NDA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	NDA 211527/IND 111091
Priority or Standard	Standard
Submit Date(s)	October 4, 2018
Received Date(s)	October 4, 2018
PDUFA Goal Date	October 4, 2019
Division/Office	DDDP/
Review Completion Date	See DARRTS electronic signature page
Established/Proper Name	Trifarotene
(Proposed) Trade Name	AKLIEF
Pharmacologic Class	Retinoid
Code Name	
Applicant	Galderma Research and Development, LLC
Dosage Form	Cream
Dosing Regiment	Once daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of acne vulgaris (b) (4) (b) (4) in patients 9 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	AKLIEF is indicated for the treatment of acne vulgaris in patients age 9 years and older
Recommended Dosing Regimen	Once daily in the evening

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis

DRISK = Division of Risk Management

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANCOVA	analysis of covariance
$AUC_{0\text{-}24h}$	area under the 24-hour concentration time-curve
BCRP	breast cancer resistance protein
BLA	biologics license application
BSA	body surface area
BSEP	bile salt export pump
BW	body weight
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DHOT	Division of Hematology Oncology Toxicology
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
EE	ethinyl estradiol
ET	early termination
FDA	Food and Drug Administration
GLP	good laboratory practice
HD	high dose
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
IND	investigational new drug
iPSP	initial pediatric study plan
IR	information request
IRT	interactive response technology
ITT	intention-to-treat
ITTT	intention-to-treat on the trunk
LNG	levonorgestrel
LOAEL	low adverse effect level
LOCF	last observation carried forward
LOQ	limit of quantification
LS	least squares
MAF	missing as failure
MAR	missing at random
MATE	multi-antimicrobial extrusion protein
MED	minimal erythema dose
MI	multiple imputation

MNAR	missing not at random
MRHD	maximum recommended human dose
MUsT	maximal usage pharmacokinetic trials
NDA	new drug application
NOAEL	no adverse effect level
OAT	organic anion transporter
OCT	organic cation transporter
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PBPK	physiologically-based pharmacokinetic
PGA	Physician Global Assessment
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PP	per-protocol
PPI	patient package insert (also known as Patient Information)
PPT	per-protocol population on the trunk
RAR	retinoic acid receptor
SAE	serious adverse event
SAF	safety population
SAFT	safety population for local tolerability on the trunk
SAP	statistical analysis plan
SC	stratum corneum
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

1. Executive Summary

1.1. Product Introduction

AKLIEF (trifarotene) Cream, 0.005% is a new molecular entity 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. The active ingredient is trifarotene, a retinoid, an agonist of retinoic acid receptors (RARs). RARs are intracellular proteins that, in conjunction with a ligand, bind to DNA and influence expression of certain genes. Retinoids mediate a number of effects, including modulation of organogenesis, cell turnover rate, cell differentiation, and apoptosis. The exact mechanism by which trifarotene may ameliorate acne vulgaris when topically applied is unknown.

The proposed indication is for the topical treatment of acne vulgaris (b) (4) in patients 9 years of age and older. The proposed dose and administration is a thin layer of cream applied to the affected areas (b) (4) in the evening, on clean and dry skin.

The Agency concluded that the proposed proprietary name, AKLIEF, was acceptable from both a promotional and safety perspective under new drug application (NDA) 211527 [Proprietary Name Review by Danielle Harris, PharmD, BCPS., Division of Medication Error Prevention and Analysis dated March 12, 2019].

1.2. Conclusions on Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials (Trials 18251 and 18252) which provided evidence of the effectiveness of trifarotene cream, 0.005% 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~~ inflammatory lesion count
- Absolute change in the ~~mean~~ noninflammatory lesion count
- Percentage of subjects who achieved an Investigator Global Assessment (IGA) score of *clear* or *almost clear* and at least two-grade improvement from baseline on the face

Trifarotene cream, 0.005% was statistically superior to vehicle (p-values ≤0.001) on the co-primary endpoints in both trials for the treatment of acne vulgaris. The Applicant has demonstrated that trifarotene cream, 0.005% is effective for its intended use in the target population and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126(a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Galderma Research and Development, Inc. submitted a new drug application (NDA) 211527 for AKLIEF (trifarotene) Cream, 0.005% 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. AKLIEF is a new molecular entity. The active ingredient is trifarotene, a retinoid, an agonist of retinoic acid receptors (RARs). RARs are intracellular proteins that, in conjunction with a ligand, bind to DNA and influence expression of certain genes. Retinoids mediate a number of effects, including modulation of organogenesis, cell turnover rate, cell differentiation, and apoptosis. The exact mechanism by which trifarotene may ameliorate acne vulgaris when topically applied is unknown. The Applicant relies on data from nonclinical trials, two pharmacokinetic (PK) maximal usage trials (MUsTs), one in pediatric subjects and one in adults, two vehicle controlled phase 3 efficacy and safety trials, and one long-term (52-week) safety trial to support the systemic (nonclinical and clinical) and long-term safety of their product.

In two, multicenter, randomized, double-blind clinical trials—Trials 18251 and 18252—enrolling 2,420 subjects age 9 years and older with acne vulgaris, trifarotene cream, 0.005% was statistically superior to vehicle for the treatment of acne vulgaris on all co-primary endpoints evaluating the face and all co-secondary endpoints evaluating the trunk. Success on the Investigator Global Assessment (IGA) was evaluated for the face and defined as at least a two-grade improvement from baseline and an IGA score of clear (0) or almost clear (1). The co-primary efficacy endpoints were success on the IGA (Trial 18251: 29.4% versus 19.5% and Trial 18252: 42.3% versus 25.7%), absolute change in facial inflammatory lesion count (Trial 18251: -19.0 versus -15.4 and Trial 18252: -24.2 versus -18.7), and absolute change in facial noninflammatory lesion count (Trial 18251: -25.0 versus -17.9 and Trial 18252: -30.1 versus -21.6) at Week 12.

Success on the Physician Global Assessment (PGA) was evaluated for the trunk and defined as at least a two-grade improvement from baseline and a PGA score of clear (0) or almost clear (1). The co-secondary efficacy endpoints were success on the PGA (Trial 18251: 35.7% versus 25.0% and Trial 18252: 42.6% versus 29.9%), absolute change in truncal inflammatory lesion count (Trial 18251: -21.4 versus -18.8 and Trial 18252: -25.5 versus -19.8), and absolute change in truncal noninflammatory lesion count (Trial 18251: -21.9 versus -17.8 and Trial 18252: -25.9 versus -20.8) at Week 12.

The safety profile for trifarotene cream, 0.005% was adequately characterized during the drug development program. Treatment with trifarotene cream, 0.005% was not associated with an increased risk of mortality or serious adverse events (SAEs). There were no deaths or drug-related serious adverse events in the phase 3 trials, Trial 18251, and Trial 18252 (referred to as Study 1 and Study 2 in labeling). In the pooled safety analysis set, SAEs occurred in 0.6% subjects in both the trifarotene 50 µg/g cream arm and the vehicle arm. Review of the data supports potential for skin irritation, skin pruritus, and effects of ultraviolet light and environmental exposure in Section 5 WARNINGS AND PRECAUTIONS of labeling. The most common adverse reactions occurred at the application site: irritation (7.5%), pruritus (2.4%), and sunburn

(2.6%). Active assessment of local tolerability indicated that the percentage of subjects who reported signs and symptoms (erythema, scaling, dryness, and burning/stinging) at a postbaseline visit was greater in the tretinoin lotion group than the vehicle group. These local tolerability signs/symptoms of erythema, scaling, dryness, and stinging/burning occurred in more than 50% of subjects on the face, and slightly fewer than 50% on the trunk. The majority of these reactions were mild to moderate in severity, with a few being severe.

