate scaling, and 1 (5.0%) subject experienced mild itching.

In the pooled Phase 3 trials, Study 301 and Study 302, most subjects in the safety population reported no signs and symptoms at Baseline. However, almost 40% of subjects had erythema

[14] Bolognia JL, Schaffer JV, Cerroni L. Dermatology 4th Edition. Elsevier. 2017. Chapter 126. Retinoids by Jean-Hilaire Saurat and Olivier Sorg. pp 2200-2214.

and approximately a third of subjects had hyperpigmentation prior to the onset of treatment in each treatment group.

In the tretinoin group, a minority subjects of subjects experienced irritation during the 12-week treatment period. Most signs and symptoms were mild to moderate in severity. However, at Week 4 more than 1% of subjects experienced erythema, hyperpigmentation and burning graded as severe. The results of the tolerability assessments at Baseline and Week 12 for the tretinoin group are summarized in the Table 47.

Table 47: Local Safety Results in the Tretinoin Group from Baseline to Week 12

	Percentage of Subjects in the Tretinoin Group (%)					
	Baseline (Prior to treatment)			**Week 12 (End of treatment)**		
	Mild	moderate	Severe	mild	Moderate	severe
Scaling	17	3	0	19	4	0
Erythema	30	12	1	23	5	0
Hypopigmentation	9	1	0	5	1	0
Hyperpigmentation	20	14	1	18	9	1
Itching	23	6	0	9	2	0
Burning	9	1	0	9	2	0
Stinging	5	1	0	6	0	0

Source: Adapted from Table 14, Summary of Clinical Safety
Safety Population. No imputation of missing values at Week 12.

The percentage of subjects experiencing irritation was greatest at Week 4. By Week 12, the percentage of subjects reporting signs and symptoms associated with tretinoin administration generally declined to Baseline levels or lower.

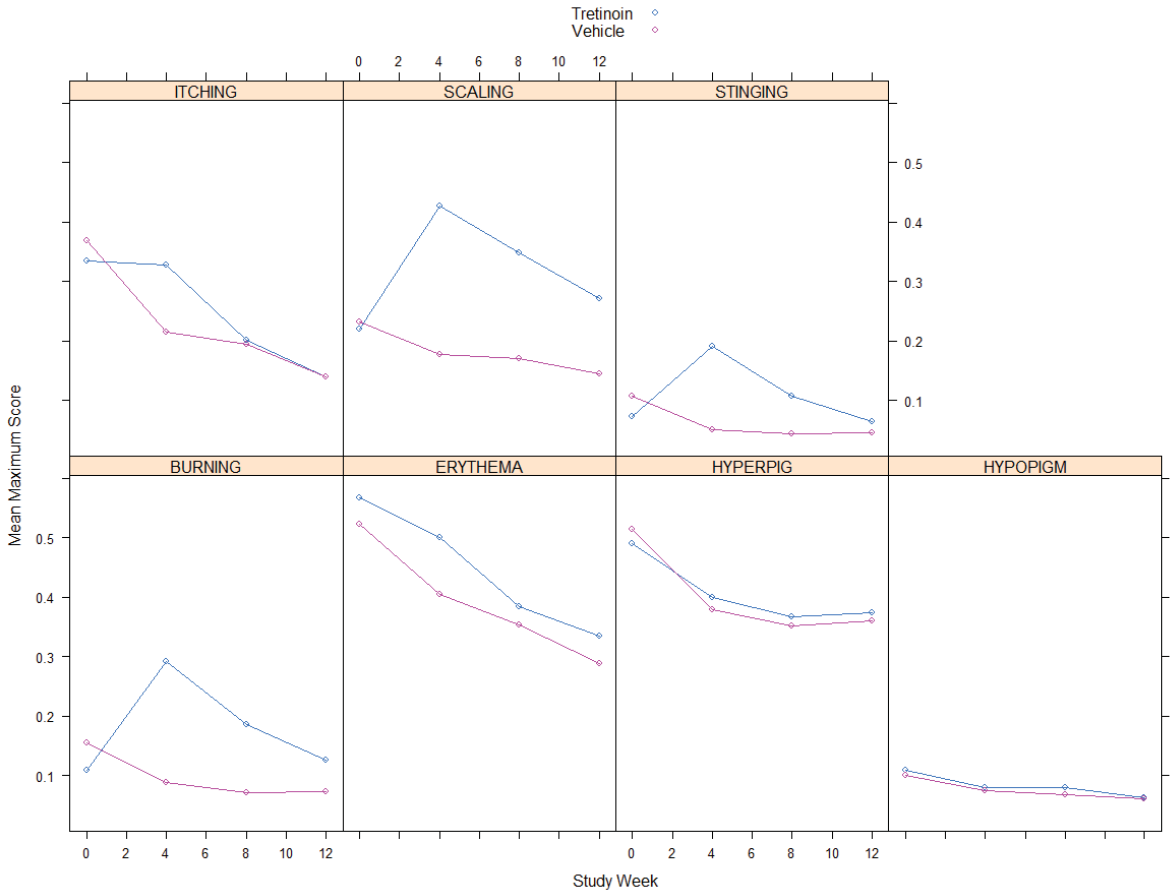


Figure 17 – Mean Local Cutaneous Safety and Tolerability Assessments by Visit (Studies 301 and 302 combined)
Source: Analysis by Statistical Reviewer, Kathleen Fritsch, PhD

The incidences of erythema, scaling, itching, burning, and stinging were more common in the tretinoin group than the vehicle group. The maximum severity of the signs and symptoms of irritation is summarized in the following table (Table 48). The high proportion of subjects reporting hyperpigmentation in both treatment groups at Baseline and end of treatment is influenced by the composition of the study population, 47% self-described as Hispanic/Latino overall.

Table 48: Maximum Post-Baseline Local Cutaneous Safety and Tolerability Assessments (Studies 301 and 302 combined)

Signs and Symptoms	Tretinoin N=760				Vehicle N=782			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Erythema	49%	37%	13%	1%	56%	33%	10%	1%
Scaling	51%	36%	13%	1%	70%	26%	3%	<1%
Hypopigmentation	88%	10%	1%	0%	90%	9%	1%	<1%
Hyperpigmentation	65%	20%	13%	3%	65%	21%	13%	2%
Itching	64%	27%	7%	1%	72%	22%	4%	1%
Burning	70%	22%	8%	1%	86%	12%	2%	<1%
Stinging	79%	15%	5%	1%	92%	7%	1%	0%

Source: Analysis by Statistical Reviewer, Kathleen Fritsch, PhD

The results of the active assessments of local safety indicate that patients may experience irritation and pigmentary changes during treatment with tretinoin lotion which may be severe. Therefore, language regarding the potential for irritation is included in Section 5 WARNINGS AND PRECAUTIONS which is similar to other tretinoin products. Compared with the adverse event data, the results of the active assessments of local safety provide data regarding the course and severity of these irritant reactions. The recommended language regarding the tolerability evaluation to be added to Section 6 Adverse Reactions section of labeling is as follows:

"Skin irritation was evaluated by active assessment of erythema, scaling, hypopigmentation, hyperpigmentation, itching, burning and stinging. The percentage of subjects who were assessed to have these signs and symptoms at a post-Baseline visits are summarized in Table 2."

Table 49: Application Site Tolerability Reactions at Any Post-Baseline Visit

	ALTRENO N=760	**Vehicle** N=782
Erythema	51%	44%
Scaling	49%	30%
Hypopigmentation	12%	10%
Hyperpigmentation	35%	35%
Itching	35%	28%
Burning	30%	14%
Stinging	21%	8%

Source: Analysis by Statistical Reviewer, Kathleen Fritsch, PhD

Photosensitivity

The labeling for all tretinoin products includes instructions to avoid ultraviolet light and when exposure is unavoidable to use sunscreens and sun protection, which may have been incorporated into labeling of precedent tretinoin products based on the findings of a nonclinical photocarcinogenicity study conducted with a different formulation (see Section 5.5.3, Carcinogenicity). The applicant conducted a nonclinical phototoxicity assay, which was negative for phototoxicity (see Section 5.5.4, pp 38-39).