In summary, acne vulgaris is a common, chronic disease which may be associated with substantial impairment of quality of life. Trifarotene 50 µg/g cream provides an additional treatment option. The available evidence of safety and efficacy supports the approval of AKLIEF (trifarotene) Cream, 0.005% for the topical treatment of acne vulgaris in the population 9 years of age and older. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. Acne occurs most frequently on the face and is characterized by two major types of lesions: noninflammatory (open or closed comedones) and inflammatory lesions (papules, pustules, and nodules). The etiology is multifactorial. Because of the chronic relapsing and remitting course and potential for scarring after lesions resolve, acne may be associated with 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 (Zaenglein et al. 2016).	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of acne vulgaris. 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 products that promote compliance by addressing patient preferences.
Benefit	• Data from two adequate and well controlled trials (Trials 18251 and 18252), provided substantial evidence of the effectiveness of trifarotene 50 µg/g cream for the treatment of acne vulgaris. These trials enrolled 2,420 subjects age 9 years and older with moderate acne vulgaris. Trifarotene cream, 0.005% was superior to vehicle in both trials for the co-primary efficacy endpoints of absolute change in noninflammatory lesion count, absolute change in inflammatory lesion count and IGA/PGA success. • Review of the safety data from clinical trials identified safety signals that are consistent with the use of topical retinoids. There was an increase in the cutaneous adverse reactions on the face compared to the trunk. There were no clinically meaningful differences in the tolerance of trifarotene cream, 0.005% in the evaluated subgroups.	Trifarotene cream, 0.005% provides an effective and safe treatment option for patients with moderate acne vulgaris.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Primary safety database (Study Pool 1) included 1,220 subjects who received trifarotene 50 ug/g cream once daily for 12 weeks. There were no deaths or serious adverse events related to the trial product. The most common adverse reactions occurring in ≥1% of subjects and greater than vehicle was localized to the applicate site: irritation, pruritus, and sunburn. Active assessment of local adverse reactions indicated that most were mild to moderate with a few severe. • Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and identified during product development. • No issues require further assessment with a postmarketing requirement or postmarketing commitment. • A risk evaluation and mitigation strategy is not recommended.	The risks associated with the use of trifarotene Cream, 0.005% are similar to other topical retinoid products. Local effects such as erythema, scaling, dryness, and burning/stinging may occur but are primarily mild to moderate in severity with a few severe reactions. Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

1.4. Patient Experience Data

Table 1. Patient Experience Data Relevant to This Application

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

2. Therapeutic Context

2.1. Analysis of Condition

Acne vulgaris is a common, chronic dermatological disorder. In the United States, acne affects more than 50 million individuals (Bhate and Williams 2013). 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 (Zaenglein et al. 2016; Thiboutot and Zaenglein 2018).

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 (Brown and Shalita 1998).

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

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

Both lesion types develop from microcomedones (Dawson and Dellavalle 2013) and most frequently occur on the face. However, lesions may be localized to other areas with a high density of sebaceous follicles such as the neck, chest and back. Factors which may influence the risk or presentation of acne are age, sex, and genetic predisposition. Variants of acne which may require more aggressive or specialized treatment include acne fulminans, acne conglobate, synovitis/acne/pustulosis/hyperostosis/osteitis syndrome, pyogenic arthritis/pyoderma gangrenosum/acne syndrome, neonatal acne, and acne complicated by Gram-negative folliculitis.

The clinical course is characterized by remissions and recurrences. In some individuals, acne may persist for decades and resolve with scarring. The association of acne with depression, anxiety and reduced quality of life is well documented (Lasek and Chren 1998). Successful treatment may produce a significant improvement in self-esteem (Newton et al. 1997).

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 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 that 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 that 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 (Zaenglein et al. 2016); 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 2. Categories of Drug Products for Acne Treatment

Category	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

[1] Azithromycin/Erythromycin, Ampicillin/amoxicillin used off-label

[2] Sprionolactone, flutamide, corticosteroids used off-label

Table 3. 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 4,340 subjects Active vs. vehicle 1.GAAS: 30% vs. 21% Inflam: 56% vs. 49% Noninfl: 45% vs. 39% -2.GAAS: 30% vs. 21% Inflam: 54% vs. 48% Noninfl: 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% Noninfl: 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	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 1,485 subjects 12 years and older with moderate to severe acne vulgaris Active vs. vehicle 1.IGA: 29% vs. 16% Inflam: 58% vs. 45% Noninfl: 55% vs. 33% Total: 56% vs. 39% -2.IGA: 28% vs. 13% Inflam: 57% vs. 41% Noninfl: 46% vs. 41% Total: 56% vs. 43%	AR: application site irritation, dryness, erythema, exfoliation, pain, photosensitivity, pruritus, dermatitis W&P: fetal risk, local irritation, irritant effect with concomitant topical medications, photosensitivity and risk for sunburn, flammability
DIFFERIN (adapalene) Lotion 0.1%, NDA 022502, (2010)	Topical treatment of acne vulgaris in patients 12 years and older	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 2,141 subjects Active vs. vehicle 1.IGA: 26% vs. 17% Inflam: 55% vs. 40% Noninfl: 50% vs. 36% Total: 52% vs. 37% -2.IGA: 24% vs. 16% Inflam: 46% vs. 37% Noninfl: 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

Product(s) Name/Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
ALTRENO (tretinoin) Lotion, 0.05%, NDA 209353, (2018)	Topical treatment of acne vulgaris in patients 9 years of age and older	Thin layer to affected areas once daily	2, 12-week R, DB, VC trials in 1,640 subjects 1.IGA: 16.5% vs. 6.9% Noninfl: 47.5% vs. 27.3% Inflam: 50.9% vs. 40.4% 2.IGA 19.8% vs. 12.5% Noninfl: 45.6% vs. 31.9%% Inflam: 53.4% vs. 41.5%	AR: application site dryness, pain, erythema, irritation, exfoliation W&P: Skin irritation, UV light and environmental exposure, fish allergies
Combination Products				
ACANYA Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%), NDA 050819, (2008)	Topical treatment of acne vulgaris in patients 12 years or older	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% Noninfl: 45% vs. 29% 2.EGSS: 0/1: 28% vs. 11% 2 grade: 37% vs. 14% Inflam: 54% vs. 23% Noninfl: 41% vs. 19%	AR: application site pain, exfoliation, irritation W&P: Colitis, UV light exposure
EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5%, NDA 207917, (2015)	Topical treatment of acne vulgaris	Thin layer of EPIDUO FORTE gel to affected areas of the face and/or trunk once daily after washing	12-week R, DB, VC trial subjects 12 years and older with moderate to severe acne vulgaris Active vs. vehicle IGA: 33.7% vs. 11.0% Inflam: 27.8% vs. 13.2% Noninfl: 40.5% vs19.7%	AR: skin irritation, eczema, atopic dermatitis, and skin 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 = noninflammatory

Table 4. Examples of Systemic Acne Products

Generic Name	Brand Name	Formulations	Applicant	Indication
Oral Antibiotics				
Minocycline Hydrochloride	SOLODYN	Extended-release tablets: 55, 65, 105, 115 mg	Medicis	Only inflammatory lesions of nonnodular moderate to severe acne vulgaris in patients 12 years of age and older.
Doxycycline hyclate	DORYX MPC	Delayed-release tablets: 60, 120 mg	Mayne pharma	In severe acne may be useful adjunctive therapy
	Doxycycline hyclate	Delayed-release tablets: 75, 100, 150, 200 mg		
Doxycycline Monohydrate	Monodox	Capsules: 50, 75, 100 mg	Aqua Pharms	
Tetracycline Hydrochloride	Tetracycline hydrochloride	Capsules: 250, 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	Capsules: 10, 20, 30, 40 mg	Douglas Pharm	
	ZENATANE, Generic	Capsules: 10, 20, 30, 40 mg	Dr Reddy's Labs, Ltd	
Hormonal Therapies				
Drospirenone 3 mg/ethinyl estradiol 0.02 mg	Yaz	Tablets	Bayer Healthcare	Moderate acne for women at least 14 years old only if patient desires an oral contraceptive for birth control
Norgestimate 0.180, 0.215, 0.250 mg/ ethinyl estradiol .035 mg	Ortho-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
Norgestimate 0.250 mg/ethinyl estradiol .035 mg	Ortho Tri-cyclen			

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The NDA for trifarotene cream, 0.005% is an original NDA and is not currently marketed in the United States. Thus, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed trifarotene under investigational new drug (IND) application 111091. The IND was opened on February 3, 2011, with a phase 1 exploratory trial to evaluate the efficacy and safety of different formulations and concentrations of CD5789 in subjects with moderate to severe acne vulgaris.