The applicant requested a waiver of required assessments for phototoxicity and photo allergenicity based on the results of trials conducted to support approval of ATRALIN® (tretinoin) Gel, 0.05% for which they obtained a right of reference. The Agency considered the initial photo studies for ATRALIN to be inadequate due to the small sample sizes and requested that the ATRALIN applicant repeat the phototoxicity and photo allergenicity trials as postmarketing commitments. Review of the postmarketing commitment final reports confirmed that "there is little or no potential of significant phototoxicity or photo allergenicity with ATRALIN Gel, 0.05%". Because adequate phototoxicity and photo allergenicity trials were

conducted with ATRALIN and the UV spectra of the proposed product and ATRALIN were similar, the Agency agreed these dermal safety studies were not needed for tretinoin lotion.

The review team analyzed adverse event data for tretinoin lotion and post marketing data for topical tretinoin products. Adverse event data indicated that an equal percentage of subjects receiving tretinoin lotion (1%, 7/767) and vehicle (1%, 7/783) experienced "application site photosensitivity" (verbatim term: sunburn). Post marketing data, FDA Adverse Event Reporting System and literature cases, indicated that topical tretinoin was associated with photosensitivity reactions. Carmen Cheng, PharmD, Office of Surveillance and Epidemiology, concluded that "it is possible that topical tretinoin is associated with [photosensitivity] based on its known mechanism to thin the stratum corneum. While the limitations of the postmarketing cases preclude a causal association, they highlight the importance of proper sunscreen use and sun protection. With adequate labeling and patient counseling, the risk of photosensitivity can be mitigated by preventative measures such as avoidance of UV light or the use of sun protection (if exposure to UV light cannot be avoided). Therefore, we support maintaining a WARNINGS AND PRECAUTIONS for photosensitivity reactions in the ALTRENO Lotion labeling (and equivalent sections for the currently approved topical tretinoin products)." See review by Dr. Carmen Cheng dated June 27, 2018.

Systemic Toxicity

Hypersensitivity Reactions

The applicant coded 2 adverse events as "application site hypersensitivity" reactions in the tretinoin lotion group (Subject (b) (6) and (b) (6) and none in the vehicle group. One of the events was "swelling of the left eyelid" and the other was "increase in skin sensitivity". A 14-year-old female ((b) (6) experienced an intermittent burning sensation on her face from Day 7 to Day 17 and reported "eyelid swelling" on Day 11. The event of eyelid swelling was assessed as mild, required no treatment, resolved the same day and did not result in interruption or discontinuation of the study product. She used a total of 8.5 grams of the study product prior to her withdrawal from the trial due to pregnancy. A 25-year-old female ((b) (6) with a history of asthma and seasonal allergies experienced mild application site hypersensitivity and exfoliation on Day 61 which resolved with interruption of treatment by Day 68 and 69 respectively. The subject also experienced moderate application site erythema, irritation, dryness and exfoliation on Day 34 and then application site pain and papules after the use of moisturizer. Most of the adverse events were assessed as related to the study product, except the pain and papules. The subject used a total of 31.9 grams of the study product and completed the trial.

Both hypersensitivity reactions were limited in duration, required no treatment and did not result in permanent discontinuation of tretinoin lotion. Increased skin sensitivity to a topical retinoid may result from the mechanism of action of the drug which results in epidermal thinning. Irritant dermatitis on the fragile skin of the eyelid may result in swelling.

In addition, the identification of some AEs as hypersensitivity reactions was impacted by coding

decisions. The applicant mapped the verbatim term of "increased skin sensitivity" with the PT of "hypersensitivity" and mapped the verbatim term of "skin sensitivity" to "application site hyperesthesia". A 21-year-old Asian female (b) (6) with no relevant medical history experienced 2 episodes of "skin sensitivity "on Day 5 and Day 57 while receiving treatment with vehicle. Both events of application site hyperesthesia were assessed as mild, not related, required no treatment, resolved the next day but resulted in interruption of the study product. The true nature of these events is not clear from the available data or diagnostic coding.

There were 2 adverse events coded as urticaria, one in each treatment group. One 19-year-old female subject (b) (6) receiving tretinoin lotion developed urticaria on her trunk and extremities on Day 5 which resolved with treatment on Day 11. The subject had a history of drug hypersensitivity reactions (lisdexamfetamine dimesylate and amphetamine/ dextroamphetamine). Her concomitant medications included fluoxetine, levonorgestrel and ethinyl estradiol, atomoxetine, cyanocobalamin and multiple therapies for episodes of urticaria (methylprednisolone acetate, diphenhydramine, and prednisone). The event was assessed as moderate and not related to tretinoin but resulted in discontinuation of the study product per subject request. A 15-year-old female subject ((b) (6) with a history of eczema and seasonal allergies receiving vehicle developed facial "application site urticaria" on Day 78 which resolved on Day 79 with treatment with diphenhydramine. The event was assessed as moderate and not related to the vehicle and did not result in discontinuation of the study product. None of these events support changes in labeling.

Fetal Retinoid Syndrome

Refer to the Consult by Catherine Roca, M.D., Medical Officer, Maternal Health Division of Pediatric and Maternal Health (DPMH Review dated June 2, 2018) and discussion in this review under Significant Adverse Events, Human Reproduction and Pregnancy.

7.3.6. Safety Analyses by Demographic Subgroups

The review team conducted multiple analyses to evaluate the safety profile of tretinoin lotion in different populations. The results indicated that there were no substantial differences in the risk of adverse reactions (ARs) in demographic subgroups. However, because the trials were not powered for these analyses, the data must be interpreted with caution. Overall, a greater proportion of females who received tretinoin lotion reported adverse reactions. Females receiving tretinoin lotion reported application site dryness (3%) and application site pain (2%) more frequently than males receiving tretinoin lotion (1% for each adverse event.) Pediatric subjects reported application site pain (2%) more frequently than adult subjects who received tretinoin lotion (1%); however, the frequency of reporting other adverse reactions was comparable between the 2 age groups. Approximately 93% of subjects in the safety population were White or African American. The rates of ARs were similar in these 2 subpopulations. Refer to Appendix 13.4 for a tabulated summary of adverse reactions (ARs) in demographic subgroups.

7.3.7. Specific Safety Studies/Additional Clinical Trial Safety Data

The applicant did not conduct a specific study or clinical trial to evaluate a potential safety concern because the safety profile of the moiety is well characterized. However, additional safety data was provided by Phase 1b Study V01-121A-501.

The applicant conducted a Phase 1b open label trial (Study 501) designed to evaluate the safety and the PK of tretinoin and its relevant metabolites (isotretinoin and 4-oxo-isotretinoin) under maximal use conditions (4 grams applied once daily to the face, neck, chest, shoulders and back) for 14 days. The trial enrolled pediatric subjects ages 9 years to 16 years 11 months with moderate (3) to severe (4) acne vulgaris on the EGSS scale. Eligibility criteria were similar to the Phase 3 trials: subjects had an inflammatory lesion count of 20-40, non-inflammatory lesion count of 20 - 100, and ≤ 2 nodules. Safety monitoring included:

- vital signs (blood pressure, pulse rate, respiration rate, and oral temperature) at Screening, Day 1 (Baseline), and Day 15
- brief physical examinations at Screening and Day 15
- safety laboratory tests (hematology, serum chemistry, and urinalysis) at Screening and Day 15
- pregnancy testing in females of child bearing potential at Screening, Day 1 (Baseline), and Day 14
- an evaluation of adverse events at all visits after subject consents to participate
- local safety assessment at all study visits after Screening which included grading application site signs and symptoms (erythema, scaling, itching, burning, and stinging) on a 4-point scale (0 = none, 1 = mild, 2 = moderate, or 3 = severe).

Refer to Section 6 for additional details regarding the study design and bioavailability findings.

Results

Study population

The safety population included 20 subjects who were enrolled and received one confirmed dose of the study product. All enrolled subjects completed the trial; none of the enrolled subjects had a major protocol deviation. The majority of the subjects in the safety population were White (80%), male (65%), and not Hispanic/Latino (80%). Subjects ranged in age from 10 to 16 years with a mean age of 14.0 ± 2.1 years. All subjects used CeraVe Cleanser and CeraVe Moisturizing Lotion, one of the protocol approved brands. Concomitant medications included: etonogestrel for contraception (Subject (b) (6)), loratadine for seasonal allergies (Subject (b) (6)) lisdexamfetamine mesilate for attention deficit hyperactivity disorder (ADHD) (Subject (b) (6)) salbutamol for asthma (Subject (b) (6)), and desmopressin for bedwetting (Subject (b) (6)) The pre-existing conditions reported by more than one subject were: seasonal allergy [8 subjects (40%)], attention-deficit/hyperactivity disorder [3 subjects (15%)] and asthma [2 subjects (10%)]. All 20 subjects received >80-100% of the intended doses. Subjects applied a mean of 48.9 grams (range 19.8-62.8 grams) during the 14-day treatment period.

Adverse Events

In Study 501, there were no deaths or serious adverse events. Among the 20 subjects enrolled in the trial, 3 (15%) subjects reported 4 AEs [arthralgia/joint injury; vomiting; and application site dermatitis on the neck and chest]. Prior to Baseline, 1 subject ((b) (6)) reported pain in the right wrist after an injury on Day -6, which was assessed as not related and resolved by Day -4 with treatment. A total of 2 subjects (10%) experienced treatment-emergent adverse events (TEAEs). One subject (b) (6) reported vomiting on Day 1, which was assessed moderate in severity and unrelated to tretinoin lotion; one subject ((b) (6)) reported application site dermatitis on Day 10, which was assessed as severe and related to tretinoin lotion. Neither subject required treatment for the adverse event. However, the investigator instructed the subject who observed application site dermatitis to reduce the amount of the study product applied daily. This event resolved on Day 22. Neither TEAE resulted in discontinuation of tretinoin lotion or withdrawal of the subject from the trial.

Active Assessments of Local safety

At Baseline, none of the subjects had signs or symptoms of irritation at the application site. The greatest number of subjects experienced application site reactions on Day 12. By the end of treatment (Day 15), investigators documented mild erythema in 6 (30%) subjects, mild or moderate scaling in 7 (35%) subjects, and mild itching in one (5%) subject. No subjects experienced severe local cutaneous signs or symptoms during the trial.

Laboratory Findings

Most laboratory values were either within the normal range or varied slightly from the normal range. However, 2 subjects had elevated CPK and liver enzymes and 1 subject with a history of enuresis treated with desmopressin had elevated liver enzymes. See Appendix 13.4 for brief narratives of these abnormal investigations and Section 7.3.2 *Laboratory Findings* for a discussion of similar results in the Phase 3 trials.

There were no positive pregnancy tests among females of child bearing potential enrolled in Study 501.

Vital Signs and Physical Examination

There were no significant changes in vital signs or brief physical examinations.

7.3.8. 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 tretinoin 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 ATRALIN Gel, 0.05% (NDA 22070). 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.

Pediatrics and Assessment of Effects on Growth

The applicant evaluated pediatric subjects in all trials which were the primary source of data to support the safety and efficacy of tretinoin lotion for the treatment of acne vulgaris. Per the entry criteria, the Phase 3 trials (Study 301 and Study 302) and maximal use pharmacokinetic (PK) trial (Study 501) enrolled pediatric subjects age 9 to <17 years. The pooled Phase 3 trials enrolled a total of 729 subjects who were less than 18 (729/1640, 44%) and 581 (581/1640, 35%) subjects who were less than 17 years of age (regulatory definition of pediatric population). Among these pediatric subjects, 59 subjects were in the youngest age group, 9 through 12 years (9 years: 3 subjects; 10 years: 5 subjects; 11 years: 16 subjects and 12 years: 35 subjects.) See Section 6.3.1 for a discussion of the age distribution in Trial V01-121A-501 which enrolled 20 subjects age 10 to 16 years. In the development program, a total of 318 subjects age 9 to < 17 years received tretinoin lotion.

The proposed product is a new dosage form of tretinoin. On this basis, approval of this product for the treatment of acne vulgaris triggers the Pediatric Research Equity Act (21 U.S.C.355c).

Pediatric Study Plan

On July 24, 2015, the applicant submitted IND 126753 which included an iPSP. As nonclinical data and regulatory justification for the partial waiver were not documented in the submission, the Agency determined that the pediatric study plan was materially incomplete. The Pediatric Study Plan-Incomplete Letter included comments regarding the size and age distribution of the study population for the proposed maximal use pharmacokinetic (PK) trial to be conducted in the pediatric population. (Pediatric Study Plan-Incomplete Letter dated October 21, 2015).

On January 20, 2016, the applicant resubmitted the iPSP. The Division discussed the proposed iPSP with the Pediatric Review Committee on March 16, 2016 and June 8, 2016 and reached agreement. (Pediatric Study Plan-Initial Agreement Letter dated June 13, 2016.)

NDA submission

In the NDA submission (Section 1.9.1), the applicant included a request to waive the requirement to conduct clinical studies with tretinoin lotion, 0.05% in the pediatric population between birth and < 9 years of age for the proposed indication of the topical treatment of acne vulgaris. The justification for waiving the required pediatric assessment was:

> "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 applicant did not request a deferral of assessments in any pediatric age group as the Phase 3 and Phase 1 trials included the target pediatric population. PeRC agreed with the

Division that the proposed partial waiver was acceptable and the applicant provided adequate data in the target pediatric population age 9 years and older (PeRC Meeting Minutes dated June 11, 2018). Therefore, the Agency will not require postmarketing assessments under Pediatric Research Equity Act.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
In the development program, no subjects reported an overdose of tretinoin lotion. There were no TEAE that occurred under maximal use conditions (Study 501: 4 g of study drug applied once daily for 14 days) that were unexpected. The applicant stated that there was no available information regarding overdose and omitted Section 10 **Overdose** in labeling for tretinoin lotion.

Drug Abuse Potential/ Withdrawal and Rebound
In view of the mechanism of action and low systemic exposure, there is no reason to anticipate any potential for abuse or dependency. The applicant did not evaluate abuse potential and did not design or conduct trials to evaluate subjects for withdrawal or rebound. Therefore, the review team did not consult with the Controlled Substance Staff.

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Tretinoin lotion is not marketed in any jurisdiction. There are no ongoing nonclinical or clinical trials that could provide additional data to inform the current or anticipated safety evaluation for this product. Therefore, no postmarketing safety data is available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the tretinoin 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 tretinoin lotion in the postmarket setting.

7.3.10. Integrated Assessment of Safety

The safety profile for tretinoin lotion was adequately characterized during the drug development program. The primary safety database consisted of 1550 subjects from Phase 3 Trials V01-121A-301 and V01-121A-302 (the pooled safety analysis set). All randomized subjects who were included in the safety analysis set were “presumed” to have used the study drug at least once and provided at least 1 post-Baseline evaluation.

The safety profile for tretinoin lotion was similar to the safety profile for other topical tretinoin products. Review of the safety data did not reveal any contraindications to treatment with tretinoin lotion to be included in Section 4 of product labeling. The data continue to support

advising patients about the potential for skin irritation and effects of ultraviolet light and environmental exposure 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, hypopigmentation, itching burning and stinging) at a post-Baseline visits was greater in the tretinoin lotion group than the vehicle group. In addition, all the adverse events which occurred in ≥ 1 % of subjects treated with tretinoin and greater than vehicle related to the application site (dryness, pain, erythema, irritation and exfoliation.) Although the adverse event data indicated that equal numbers of subjects reported photosensitivity reactions in the tretinoin and vehicle groups, FDA Adverse Event Reporting System data supports a relationship between topical tretinoin products and photosensitivity. (Review by Carmen Cheng, PharmD dated June 27, 2018.)

Treatment with tretinoin lotion was not associated with an increased risk of mortality or serious adverse events. There were no deaths in the development program for tretinoin lotion and there were no serious adverse events assessed as related to either study product. In the pooled safety analysis set, serious adverse events occurred in 0.9% subjects in the tretinoin lotion group and 0.5% subjects in the vehicle group. Among subjects in the tretinoin lotion group, the serious adverse events included pregnancy (4 subjects), and appendicitis, calculus ureteric, and asthma (1 subject each). Among subjects in the vehicle group, serious adverse events included pregnancy (2 subjects), and abortion missed, alcoholic pancreatitis, pancreatitis, postprocedural hemorrhage, and suicidal ideation (1 subject each).