During their development program, the Applicant interacted with the Agency at the following milestones/meetings: Guidance meeting April 4, 2012; end-of-phase 2 meeting April 30, 2014; and Pre-NDA meeting April 4, 2018.

A guidance meeting was held with the Applicant on April 4, 2012. In that meeting the Applicant was advised to evaluate two co-primary efficacy endpoints in their phase 2 trial: (1) success rate at Week 12 defined as "clear" (Grade 0) or "almost clear" (Grade 1) with a two-grade improvement in the Physician Global Assessment (PGA) and (2) absolute change in inflammatory and noninflammatory lesion counts, baseline to Week 12. The Agency advised the Applicant that the proposed PGA scale was not acceptable, as the category of "clear" should represent the absence of disease (e.g., no erythema present). In their phase 2 protocol the Applicant planned to investigate three doses of trifarotene: 25 µg/g, 50 µg/g, and 100 µg/g in the treatment of acne vulgaris. The Applicant also proposed to evaluate the presence of acne on the chest and back. The Agency recommended that the same severity scale used to assess acne severity on the face should also be used to assess acne of the chest and back.

An end-of-phase 2 meeting was held with the Applicant on April 16, 2014. Based on phase 2 trial results, the Applicant determined that the 50 µg/g concentration of trifarotene would be evaluated in two phase 3 trials and one long-term safety trial. The Agency advised the Applicant, who agreed, that the target population should consist of subjects 9 years and older, that the evaluation of "truncal acne" must be evaluated in the same manner as the primary efficacy endpoint, that is, the following:

- An IGA of clear or almost clear with a two-grade improvement
- Change in inflammatory lesion counts at Week 12
- Change in noninflammatory lesion counts at Week 12

The Applicant was also advised that percent reduction in inflammatory and noninflammatory lesions should be supportive endpoints in their phase 3 trials.

It was agreed that laboratory monitoring would be performed on all subjects at baseline and end of treatment. At the time of this meeting, the Applicant stated that a thorough QT (TQT) study was conducted in accordance with the International Conference on Harmonisation (ICH) guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) to investigate any effect of trifarotene on ventricular repolarization. Under supratherapeutic exposure there was no effect of trifarotene on ventricular repolarization. This was corroborated later by the Agency's cardiac team (reviewed by Moh Jee Ng on August 9, 2014) and it was communicated to the Applicant on August 25, 2014, that electrocardiogram (ECG) monitoring would not be required in the phase 3 trials as part of the safety assessment.

On October 8, 2014, the Applicant submitted two protocols, RD.06.SPR.18251 and RD.06.18252 for special protocol assessment. These were two identical protocols entitled, "A Multi-Center, Randomized, Double-Blind, Parallel-Group Vehicle Controlled Study to Compare the Efficacy and Safety of CD5789 50 µg/g Cream Versus Vehicle Cream in Subjects With Acne Vulgaris."

The Applicant submitted its initial pediatric study plan (iPSP) on June 5, 2014, and agreed iPSP on October 7, 2014. The Applicant requested a partial waiver of assessments in pediatric subjects from birth to less than 9 years of age because "studies are highly impracticable." The agreed iPSP-agreement letter was sent on October 27, 2014. The sponsor submitted an amendment to the agreed iPSP on April 13, 2017. In this amendment the key issue was the use of PBPK modeling to simulate systemic exposure in subjects 9 to 11 years of age. An agreement letter was sent for the amended iPSP on June 13, 2017.

On November 13, 2014, two special protocol assessment agreement letters were sent to the Applicant. The Agency agreed that the design and planned analysis of the trials were adequate to address the objectives necessary to support a regulatory submission. In this assessment letter, the Agency agreed with the following:

- Three endpoints for facial acne will be co-primary endpoints that all must demonstrate statistical significance at two-sided 5%.
- Inclusion criteria for truncal acne.
- Proposed co-secondary endpoints: the percentage of subjects who achieve a PGA score of 1 (almost clear) or 0 (clear) and at least a two-grade improvement from baseline to Week 12 and absolute change in truncal inflammatory lesion count from baseline to Week 12.
- All subjects who meet the criteria for truncal acne at baseline will be assessed for local tolerability regardless of age.
- Proposed IGA/PGA scales.
- Proposed sample size of 1,500 subjects.

- Proposal to enroll a minimum of eight subjects per center at approximately 70/95 centers for Studies 18251/18252 respectively and the proposal to pool the smallest center with fewer than eight subjects with the largest center with fewer than eight subjects (within a country) and continuing until all centers have a minimum of eight subjects.
- PK analysis of subjects 9 to 11 years could be collected in the long-term safety trial.
- EGG monitoring was not necessary in the phase 3 trials.

On April 4, 2018, a pre-NDA meeting was held. At the meeting, the Agency agreed with the Applicant that the following studies were sufficient to support the filing of the NDA:

- Five dermal safety phase 1 studies to assess the 21-day cumulative irritation (Studies 40055E and 40209), sensitization (Study 40190), phototoxicity (Study 40208), and photosensitization (Study 40189) potential of trifarotene cream in healthy volunteers
- One phase 1 pharmacokinetic study to assess the linearity of trifarotene PK profile over potential therapeutic doses in healthy volunteers (Study 40128)
- One QT/QTc study to evaluate the effect of trifarotene on ventricular repolarization under supratherapeutic conditions (Study 40196)
- One drug-drug interaction phase 1 study to assess the ability of trifarotene to interfere with systemic levels of hormonal contraception in female healthy volunteers (Study 103918)
- One phase 2b, dose-range study to assess the efficacy and safety of different concentrations of trifarotene cream, tazarotene 0.1% gel compared with vehicle cream in subjects with moderate and severe acne vulgaris (Study 18223)
- Two PK maximal usage trials (MUsTs) to characterize the PK profile of trifarotene under maximal use conditions in 9- to 17-year-old pediatric subjects with acne and adult subjects with acne (Studies 18237 and 40182).
- Two phase 3 independent, well-controlled, pivotal studies (Studies 18251 and 18252) to assess the efficacy and safety of trifarotene 50 µg/g cream compared with vehicle cream (12-week study duration)
- One long-term (52-week study duration) open-label safety study in patients 9 years of age and older with moderate facial and truncal acne vulgaris (Study 18250)

The sponsor was advised that the container closure system of their product met the regulatory definition of a device and therefore would be considered a device constituent of the combination product. The sponsor was advised of avenues they could take if they wanted to dispute this combination product designation.

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

4.1. Office of Scientific Investigations

Site investigations through the Office of Scientific Investigations (OSI) were conducted by Cheryl Grandinetti, Pharm.D. Four sites were chosen to be inspected based on numbers of enrolled subjects, site efficacy, active complaints for associated INDs, and prior inspectional history. Table 5 delineates the clinical inspection summary.