The applicant defined pregnancy as a serious adverse event. Subjects who became pregnant withdrew from treatment and, where feasible, were followed until delivery. There were 4 pregnancies among subjects who received tretinoin lotion and 2 pregnancies among subject who received vehicle. Pregnancy outcomes in the tretinoin group included: 2 normal deliveries, 1 elective termination and 1 unknown outcome. Pregnancy outcomes in the vehicle group included: 1 normal delivery, and 1 missed abortion. There were no documented congenital anomalies. Catherine Roca, M.D., the reviewer from the Division of Pediatric and Maternal Health (DPMH), concluded that the available data from the literature and submission do not indicate a clear risk for use during pregnancy or infertility. (Review dated 5/25/2018.) The review team revised Section 8 of labeling to convey the uncertainty regarding a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

The currently available safety data from 2 12-week Phase 3 trials demonstrate that tretinoin lotion appears safe for the treatment of acne vulgaris in patients 9 years of age and older. The applicant relied on long-term safety data from other tretinoin products [RENOVA (tretinoin cream) 0.05%, NDA 019963 and RENOVA (tretinoin cream) 0.02%, NDA 021108] for which they submitted a right of reference. The safety profile of long- term use of tretinoin (24 to 52 weeks) appears to be the same as short-term use. 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 post marketing studies).

SUMMARY AND CONCLUSIONS

7.4. Statistical Issues

There were no major statistical issues affecting the overall conclusions for Studies 301 and 302. The primary efficacy endpoints and key secondary endpoints were statistically significant. Approximately 16% of subjects discontinued from Studies 301 and 302 prior to Week 12, though the results were consistent across different ways of handling missing data. Trial 301 was conducted at 42 centers and Study 302 was conducted at 36 centers. There was variability across centers in each study with treatment-by-center interactions meeting the statistical significance criterion for the analysis of change in non-inflammatory lesions in Study 301 and for the change in inflammatory lesions in Study 302, though no consistent patterns across centers were observed, and the results were not driven by the results from any one center. The results were consistent across demographic and disease severity subgroups.

7.5. Conclusions and Recommendations

To establish the effectiveness of tretinoin lotion, the applicant submitted data from two randomized, multicenter, vehicle-controlled, Phase 3 trials (Study 301 and Study 302). The trials enrolled subjects 9 years of age and older with moderate (3) or severe (4) acne vulgaris on the EGSS. Enrolled subjects had 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory lesion (open and closed comedones) and two or fewer facial nodules. In both trials, subjects were randomized in a 1:1 ratio to receive tretinoin 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 co-primary 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 non-inflammatory lesion counts and percent change in inflammatory lesion counts. In both trials, tretinoin was statistically superior to vehicle (p-values ≤0.007) for both co-primary efficacy endpoints and secondary efficacy endpoints at Week 12 (see Section 7.2).

The applicant conducted a comprehensive assessment of the safety of tretinoin lotion in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

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

8 Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application because the safety profile of the moiety is well characterized and was expected to be similar to other tretinoin products approved for this indication.

9 Pediatrics

In the Phase 3 and Phase 1 trials, the applicant established the safety and efficacy of tretinoin lotion for use in the target pediatric population age 9 to less than 17 years for the treatment of acne vulgaris. 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 (May 16, 2018). 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 for a discussion regarding the Pediatric Study Plan.

10 Labeling Recommendations

10.1. Prescribing Information

The applicant submitted proposed Prescribing Information (PI) and carton/container labels for tretinoin lotion. The review team provided recommendations regarding PI which are provided throughout this review. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis reviewed the proposed PI for ALTRENO (tretinoin) Lotion and the carton and container labels and provided comments. DMEPA concluded that the PI was acceptable from a medication error perspective and the carton and container labels could be improved to increase the clarity of information to promote the safe use of the product. (See Review dated April 3, 2018). Dr. Patel reviewed the revised container labels and carton labeling for ALTRENO and found them acceptable from a medication error perspective. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, and carton/container. Refer to the OPDP review by Laurie Buonaccorsi, PharmD, dated July 9, 2018. These comments are reflected in final labeling. The following table (Table 50) provides the location of the labeling discussion for each section.

Table 50: Location of the Labeling Discussion for Significant High Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1, 5.6
2 DOSAGE AND ADMINISTRATION	Section 6.9
4 CONTRAINDICATIONS	Section 7.3.10 Integrated Summary of Safety
5 WARNINGS AND PRECAUTIONS	Section 7.3.1.0
6 ADVERSE REACTIONS	Section 7.3.4
7 DRUG INTERACTIONS	Section 6.3.2
8 USE IN SPECIFIC POPULATIONS	Section 5.6, Appendix 13.3
12 CLINICAL PHARMACOLOGY	Section 6.6
14 CLINICAL STUDIES	Section 7
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6 and 14.

Source: Reviewer's Table

10.2. Patient Labeling

The applicant submitted a proposed patient package insert (PPI) for tretinoin lotion. The Division of Medical Policy Programs (DMPP) and OPDP reviewed and provided comments regarding the PPI. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Morgan Walker, PharmD, MBA, CPH and Laurie Buonaccorsi, PharmD dated July 10, 2018.

11 Risk Evaluation and Mitigation Strategies

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard post-marketing 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 Commitments

None.

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 sub-investigators who participated in covered clinical studies for tildrakizumab. 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 V01-121A-301 and Trial V01-121A-302 which provided the primary data to establish effectiveness and safety of this product. Refer to Section 7.2.1 for the trial designs.

There were 4 investigators who reported **significant payments of other sorts** from the sponsor of the covered study [21 CFR 54.4(a) (3) (ii), 54.2(f)]. These disclosures were as follows:

- **121A-301**:
  - (b) (6)
- **121**
  - (b) (6)

There was one investigator who reported a **significant equity interest** in the sponsor of the covered study product (21 CFR 54.4(a) (3) (iv), 54.2(b)]. This disclosure was as follows:

- **121A-301**:
  - (b) (6)

Table 51: Covered Clinical Study (V01-121A-301)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 42		
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): 4		
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: 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) NA

Table 52: Covered Clinical Study (V01-121A-302)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 42		
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): 4		
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: 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) NA

Table 53: Investigators with Financial Disclosure Forms 3455 for Trials V01-121A-301 and V01-121A-302

Investigator	Trial/Site	Country	# Subjects Randomized	Description of Disclosure
(b) (6)				Significant Payments of Other Sorts Amount: Amount: $15,000 - <$25,000 in 2016; $15,000 - <$25,000 in 2017 Comment: speaker, consultant
				Significant Payments of Other Sorts: Amount: $51862.74 in 2014; $12,100.00 in 2015 Comment: speaker, advisory boards, honoraria, consultant, reimbursement for travel.
				Significant Payments of Other Sorts Amount: Amount: $2,400 in 2017; $2,000 in 2016; $1800 for 2015 Comment: speaker, advisory boards, honoraria
				Significant Payments of Other Sorts Amount: $7,500 in 2015; $7,500 in 2016; $7,500 in 2017 Comment: speaker, advisory boards, consultant
				Equity Interest Amount: 20,000 shares of Valeant stock Comment: stock

Source: Reviewer's table, data from NDA 209353 SD 1 Module 1.3.4 dated 10/27/2017 and SD 9 dated 4/11/2018
*Investigators reported financial disclosures for the Phase 3 trials even though the payments were under the $25,000 reportable amount per year.

Strategy to minimize bias

The applicant minimized bias by including language in the Informed Consent Forms (ICFs) disclosing this potential conflict of interest and requesting that subjects report any concerns. In addition, sites with high enrollment and/or potential conflicts of interest received more frequent site visits to ensure protocol compliance and data integrity. Furthermore, the number of investigators with financial disclosures was limited and assessments were blinded.

Therefore, the applicant adequately disclosed financial interests involving clinical investigators and the strategies employed by the applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

13.3. Nonclinical Pharmacology/Toxicology

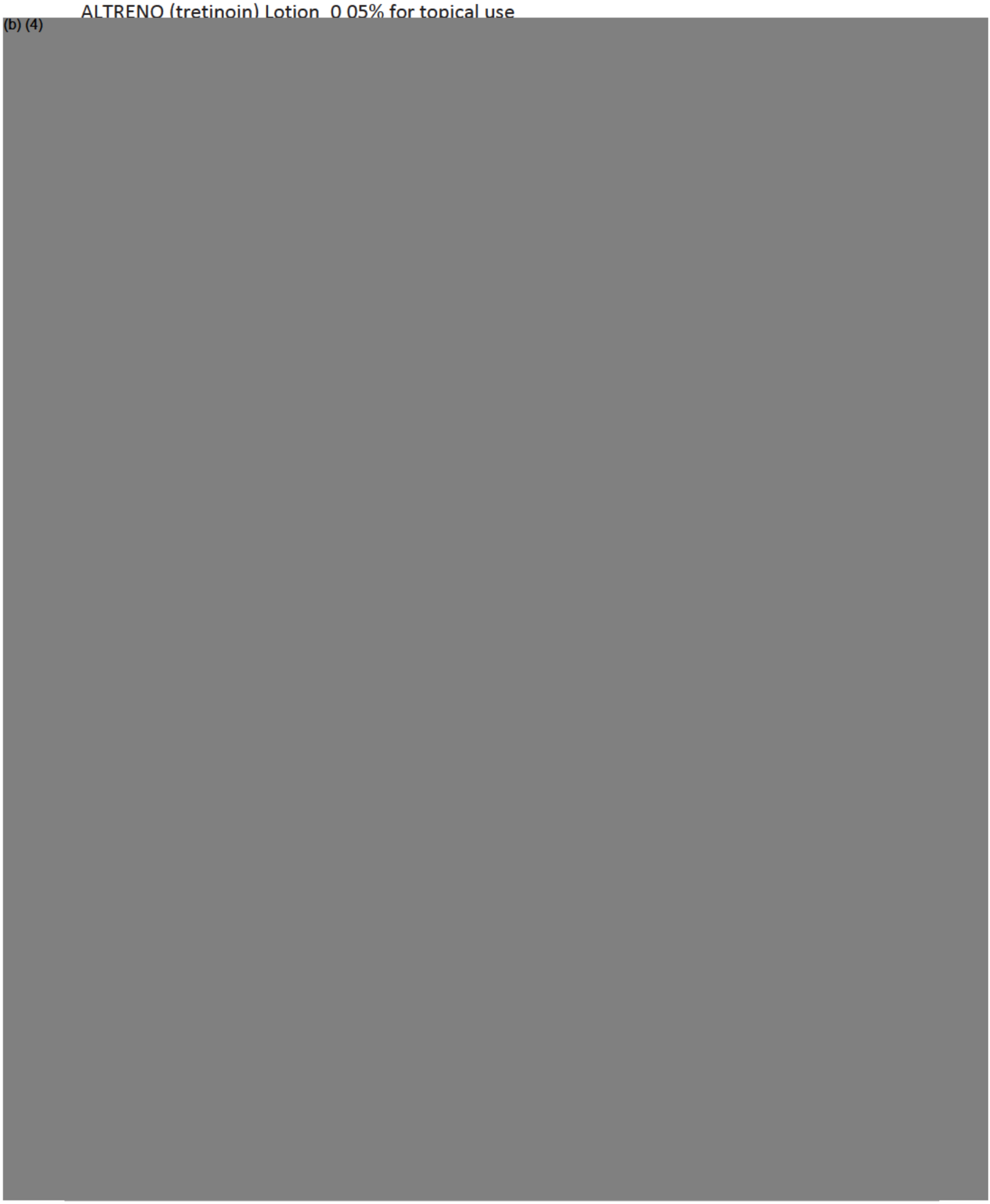
Revisions to the applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. Except as where designated by PLLR format, it is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the sponsor's label text. Reference to rodent fetal malformations after oral administration of tretinoin was (b) (4) but modified and maintained under *Animal Data*. (b) (4)

(b) (4) . A clean copy of these revised labeling sections is provided at the end of this section.

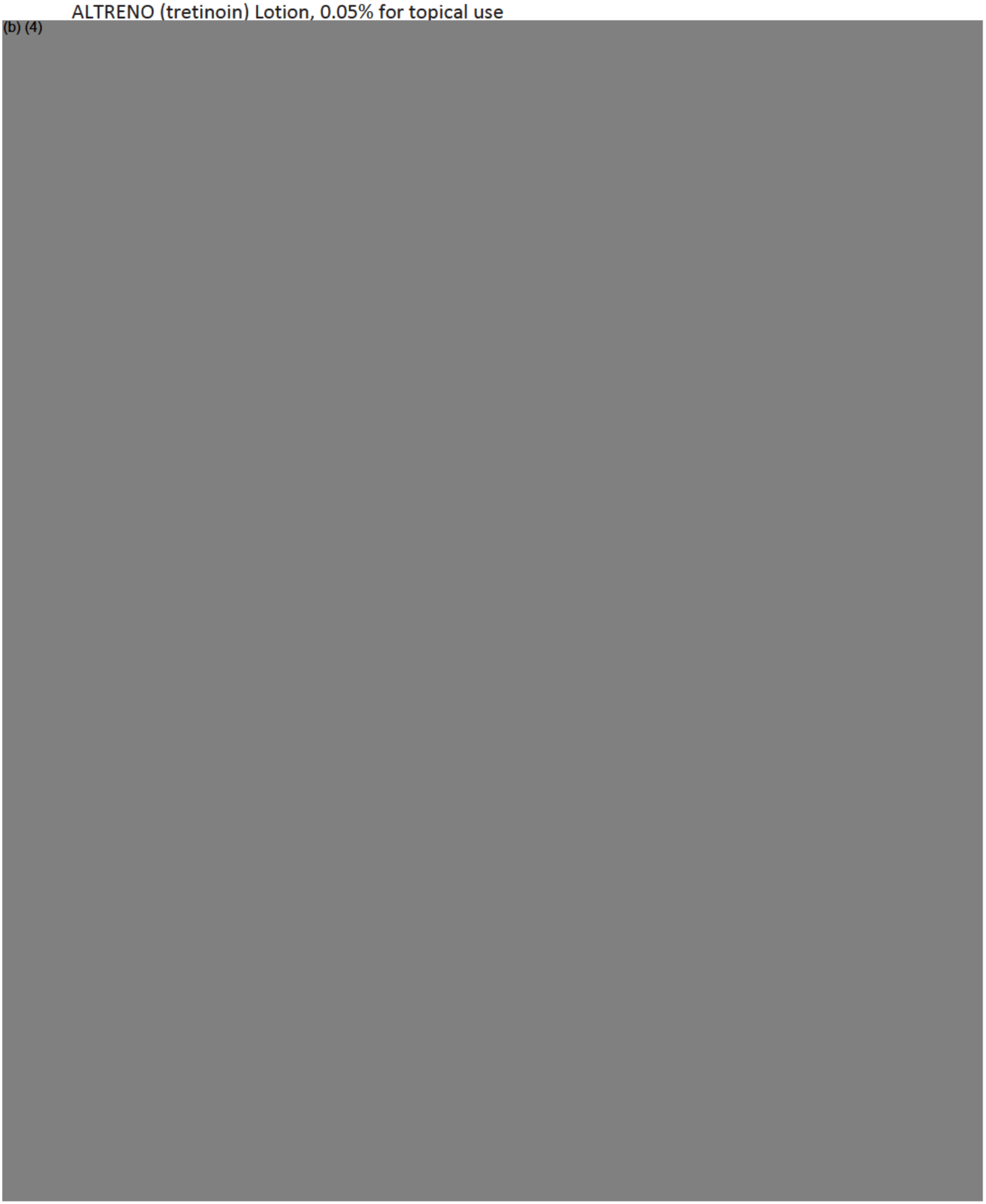
HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

(b) (4)