Table 5. Clinical Inspection Summary

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification	Inspection Dates
Site #8580: Kyle Coleman, MD Etre Cosmetic Dermatology & Laser Center 1224 St. Charles Ave., Suite C8, New Orleans, LA 70130	RD.06.SPR.18251	20	VAI*	3/18/2019 to 3/20/2019
Site #8592: Nestor Sanches, MD Hospital General Menonita de Aibonito Jose C Vasquez St. Professional Bldg., Suite 304, Aibonito, PR 00705	RD.06.SPR.18251	32	NAI#	2/25/2019 to 2/27/2019
Site #8447: Sandy Johnson, MD Johnson Dermatology 5921 Riley Park Dr., Fort Smith, AR 72916	RD.06.SPR.18252	30	NAI#	1/28/2019 to 1/31/2019
Site #5532: Lajos Kemeny, MD University of Szeged Albert Szent-Gyorgyi Clinical Center Dept. of Dermatology and Allergology Koranyi Fasor 6-8 H-6720 Szeged, Hungary	RD.06.SPR.18252	55	VAI*	2/18/2019 to 2/22/2019

Source: OSI Review: Section III, Results in DARRTs dated 4/18/19
* No deviation from regulations
# VAI+deviation(s) from regulations
Abbreviations: NAI = no action indicated; VAI = voluntary action indicated

The overall conclusion from the OSI review was the following: "Despite minor drug accountability issues at the clinical site of Dr Coleman and minor discrepancies between the source data and the data listings provided by the sponsor for the primary and secondary efficacy endpoint data that occurred at the clinical sites of Drs Johnson and Kemeny, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of Drs. Sanchez and Johnson was No Action Indicated (NAI). The final classification of the inspection of Drs Coleman and Kemeny was Voluntary Action Indicated (VAI)."[3]

[3] OSI Review: Section 1, p. 1, DARRTs-4/18/2019

Dr Coleman's VAI rating was due to inadequate and inaccurate drug accountability records for 6 of the 20 subjects. After he responded to the inquiry, it was found that subjects did receive the correct treatment per their randomization assignment and no drug dispensing errors occurred. The discrepancies appeared to be due to inconsistent procedures for processing and documenting subject investigational product receipt and returns.

Dr Coleman's VAI rating was due to discrepancies involving the primary and secondary efficacy endpoints for five subjects, one on trial drug and four on vehicle. Only the subject on trial drug had missing data for Week 12, the primary and secondary efficacy time point for efficacy evaluation. As this was only one subject, this would not have an impact on the overall results of the trial. For all four sites, no under-reporting of adverse events (AEs) was found. Thus, in conclusion, the results of the inspection of these sites found that the quality of the clinical information in this application is adequate to support the proposed indication. The final NAI letter was sent to the Applicant on May 9, 2019, stating that they did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

4.2. Product Quality

Summary and Recommendation

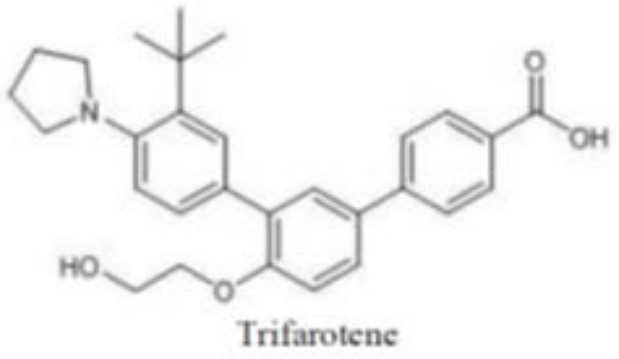
- The Applicant of this 505(b)(1) NDA has provided sufficient chemistry, manufacturing, and controls information to assure the identity, purity, strength, and quality of the drug substance and drug product.
- All labels/labeling issues have been satisfactorily resolved.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for approval with the drug product expiration dating period of 36 months.

Drug Substance

AKLIEF (trifarotene) Cream, 0.005% contains 50 µg of the drug substance, trifarotene, per each gram of the cream formulation. Trifarotene is a terphenyl acid derivative and is a retinoid. Trifarotene has not been previously approved an active ingredient in any marketed drug product and therefore, it is classified as a new molecular entity. The chemical name for trifarotene is 3"-tert-Butyl-4'-(2-hydroxy-ethoxy)-4"-pyrrolidin-1-yl-[1,1',3',1"]terphenyl-4-carboxylic acid. It has the chemical formula of $C_{29}H_{33}NO_4$, the molecular weight of 459.59, and the chemical structure shown in Figure 1.

Figure 1. Chemical Structure of Trifarotene



Trifarotene is manufactured [(b) (4)] in accordance to cGMP requirements and is tested against an adequate specification that assures identity, strength, purity, and quality of drug substance at release and throughout its proposed retest date of [(b) (4)] months. Information regarding the manufacture of trifarotene produced [(b) (4)] [(b) (4)] is provided in DMF [(b) (4)] which has been reviewed and found to be adequate to support this new drug application.

Drug Product

AKLIEF (trifarotene) Cream, 0.005% is produced as a light cream for topical administration to the face and/or trunk for the treatment of acne vulgaris in patients 9 years of age or older.

Each gram of AKLIEF contains 50 µg of the active ingredient, trifarotene, and the following excipients: propylene glycol, allantoin, medium-chain triglycerides, phenoxyethanol, cyclomethicone, and copolymer of acrylamide and sodium acryloyldimethyltaurate ethanol, and purified water. The inactive ingredients used in the composition of AKLIEF Cream are all compendial excipients with exception of the copolymer of acrylamide and sodium acryloyldimethyltaurate which are dispersed in 40% isohexadecane. However, these noncompendial excipients have been previously approved [(b) (4)] in the composition of the currently marketed drug product, Epiduo® Gel.

This drug product is manufactured [(b) (4)] in accordance to cGMP requirements. The manufacturing process for AKLIEF consists of [(b) (4)] The cream formulation is filled as [(b) (4)] 30 g, 45 g, and 75 g drug product into [(b) (4)] /high-density polyethylene [(b) (4)] bottles with white [(b) (4)] pumps and white [(b) (4)] overcaps. [(b) (4)] The use of the proposed container closure systems is supported by results from extractables/leachables and stability studies.

AKLIEF Cream is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for the assurance of the identity, strength, purity, and quality of the drug product throughout its proposed shelf-life of 36 months.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Trifarotene is a retinoid, i.e., an agonist of retinoic acid receptors (RARs). RARs are intracellular proteins that, in conjunction with a ligand, bind to DNA and influence expression of certain genes. Retinoids mediate a number of effects, including modulation of organogenesis, cell turnover rate, cell differentiation, and apoptosis. The exact mechanism by which trifarotene may ameliorate acne vulgaris when topically applied is unknown.

Formulations containing trifarotene in the vehicle of the clinical formulation at concentrations up to 0.01% were topically applied to 10% of the body surface area (BSA) of minipigs once daily for 39 weeks (0.25 mL/kg/day). Treatment was well tolerated; treatment-related effects were limited to erythema at the application site. There were no effects of treatment on survival, clinical pathology, or histopathology (with the exception of minimal evidence of irritation/inflammation at the treatment site).

Trifarotene was orally administered to rats for 26 weeks at dosages of 0, 0.1, 0.5, 1.25 mg/kg/day in males, and 0, 0.05, 0.2, 0.5 mg/kg/day in females. One high-dose (HD) group female was sacrificed on Day 127 of treatment due the presence of numerous scabs and sores on the neck and back. These sores were likely treatment-related, but likely would not have directly resulted in mortality. There were no other unscheduled deaths. Mean body weight (BW) at termination of dosing, and mean BW change over the period of dosing, were significantly lower in HD group males and females, compared to controls. There were no treatment-related effects on hematology or blood chemistry. Treatment-related histological observations primarily occurred in the stifle joint (minimal to slight disorganization/closure of the tibial growth plate) and stomach (minimal hyperplasia and hyperkeratosis of the epithelium). Dosages of 0.5 mg/kg/day in males and 0.2 mg/kg/day in females were established as no adverse effect levels (NOAELs); comparison of area under the 24-hour concentration time-curve ($AUC_{0\text{-}24h}$) values at these dosages to the maximum observed clinical AUC provides safety margins of 600-fold and 1877-fold in males and females, respectively.