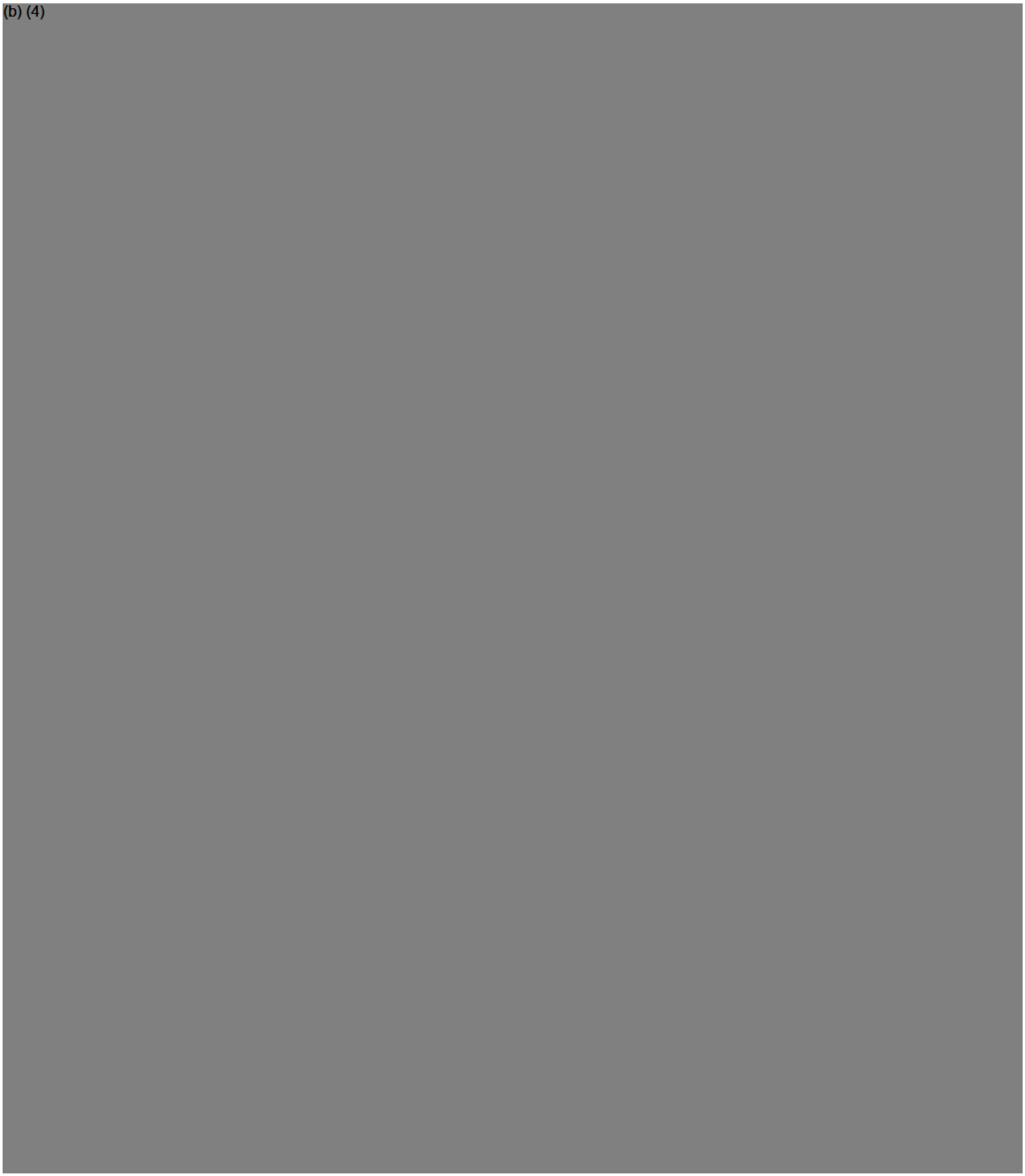
(b) (4)



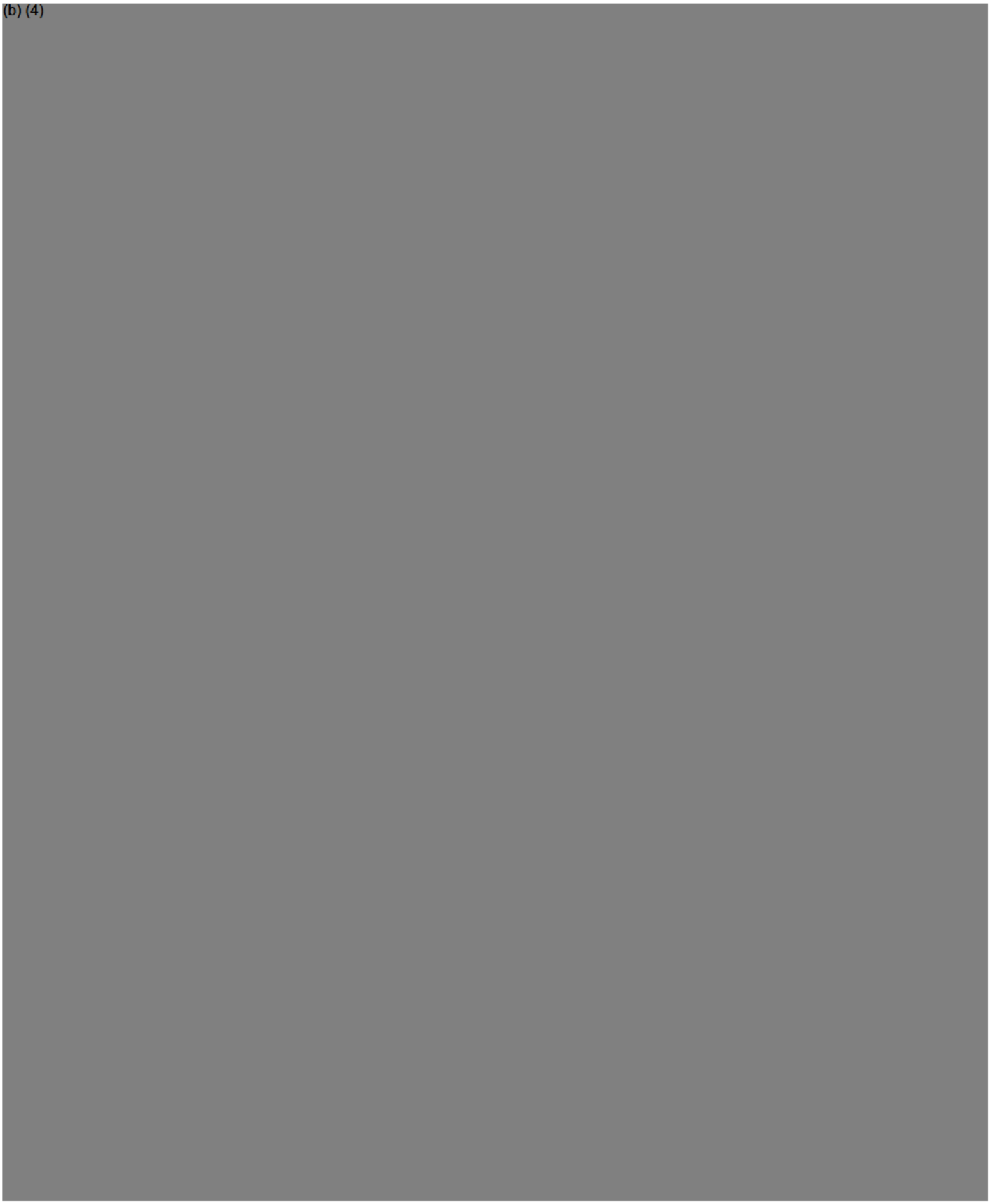
(b) (4)



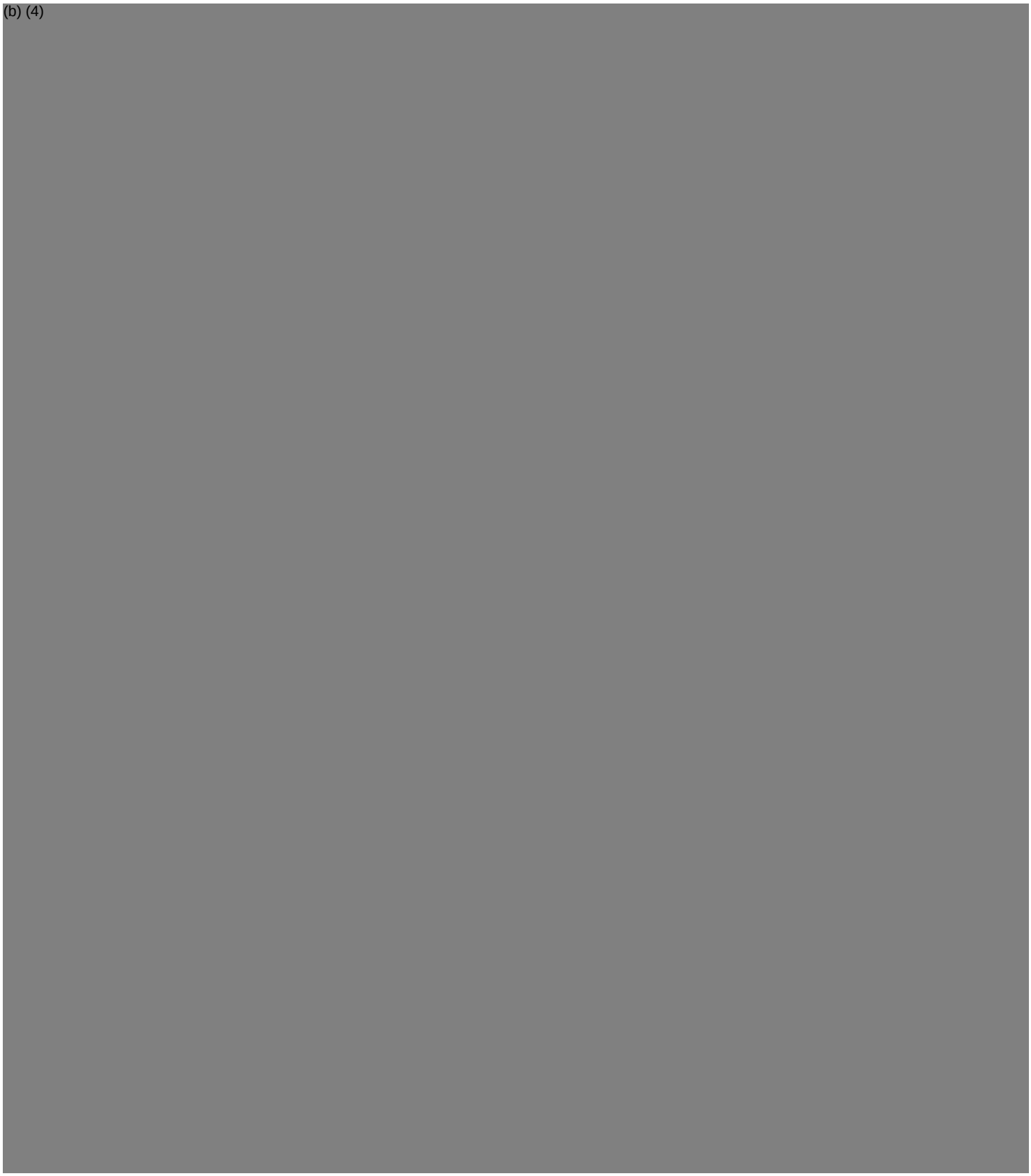
(b) (4)



(b) (4)



(b) (4)



(b) (4)

[redacted]

13.4. Clinical/Biostatistics Supporting Data

Demographics and Disposition of the Safety Population

Table 54: Demographics and Disposition

Characteristics	Statistics	Tretinoin Lotion	Vehicle Lotion
Sex [n (%)]	F	404 (52.67%)	452 (57.73%)
	M	363 (47.33%)	331 (42.27%)
Age Cat 18 [n (%)]	<18 years of age	353 (46.02%)	352 (44.96%)
	>=18 years of age	414 (53.98%)	431 (55.04%)
Race [n (%)]	White	555 (72.36%)	592 (75.61%)
	African American	155 (20.21%)	136 (17.37%)
	Asian	34 (4.43%)	31 (3.96%)
	Other	16 (2.09%)	15 (1.92%)
	Native Hawaiian or Pacific Islander	4 (0.52%)	7 (0.89%)
	American Indian or Alaska Native	3 (0.39%)	2 (0.26%)
Ethnicity [n (%)]	Hispanic or Latino	345 (44.98%)	379 (48.40%)
	Not Hispanic or Latino	421 (54.89%)	404 (51.60%)
AE [n (%)]		182 (23.73%)	157 (20.05%)
SAE [n (%)]		7 (0.91%)	4 (0.51%)
Non-fatal SAE [n (%)]		7 (0.91%)	4 (0.51%)
AE resulted in drug interruption [n (%)]		55 (7.17%)	26 (3.32%)
AE resulted in drug withdrawal [n (%)]		12 (1.56%)	0 (0.00%)
AE Causality [n (%)]	Not related	145 (18.90%)	144 (18.39%)
	Related	62 (8.08%)	15 (1.92%)
Disposition [n (%)]	Adverse event	7 (0.91%)	0 (0.00%)
	Completed	680 (88.66%)	701 (89.53%)
	Lack of efficacy	1 (0.13%)	2 (0.26%)
	Lost to follow-up	36 (4.69%)	32 (4.09%)
	Non-compliance	2 (0.26%)	2 (0.26%)
	Other	2 (0.26%)	1 (0.13%)
	Physician decision	0 (0.00%)	1 (0.13%)
	Pregnancy	3 (0.39%)	0 (0.00%)

Characteristics	Statistics	Tretinoin Lotion	Vehicle Lotion
	Protocol deviation	1 (0.13%)	2 (0.26%)
	Withdrawn by parent/ guardian	7 (0.91%)	12 (1.53%)
	Withdrawn by subject	28 (3.65%)	28 (3.58%)
	Worsening condition	2 (0.26%)	2 (0.26%)
Countries [n (%)]	Dominican Republic	30 (3.91%)	30 (3.83%)
	Honduras	40 (5.22%)	40 (5.11%)
	El Salvador	60 (7.82%)	59 (7.54%)
	USA	637 (83.05%)	654 (83.52%)
Total Subjects		767	783

Table 55: Disposition: Reasons Given for Discontinuation

Treatment Arm	Discontinuation (CRF)	Statistical Reviewer Classification (n)	Reason (CRF)
Tretinoin Lotion	Subject request	Lack of Efficacy (7)	Worsening of acne (3) Acne not better, wanted something to fix it quickly (1) Lack of efficacy (1) Worsening of condition (1) No improvement with treatment (1)
		Adverse event (1)	Rash (1)
		Other (30)	Withdrew consent (7) Did not want to continue (9) No longer lives in area (8) Schedule/transportation issues (5) Refused to come back to site (1)
	Withdrawal by Parent / Guardian	Lack of Efficacy (3)	Worsening of acne (1) Not feeling well and felt lotion was not helping (1) Need to start treating acne (1)
		Other (6)	Withdrew consent (1) Personal reasons (2) No longer lives in area (1) Schedule/transportation issues (2)

	Other	Adverse event (1)	Burning, itching, stinging
Vehicle	Subject request	Lack of efficacy (12)	Dissatisfied with results (12) Wants to use stronger medication (1) Worsening of acne (2) Due to flaring, wants to try other options (1) Lack of efficacy (2) No improvement (4)
		Other (26)	Withdrew consent (13) Did not want to continue (4) No longer lives in area (4) Schedule/transportation issues (4) Wanted to begin medicine before school (1)
	Withdrawal by parent/guardian	Lack of efficacy (2) Other (12)	Medication not helping (1) No improvement, worsening of acne (1) Withdrew consent (1) Did not want to continue (4) Personal reasons (2) No longer lives in area (2) Schedule/transportation issues (3)
	Other	Other (1)	Subject ran out of investigational product (1)

[a] Classification assigned by statistical reviewer based on reason provided.
Source: Statistical reviewer analysis.

Pregnancy data

Key findings for all subjects who became pregnant during the Phase 3 trials are tabulated below (Table 56).

Table 56: Summary of Pregnancies in the Phase 3 Trials

Subject ID /Treatment	Outcome	OB History	Risk Factors	Lifestyle Factors	Congenital Anomalies
(b) (4) None	N/A	N/A	N/A	N/A	N/A
(b) (4) None	N/A	N/A	N/A	N/A	N/A
(b) (4) Vehicle	Missed abortion	G3P3	Gestational Diabetes	None Reported	None Reported
(b) (4) Tretinoin	Elective Termination	G0	None Reported	None Reported	None Reported
(b) (4) Tretinoin	Normal Delivery	G7P6A1; 1 Pre-term labor	X-ray exposure	None Reported	None Reported
(b) (4) Tretinoin	Unknown	G4P3; 1 early fetal death (twin)	Alcohol use; hypertension	None Reported	Unknown
(b) (4) Vehicle	Normal Delivery (vaginal)	G2P1A1	None Reported	None Reported	None Reported
(b) (4) Tretinoin	Normal Delivery (C-Section)	G0	None Reported	None Reported	None Reported

*positive pregnancy testing at screening with no exposure to study products.
Source: Modified from data in NDA 209353 SD 7 submitted 3/27/2018

Abbreviations: G = gravida, P = para, A = abortion, C = Caesarian

Treatment Emergent Adverse Reactions (TEAR) by Demographic Subgroup

The following tables (Table 57 through Table 59) present TEAR by age, sex, and race.