Trifarotene was orally administered to dogs for 39 weeks at dosages of 0, 0.02, 0.06, and 0.18 mg/kg/day in both sexes. Trifarotene was well tolerated at all dosages that were evaluated. There were no treatment-related effects on survival, ECG/cardiovascular parameters, clinical pathology parameters, or mean organ weights. Treatment-related effects included observations of redness of the skin and the buccal and ocular mucous membranes, ear secretion, and trends toward reductions in mean BW gain values in males at 0.18 mg/kg/day and in females at ≥0.06 mg/kg/day. Treatment-related histopathological lesions were limited to the testes, epididymides, skin (head and abdomen), and ears, were of minimal to slight severity, occurred in a minority of animals, and were primarily observed in high-dose group animals. A dosage of

0.02 mg/kg/day was a low adverse effect level (LOAEL), approaching the level of being a NOAEL, in both sexes, and resulted in $AUC_{0\text{-}24h}$ values of 124 ng•h/mL in males and 166 ng•h/mL in females. Comparison of these values to the maximum observed clinical AUC suggests safety margins of more than 1000-fold in each sex.

Trifarotene was negative in a battery of genetic toxicology studies that included a bacterial reverse mutation (Ames) assay, a micronucleus assay in primary human lymphocytes, a mouse lymphoma assay with L5178Y/$TK^{+/-}$ cells, and an in vivo micronucleus assay in rats. This information will be included in the product labeling (Section 13).

Trifarotene was not carcinogenic when topically applied to mice daily for up to 24 months in the vehicle of the product (AKLIEF Cream) at concentrations of 0.0005% or 0.001% w/w. The systemic exposures at the highest doses evaluated in mice were approximately 82 (males) and 99 (females) times higher than the human exposure at the maximum recommended human dose (MRHD) of AKLIEF Cream. This information will be included in the product labeling (Section 13).

Trifarotene was not carcinogenic when orally administered to rats daily for up to 24 months at doses up to 0.75 mg/kg/day in males and 0.2 mg/kg/day in females. The systemic exposures at the highest doses evaluated in rats were approximately 645 (males) and 1642 (females) times higher than the human exposure at the MRHD of AKLIEF Cream. This information will be included in the product labeling (Section 13).

Trifarotene was evaluated for effects on fertility or reproductive performance in a study that involved administration by oral gavage to rats at dose levels of (males/females) 0/0 (controls), 0.1/0.05, 0.5/0.1, and 0.75/0.2 mg/kg/day. The males were treated for 4 weeks and the females for 2 weeks prior to pairing. Treatment then continued throughout mating and up to necropsy of the males or until Day 7 of gestation (inclusive) for the females. The males were sacrificed after approximately 8 weeks of treatment and subjected to necropsy. The testes and epididymides were weighed and sperm analysis was performed. The inseminated females were subjected to C-section on Day 13 of gestation. No effects of treatment were observed in any group, including no unscheduled deaths, treatment-related clinical signs, effects on mean body weight gain, food consumption, mating performance, fertility, observations during gross necropsy, sperm motility or count, or embryo survival. The NOAEL for gonadal function, mating behavior and reproductive performance in the male was 0.75 mg/kg/day, and the NOAEL for gonadal function, mating behavior, reproductive performance and early gestation in the female was 0.2 mg/kg/day (the highest dosages evaluated). These dosages resulted in estimated $AUC_{0\text{-}24h}$ values of 186 ng•h/mL in males and 183 ng•h/mL in females. Comparison of these values to the maximum observed clinical AUC suggests safety margins of more than 1700-fold in each gender. This information will be included in the product labeling (Section 13).

Trifarotene was evaluated for effects on embryofetal development in a study that involved administration by oral gavage to female rats on days 6 to 17 of gestation at dosages of 0, 0.03, 0.1, 0.3, and 1 mg/kg/day. There were no effects on survival. Mean BW change over days 6 to 18 was significantly reduced at both 0.3 and 1 mg/kg/day. At 1 mg/kg/day, treatment-related effects observed during C-section included reduced fetal survival due to increased incidence of both early and late resorptions and reduced mean fetal weight. All fetuses from the 1 mg/kg/day group exhibited external abnormalities; observations included a short jaw with protruding tongue, reduced eye bulge, exencephaly, malformed limbs (hemimelia/micromelia), spina bifida, anal atresia, and acaudia. Similar (but less severe) external malformations were noted in fetuses from the 0.3 mg/kg/day group. No external malformations were observed in offspring of animals treated at 0.1 mg/kg/day or less.

All examined fetuses from the 1 mg/kg/day group were found to have multiple abnormalities of the viscera, including abnormalities of the urogenital organs, malpositioned testes, marked dilation of the renal pelvis and/or ureters, and a malformed brain (associated with exencephaly). The majority of these fetuses also had eye abnormalities and a cleft palate. Similar (but less severe) visceral malformations were noted in fetuses from the 0.3 mg/kg/day group. No visceral malformations were observed in offspring of animals treated at 0.1 mg/kg/day or less.

All examined fetuses from the 1 mg/kg/day group had a generalized gross disruption of the skeleton, and the majority of fetuses from the 0.3 mg/kg/day group exhibited skeletal malformations, including defects of the mandible, pectoral girdle, pelvis, and limbs. Acrania was also noted. Treatment at 0.3 mg/kg/day was associated with increased incidences of less severe skeletal anomalies and variations, including reduced ossification of many areas. Other skeletal disturbances including a paradoxical advance in ossification in a few areas, fused vertebrae, and rudimentary/extra 14th rib(s) were noted. Treatment-related increased incidences of less severe skeletal anomalies and variations were noted at 0.1 mg/kg/day. 0.1 mg/kg/day ($AUC_{0\text{-}24h}$ of 172 ng•h/mL) was an apparent NOAEL for maternal toxicity, while 0.03 mg/kg/day ($AUC_{0\text{-}24h}$ of 57 ng•h/mL) was regarded to be a NOAEL for fetal effects. Comparison of these values to the maximum observed clinical AUC suggests safety margins on the order of 1622-fold and 538-fold, respectively. This information will be included in the product labeling (Section 8).

Trifarotene was evaluated for effects on embryofetal development in a study that involved administration by oral gavage to female rabbits on days 6 to 19 of gestation at dosages of 0, 0.5, and 5 mg/kg/day. An additional dosage, 50 mg/kg/day, similarly administered, was not tolerated and dosing of that treatment group was stopped. No evidence of maternal toxicity was observed in animals dosed at 5 mg/kg/day or less, including no treatment-related effects on maternal BW, feed consumption, or gross necropsy or C-section parameters. A dosage of 5 mg/kg/day affected fetal morphology, including increased incidence of defects of the tail, limbs, urogenital organs, and vertebral column. There were no apparent treatment-related fetal effects at 0.5 mg/kg/day. 5 mg/kg/day ($AUC_{0\text{-}24h}$ of 84.8 ng•h/mL) was an apparent NOAEL for

maternal toxicity, while 0.5 mg/kg/day ($AUC_{0\text{-}24h}$ of 10.4 ng•h/mL) was regarded to be a NOAEL for fetal effects. Comparison of these values to the maximum observed clinical AUC suggests safety margins on the order of 800-fold and 98-fold, respectively. This information will be included in the product labeling (Section 8).

Trifarotene was evaluated for effects on prenatal and postnatal development, including maternal function, in a study that involved administration by oral gavage to female rats from Day 6 of gestation until Day 20 of lactation, at dosages of 0, 0.01, 0.03, and 0.1 mg/kg/day. There were no effects on any parameter assessed, including survival, clinical signs, body weight gain, physical or neurological development of pups, or reproductive function of pups. A dosage of 0.1 mg/kg/day was a NOAEL and resulted in an $AUC_{0\text{-}24h}$ value of 63 ng•h/mL; comparison of this value to the maximum observed clinical AUC establishes a safety margin of 594-fold. This information will be included in the product labeling (Section 8).

The available database acceptably addresses all nonclinical issues. No nonclinical postmarketing requirements are necessary. The nonclinical Pharmacology/Toxicology team recommends approval of NDA 211527 with respect to nonclinical concerns. Recommended labeling that concerns nonclinical data is presented in Section 18.3.1 of this review.

5.2. Referenced NDAs, BLAs, DMFs

IND 111091

5.3. Pharmacology

Primary Pharmacology

RARs are “nuclear” receptors, meaning that they are intracellular proteins that, in conjunction with a ligand, bind to DNA and influence gene expression. RARs have been divided into three primary subclasses, designated RAR-α, RAR-β, and RAR-γ. Retinoids are compounds that bind to and activate RARs; endogenous retinoids include all-trans retinoic acid and 9-cis retinoic acid. Retinoids mediate a number of effects, including modulation of organogenesis, cell turnover rate, cell differentiation, and apoptosis.

Trifarotene was assessed for agonistic activity at α, β, and γ-retinoic acid receptors, using a transactivation assay. EC_{50} (half maximal response) values of approximately 517, 126, and 7.6nM, respectively, were calculated. These data indicate that trifarotene is a potent agonist of RAR-γ-receptors, with less activity at RAR-α or RAR-β-receptors.

In cultured keratinocytes, trifarotene demonstrated potential to modulate retinoid target genes for keratinization, metabolism and adhesion at concentrations which were approximately 10 times lower than those for tazarotene and about 100 times lower than those for tretinoin.

Safety Pharmacology

CNS

In an Irwin assay, trifarotene induced dose-dependent sedative/myorelaxant effects associated with increased respiration at single intravenous doses between 2 and 32 mg/kg. Mortality was observed at doses of 32 and 64 mg/kg.

Cardiovascular

When orally administered to conscious dogs at dosages up to 2.5 mg/kg, resulting in mean plasma levels up to 614 ng/mL, trifarotene had no effects on arterial blood pressure, heart rate, or the ECG. In a hERG assay, trifarotene had no effect on I_{Kr} at concentrations up to 1µM. At 10µM (the highest concentration tested), trifarotene reduced the amplitude of I_{Kr} by -35.5±7.1%, versus -5.5±4.2% in the vehicle control group ($p<0.01$). It was concluded that the IC_{50} was greater than 10µM. These data suggest that trifarotene would not be arrhythmogenic under the proposed conditions of clinical use, which would involve low levels of systemic exposure.

Respiratory

Trifarotene, administered orally to conscious female rats at doses of 5, 15 and 45 mg/kg, had no apparent effects on respiratory function.

5.4. ADME/PK

Table 6. ADME/PK Results

Type of Study	Major Findings
Absorption	
Absorption, Distribution, Metabolism, and Excretion of CD5789 in the Wistar Rat After a Single Oral and Intravenous Dose, Study RDS.03.SPR31094	Absorption, distribution, metabolism, and excretion of [^{14}C]-trifarotene were evaluated in the Wistar rat following single oral and intravenous doses. T_{max} was reached 1 to 2 hours following oral dosing. Oral bioavailability was 41% in males and 34% in females. By either route, the plasma exposure to trifarotene was lower in males than in females, apparently due to a higher rate of metabolism in males compared to females. In the plasma, trifarotene was the major circulating radioactive constituent at all time points. Radioactivity tended to localize within the liver. Excretion was rapid and almost complete within 48 hours. Elimination occurred primarily within feces following either intravenous or oral administration. The parent compound was the major radioactive constituent in feces.
[^{14}C]-CD5789 Absorption, metabolism, and excretion in the Beagle dog following a single intravenous or oral administration, Study RDS.03.SRE.31095	Absorption, metabolism, and excretion of [^{14}C]-trifarotene were evaluated in Beagle dogs following single oral and intravenous doses. Oral bioavailability of trifarotene was 44%. Parent compound was the major circulating radioactive constituent in plasma. Excretion was almost complete within 48 hours, primarily as parent compound within feces. Eight metabolites were detected.
Distribution	
The Tissue Distribution of Total Radioactivity in the Rat Following Single Oral and Intravenous Administration of [^{14C}]-CD5789 (Quantitative Whole Body Autoradiography), Study RDS.03.SRE.102423	Tissue distribution of radioactivity was evaluated through quantitative whole body autoradiography following oral and intravenous administration of [^{14}C]-trifarotene to rats. [^{14}C]-trifarotene was widely distributed throughout the body of the rats, following both oral and intravenous administration. Highest levels of radioactivity were measured in the liver, kidney, preputial gland, adrenal cortex, and salivary gland, with the highest concentrations observed in the liver. The distribution to the brain and melanin-containing tissues was relatively low. Radioactivity was not detectable at 24 and 48 h postdose for males and females, respectively, in the majority of tissues.
In Vitro Determination of the Plasma Protein Binding of [^{14}C]-CD5789 in 6 Species, Study RDS.03.SPR.31089	Trifarotene was highly bound (>99%) to plasma proteins in all species tested, including mouse, rat, rabbit, dog, minipig, and human, over the concentration range evaluated (50 ng/mL to 1000 ng/mL).
The Secretion of Total Radioactivity in Milk Following Single Oral Administration of [^{14}C]-CD5789 in the Wistar Rat, Study 174296	Nursing female Wistar rats on Day 20 after parturition received a single oral dose of 0.1 mg/kg trifarotene, spiked with ^{14}C-trifarotene. At time points of 1, 2, 4, 8, and 24-hours postdosing, levels of unchanged trifarotene and total radioactivity in milk and plasma samples from dams and sucking pups were determined. The ratio of the concentration of radioactivity in milk to the concentration of radioactivity in plasma increased over the sampling period from 0.53 (1 h postdose) to 2.42 (8 h postdose). Concentrations of trifarotene in milk and maternal plasma were highest at 1 h postdose and remained above the lower limit of quantification (LOQ) until 24 h postdose. Concentrations of trifarotene and levels of total radioactivity in pup plasma were below the lower LOQ at each timepoint. These data indicate that trifarotene is excreted in milk of lactating rats following oral dosing.

Type of Study	Major Findings
Metabolism	
In Vitro Metabolism of [^{14}C]-CD5789 by Hamster, Mouse, Rat, Rabbit, Dog, Minipig, Monkey and Human Hepatocytes in Suspension, Study RDS.03.SPR.31107	Metabolism of ^{14}C-trifarotene was studied in vitro using suspended hepatocytes from Syrian hamster, CD1 mouse, Wistar rat, New Zealand White rabbit, Beagle dog, Gottingen minipig, Cynomolgus monkey and humans. Eighteen metabolites were detected in suspensions of human cells, eight of which represented 2% or more of the total radioactivity eluted. The primary human metabolites were subsequently designated CD06530 (accounting for 40% of total), CD09717 (12%), glucuro conjugate of CD06530 (10%), M5789-12, CD06700, and CD09986 (7% each), and M5789-01 and M5789-26 (2% each). Opening of the pyrrolidine ring and hydroxylation reactions are the main metabolic pathways observed, followed by ketone formation and glucuronic acid conjugation. The primary human metabolites were all formed at substantial levels in rats.
Bioanalytical and Toxicokinetic Evaluation of CD5789 Metabolites in Rat, Study RDS.03.SPR.4938	The toxicokinetic parameters of three major human trifarotene metabolites, CD06530, CD06700, and CD09986, were assessed in male and female Wistar rats following administration of trifarotene for 26 weeks, using plasma samples of rats treated at 0.5 mg/kg/day (males) and 0.2 mg/kg/day (females; these doses were the NOAELs in the 26-week repeated-dose toxicity study with rats (Study RDS.03.SPR.12863)). Sex-combined $AUC_{0\text{-}24h}$ values on Day 168 were: CD06530=5.4 ng•h/mL; CD06700=1.1 ng•h/mL; CD09986=30.2 ng•h/mL. Under conditions of enhanced clinical exposure (using a double-strength formulation under maximum exposure conditions), the maximum observed human exposure to CD06530 (the primary human metabolite) was 0.37 ng•h/mL (Trial RD.06.SRE.18237). Exposures to CD06700 and CD09986 were not calculable in humans. The available data adequately qualify the anticipated clinical exposures to metabolites.
Excretion	
Absorption, Distribution, Metabolism, and Excretion of CD5789 in the Wistar Rat After a Single Oral and Intravenous Dose, Study RDS.03.SPR31094	See above.