Table 57: Treatment Emergent Adverse Reactions by Age

Treatment Emergent ARs	Age < 18 years		Age ≥18 years	
Preferred Term	Tretinoin Lotion, N (%)	Vehicle Lotion, N (%)	Tretinoin Lotion, N (%)	Vehicle Lotion, N (%)
Application site pain	13 (1.84%)	1 (0.14%)	11 (1.30%)	2 (0.24%)
Application site dryness	12 (1.70%)	0 (0.00%)	16 (1.89%)	1 (0.12%)
Application site erythema	5 (0.71%)	0 (0.00%)	6 (0.71%)	1 (0.12%)
Application site irritation	3 (0.43%)	1 (0.14%)	4 (0.47%)	0 (0.00%)
Application site exfoliation	2 (0.28%)	1 (0.14%)	3 (0.36%)	2 (0.24%)
Application site pruritus	2 (0.28%)	0 (0.00%)	5 (0.59%)	4 (0.47%)
Application site swelling	2 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Application site hypersensitivity	1 (0.14%)	0 (0.00%)	1 (0.12%)	0 (0.00%)
Application site photosensitivity reaction	1 (0.14%)	0 (0.00%)	0 (0.00%)	2 (0.24%)
Application site rash	1 (0.14%)	0 (0.00%)	1 (0.12%)	0 (0.00%)
Application site acne	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.24%)
Application site coldness	0 (0.00%)	0 (0.00%)	1 (0.12%)	0 (0.00%)
Application site dermatitis	0 (0.00%)	0 (0.00%)	3 (0.36%)	0 (0.00%)
Subjects	29 (4.11%)	3 (0.43%)	33 (3.91%)	12 (1.42%)
Total Subjects	705	705	845	845

Source: Reviewer's Table using JReview

Table 58: Treatment Emergent Adverse Reactions by Sex

Treatment Emergent ARs	Female		Male	
Preferred Term	Tretinoin Lotion, N (%)	Vehicle Lotion, N (%)	Tretinoin Lotion, N (%)	Vehicle Lotion, N (%)
Application site dryness	22 (2.57%)	0 (0.00%)	6 (0.86%)	1 (0.14%)
Application site pain	16 (1.87%)	2 (0.23%)	8 (1.15%)	1 (0.14%)
Application site erythema	7 (0.82%)	0 (0.00%)	4 (0.58%)	1 (0.14%)
Application site pruritus	6 (0.70%)	2 (0.23%)	1 (0.14%)	2 (0.29%)
Application site irritation	5 (0.58%)	0 (0.00%)	2 (0.29%)	1 (0.14%)
Application site exfoliation	4 (0.47%)	3 (0.35%)	1 (0.14%)	0 (0.00%)
Application site dermatitis	2 (0.23%)	0 (0.00%)	1 (0.14%)	0 (0.00%)
Application site hypersensitivity	2 (0.23%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Application site swelling	2 (0.23%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Application site coldness	1 (0.12%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Application site acne	0 (0.00%)	2 (0.23%)	0 (0.00%)	0 (0.00%)
Application site photosensitivity reaction	0 (0.00%)	0 (0.00%)	1 (0.14%)	2 (0.29%)
Application site rash	0 (0.00%)	0 (0.00%)	2 (0.29%)	0 (0.00%)
Subjects	43 (5.02%)	7 (0.82%)	19 (2.74%)	8 (1.15%)
Total Subjects	856	856	694	694

Source: Reviewer's Table using JReview

Table 59: Treatment Emergent Adverse Reactions by Race (White and African American)

Treatment Emergent ARs	White		Black/African American	
Preferred Term	Tretinoin Lotion, N (%)	Vehicle Lotion, N (%)	Tretinoin Lotion, N (%)	Vehicle Lotion, N (%)
Application site dryness	21 (1.8%)	1 (0.1%)	4 (1.4%)	0 (0.0%)
Application site pain	19 (1.7%)	2 (0.2%)	4 (1.4%)	1 (0.3%)
Application site erythema	7 (0.6%)	0 (0.0%)	2 (0.7%)	1 (0.3%)
Application site pruritus	5 (0.4%)	4 (0.3%)	1 (0.3%)	0 (0.0%)
Application site irritation	4 (0.3%)	1 (0.1%)	2 (0.7%)	0 (0.0%)
Application site dermatitis	3 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Application site exfoliation	2 (0.2%)	2 (0.2%)	2 (0.7%)	0 (0.0%)
Application site rash	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Application site coldness	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Application site photosensitivity reaction	1 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Application site swelling	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Application site acne	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Application site hypersensitivity	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Subjects	45 (3.9%)	12 (1.0%)	12 (4.1%)	2 (0.7%)
Total Subjects	1147	1147	291	291

Source: Reviewer's Table using JReview

Phase 1b Study V01-121A-501

Narratives for subjects with elevated liver enzymes and/or creatine kinase (CPK)

- 16-year-old White male (Subject (b) (6)) with a history of seasonal allergies and enuresis who was treated with desmopressin had an ALT value of 93 U/L (normal range = 5 – 30 U/L) and AST of 42 U/L (normal range: 0 to 38 U/L) on Day 15 with screening values of 47 U/L and 33 U/L respectively. Other parameters were normal [ALP, bilirubin, GGT and CPK] at screening and Day 15. He used a total of 15.6 g of study product. The Applicant reported no additional AEs or relevant follow-up information.
- 14-year-old White male (Subject (b) (6)) with no relevant medical history had a creatine kinase (CPK) value of 1111 U/L (normal range = 2 – 251 U/L) and AST of 43 on Day 15 with screening values of 205 U/L and 23 U/L respectively. Other parameters were normal [ALT, ALP, bilirubin, and GGT] at screening and Day 15. He used a total of 15.9 g of study product. The Applicant reported no additional AEs or relevant follow-up information. Activity levels were not documented
- 15-year-old White male (Subject (b) (6)) with a history of asthma which was treated with albuterol had a CPK value of 583 U/L on Day 15 with a screening value was 1233 U/L. At screening ALT and AST were slightly elevated at 31 and 48 respectively but normalized by Day 15. Urinalysis at Day 15 showed occult blood 1+, protein at 2+, erythrocytes at 39/high power field, specific gravity at 1.036 (normal range: 1.01 to 1.03), and leukocytes at 6 per high power field (normal range: 0 to 5 /high power field). All other parameters were within normal limits. He used a total of 11.8 g of study

product. The applicant reported no additional AEs or relevant follow-up information. Activity levels were not documented.

Interpretation of these cases is limited by the lack of historical information and/or repeated laboratory testing to evaluate whether the elevated liver enzymes and CPK levels were related to the drug product or a transient cause. Total CPK levels vary with age, gender, race, muscle mass, type and duration of physical activity and climatic conditions.[15] Strenuous exercise (e.g., prolonged, weight-bearing exercises, downhill running and eccentric muscle actions) may damage skeletal muscle cells resulting in increased total serum CPK.[16]Total serum CPK levels are markedly elevated for 24 h after exercise and gradually return to basal levels with rest.[1] Because the protocol did not restrict physical activity and the levels of CPK were not reassessed after a period of rest (1 week), the significance of the variability in the laboratory values is uncertain.[17]

[15] Brancaccio P et al. Creatine kinase monitoring in sport medicine. British Medical Bulletin 2007; 81 and 82: 209–230

[16] Brown S et al. Indirect evidence of human skeletal muscle damage and collagen breakdown after eccentric muscle actions. J Sports Sciences.1999. Vol 17; Issue 5. 397-402.

[17] Hunt A. Elevated Serum Creatine Phosphokinase Levels in Healthy Teen-aged Boys. Arch Neurol. 1975;32(8):576.

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/s/

BARBARA J GOULD
08/23/2018

JILL A LINDSTROM
08/23/2018