Type of Study	Major Findings
TK data from general toxicology studies	
CD5789 cream: 9-month topical (dermal application) toxicity study in the Göttingen minipig followed by a 4-week treatment-free period, Study RDS.03.SRE.12875	Minipig No animals exhibited quantifiable concentrations of trifarotene on Day 0. On Day 272 two animals that received 0.005% material (both female) and the majority of animals that received 0.01% material had plasma levels of trifarotene above the lower LOQ (0.05 ng/mL; individual concentrations ranged from 0.0501 to 0.307 ng/mL). Meaningful pharmacokinetic parameters could not be calculated from those data, but it may be concluded that systemic exposure to trifarotene was low under the conditions of this study.
CD5789: 26-week oral (gavage) toxicity study in the Wistar rat followed by a 6-week treatment-free period, Study RDS.03.SRE.12863	Rat (Day 168) @ NOAEL (Males: 0.5 mg/kg/day; females: 0.2 mg/kg/day) • Males C_{max}: 8.69 ng/mL AUC_{0-24h}: 63.7 ng•h/mL $t_{1/2}$: Not calculated • Females C_{max}: 20.6 ng/mL AUC_{0-24h}: 199 ng•h/mL $t_{1/2}$: Not calculated
CD5789: 39-week oral (gavage) toxicity study in the beagle dog followed by an 8-week treatment-free period, Study RDS.03.SRE.12864	Dog (Day 269) @ NOAEL (0.02 mg/kg/day for both sexes) • Males C_{max}: 15.6 ng/mL AUC_{0-24h}: 124 ng•h/mL $t_{1/2}$: Not calculated • Females C_{max}: 20.6 ng/mL AUC_{0-24h}: 166 ng•h/mL $t_{1/2}$: Not calculated
TK data from reproductive toxicology studies	
Fertility: CD5789: Fertility toxicity study by the oral route (gavage) in the rat (Segment I), Study RDS.03.SRE.12759	Rat @ NOAEL (Males: 0.75 mg/kg/day; females: 0.2 mg/kg/day) AUC_{0-24h}: 186 ng•h/mL and 183 ng•h/mL in males and females, respectively
Embryo/fetal development: CD5789: Embryo toxicity study by the oral route (gavage) in the rat (segment II), Study RDS.03.SRE.12521	Rat @ NOAEL 0.1 mg/kg/day (AUC_{0-24h} =172 ng•h/mL on Day 17) was an apparent NOAEL for maternal toxicity, while 0.03 mg/kg/day (AUC_{0-24h} =56.8 ng•h/mL on Day 17) is regarded to be a NOAEL for fetal effects
Embryo/fetal development: CD5789: Embryo toxicity study by the oral route (gavage) in the rabbit (segment II), Study RDS.03.SRE.12520	Rabbit @ NOAEL 5 mg/kg/day (AUC_{0-24h} =84.8 ng•h/mL on Day 19) was an apparent NOAEL for maternal toxicity, while 0.5 mg/kg/day (AUC_{0-24h} =10.4 ng•h/mL on Day 19) is regarded to be a NOAEL for fetal effects

Type of Study	Major Findings
Prenatal and postnatal development: CD5789: Pre and postnatal development study by the oral route (gavage) in the Wistar rat (segment III), Study RDS.03.SRE.12758	Rat @ NOAEL 0.1 mg/kg/day ($AUC_{0\text{-}24h}$ =63 ng•h/mL on postnatal Day 20) was an apparent NOAEL
TK data from carcinogenicity studies	
CD5789 cream: 104-week dermal carcinogenicity study in the CD1 mouse, Study AB02557, Study RDS.03.SRE.12847	Mouse @ Highest Dose Tested (0.001% cream) $AUC_{0\text{-}24h}$: 8.64 ng•h/mL and 10.5 ng•h/mL in males and females, respectively
CD5789: 104-week oral (gavage) carcinogenicity study in the Wistar rat, Study AB02556, study report no. RDS.03.SRE.12846	Rat @ Highest Dose Tested (Males: 0.75 mg/kg/day; females: 0.2 mg/kg/day) $AUC_{0\text{-}24h}$: 68.4 ng•h/mL and 174 ng•h/mL in males and females, respectively

5.5. Toxicology

5.5.1. General Toxicology

CD5789 Cream: 9-Month Topical (Dermal Application) Toxicity Study in the Göttingen Minipig Followed by a 4-Week Treatment-Free Period, Study RDS.03.SRE.12875

Treatment was well tolerated; treatment-related effects were limited to erythema at the application site. There were no effects of treatment on survival, clinical pathology, or histopathology (with the exception of minimal evidence of irritation/inflammation at the treatment site).

Conducting laboratory and location: (b) (4)

Good laboratory practice (GLP) compliance: Yes

Table 7. Methods for CD5789 Cream: 9-Month Topical (Dermal Application) Toxicity Study in the Göttingen Minipig Followed by a 4-Week Treatment-Free Period, Study RDS.03.SRE.12875

Method	
Dose and frequency of dosing	Formulations containing 0% (vehicle), 0.001%, 0.005%, and 0.01% trifarotene, applied once daily at a rate of 0.25 mL/kg/day on approximately 273 consecutive days. This resulted in nominal exposures of 0, 2.5, 12.5, and 25 µg/kg/day, although it is unclear what portion of each applied dose was subsequently removed when the site was cleansed following each 6-hour treatment period.
Route of administration	Topical to skin (10% of BSA)
Formulation/vehicle	Each formulation utilized the vehicle of the commercial product.
Species/strain	Minipig/Gottiningen
Number/sex/group	4
Age	Approx. 3 to 4 months at initiation of dosing
Satellite groups/ unique design	Yes; 2/sex in control and high-dose groups allowed to “recover” 4 weeks following treatment
Deviation from study protocol affecting interpretation of results	No

Table 8. Observations and Results, Changes From Control for CD5789 Cream: 9-Month Topical (Dermal Application) Toxicity Study in the Göttingen Minipig Followed by a 4-Week Treatment-Free Period, Study RDS.03.SRE.12875

Parameter	Major Findings
Mortality	No treatment-related deaths
Clinical signs	No systemic clinical signs which were related to treatment. A dose-related very slight to severe erythema was observed at the application sites
Body weights	No treatment-related effects
Ophthalmoscopy	No treatment-related effects
ECG	No treatment-related effects
Hematology	No treatment-related effects
Clinical chemistry	No treatment-related effects
Urinalysis	No treatment-related effects
Gross pathology	No treatment-related effects
Organ weights	No treatment-related effects

Parameter	Major Findings
Histopathology Adequate battery: Yes	Observations that were considered to be related to treatment were limited to skin at the application site, were graded as minimal to slight, and were described as "acanthosis with spongiosis (increased intercellular fluid), parakeratosis, crusts and dermal mononucleated inflammatory infiltrates." These observations were essentially limited to females at ≥0.005% and males at 0.01%. These minor lesions reversed during a 4-week recovery period.

5.5.2. General Toxicology; Additional Studies

CD5789: 26-Week Oral (Gavage) Toxicity Study in the Wistar Rat Followed by a 6-Week Treatment-Free Period, Study RDS.03.SRE.12863

Wistar rats received oral doses of trifarotene for 26 weeks at dosages of 0, 0.1, 0.5, 1.25 mg/kg/day in males, and 0, 0.05, 0.2, 0.5 mg/kg/day in females.

- One high-dose (HD) group female was sacrificed on Day 127 of treatment due to the presence of numerous scabs and sores on the neck and back. These sores were likely treatment-related, but likely would not have directly resulted in mortality. There were no other unscheduled deaths.
- Mean BW at termination of dosing, and mean BW change over the period of dosing, were significantly lower in HD group males and females, compared to controls.
- There were no treatment-related effects on hematology or blood chemistry.
- Treatment-related histological observations primarily occurred in the stifle joint (minimal to slight disorganization/closure of the tibial growth plate) and stomach (minimal hyperplasia and hyperkeratosis of the epithelium). Minor epithelial hyperplasia of the skin of the head was observed in HD group females.
- The NOAEL in males approximated 0.5 mg/kg/day (C_{max} =8.69 ng/mL, AUC_{0-24h} =63.7 ng•h/mL); the NOAEL in females approximated 0.2 mg/kg/day (C_{max} =20.6 ng/mL, AUC_{0-24h} =199 ng•h/mL).

CD5789: 39-Week Oral (Gavage) Toxicity Study in the Beagle Dog Followed by an 8-Week Treatment-Free Period, Study RDS.03.SRE.12864

Beagle dogs received oral doses of trifarotene for 39 weeks at dosages of 0, 0.02, 0.06, and 0.18 mg/kg/day in both sexes.

- Trifarotene was reasonably well tolerated at all dosages that were evaluated.
- There were no treatment-related effects on survival, ECG/cardiovascular parameters, clinical pathology parameters, or mean organ weights.
- Treatment-related effects included observations of redness of the skin and the buccal and ocular mucous membrane, ear secretion, and reductions in mean BW gain values in males at 0.18 mg/kg/day and in females at ≥0.06 mg/kg/day.
- Treatment-related histopathological lesions were limited to the testes, epididymides, skin (head and abdomen), and ears, were of minimal to slight severity, occurred in a minority of animals, and were primarily observed in high-dose group animals.

- A dosage of 0.02 mg/kg/day approximated a NOAEL in both sexes and resulted in mean C_{max} and $AUC_{0\text{-}24h}$ values of 15.6 ng/mL and 124 ng•h/mL in males, and 20.6 ng/mL and 166 ng•h/mL in females.

5.5.3. Genetic Toxicology

5.5.3.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

CD5789: Reverse Mutation in Five Histidine-Requiring Strains of *salmonella typhimurium*, Study RDS.03.SRE.12526

Key study findings:

- Trifarotene was negative in an Ames assay, either with or without metabolic activation.
- These data suggest trifarotene is not mutagenic.

GLP compliance: Yes

Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA102

Study is valid: Yes

5.5.3.2. In Vitro Assays in Mammalian Cells

CD5789: Induction of Micronuclei in Cultured Human Peripheral Blood Lymphocytes, Study RDS.03.SRE.12522

Key study findings:

- Trifarotene did not induce relevant increases in micronuclei in cultured human peripheral blood lymphocytes following treatment in the absence and presence of a rat liver metabolic activation system (S-9).
- These data suggest trifarotene is not clastogenic.

GLP compliance: Yes

Test system: Blood from two healthy, nonsmoking male volunteers.

Study is valid: Yes

CD5789: Mutation at the Thymidine Kinase (TK) Locus of Mouse Lymphoma L5178Y Cells Using the Microtitre® Fluctuation Technique, Study RDS.03.SRE.12523

Key study findings:

- Trifarotene did not demonstrate mutagenic potential in an in vitro mutation assay with mammalian cells (mouse lymphoma assay with L5178Y cells), with or without metabolic activation.
- These data suggest trifarotene is not mutagenic.

GLP compliance: Yes

Test system: Mouse lymphoma L5178Y cells.

Study is valid: Yes

5.5.3.3. In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Induction of Micronuclei in the Bone Marrow of Treated Rats, Study RDS.03.SRE.12600

Key study findings:

- Trifarotene was not clastogenic in an in vivo rodent (micronucleus) assay.

GLP compliance: Yes

Test system: Sprague-Dawley rats dosed intravenously twice at a 24 hour interval at doses up to 15 mg/kg/day.

Study is valid: Yes

5.5.4. Carcinogenicity

CD5789 Cream: 104-Week Dermal Carcinogenicity Study in the CD1 Mouse, Study AB02557, Study Report No. RDS.03.SRE.12847

Groups of CD-1 mice were treated topically with formulations containing trifarotene in the vehicle of the clinical formulation at concentrations of 0.0005% or 0.001% w/w once daily at a volume of 2 mL/kg/dose to 10% of the BSA, 7 days per week for approximately 2 years, in both males and females. The study initially involved more concentrated formulations as well, but those formulations were not acceptably tolerated. The vehicle contained water, propylene glycol, allantoin, medium-chain triglycerides, phenoxyethanol, cyclomethicone, (b) (4) (b) (4) and ethanol. Control groups included a negative control group that received topical application of water, and a vehicle control group. The key finding of this study was that topical exposure of mice to trifarotene for a lifetime did not result in a significantly increased incidence of tumors in either males or females.

CD5789: 104-Week Oral (Gavage) Carcinogenicity Study in the Wistar Rat, Study AB02556, Study Report No. RDS.03.SRE.12846

Groups of Wistar Han rats received oral doses of trifarotene once daily, 7 days per week for approximately 2 years, at dosages of 0, 0.1, 0.3, 0.75 mg/kg/day in males and 0, 0.05, 0.1, 0.2 mg/kg/day in females. The vehicle used consisted of 0.5% carboxymethyl cellulose and 0.1% Tween 80 in water. The key finding of this study was that oral exposure of rats to trifarotene for a lifetime did not result in a significantly increased incidence of tumors in either males or females.

See Appendix 18.3.2 for additional information concerning the carcinogenicity studies that were conducted with trifarotene.

5.5.5. Reproductive and Developmental Toxicology

5.5.5.1. Fertility and Early Embryonic Development

CD5789: Fertility Toxicity Study by the Oral Route (Gavage) in the Rat (Segment I), Study RDS.03.SRE.12759

Key study findings:

- No effects of treatment were observed in any group, including no unscheduled deaths, treatment-related clinical signs, effects on mean body weight gain, food consumption, mating performance, fertility, observations during gross necropsy, sperm motility or count, or embryo survival.
- The NOAEL for gonadal function, mating behavior and reproductive performance in the male was 0.75 mg/kg/day and the NOAEL for gonadal function, mating behavior, reproductive performance and early gestation in the female was 0.2 mg/kg/day (the highest dosages evaluated).
- Although TK data were not obtained in this study, data obtained in Study RDS.03.SRE.12650 (CD5789: 13-week oral (gavage) toxicity study in the Wistar rat followed by a 4-week recovery period) indicate that oral doses of 0.75 mg/kg/day in males, and 0.2 mg/kg/day in females, yield $AUC_{0\text{-}24h}$ values of 186 ng•h/mL and 183 ng•h/mL, respectively.
- Although no toxicity was observed, this study is considered to have adequately challenged the test system, since the systemic exposures achieved were greater than 1700 times the maximum systemic exposure observed during clinical use of the product (maximum observed clinical $AUC_{0\text{-}24h}$ =0.106 ng•h/mL).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 9. Methods for CD5789: Fertility Toxicity Study by the Oral Route (Gavage) in the Rat (Segment I), Study RDS.03.SRE.12759

Method	
Dose and frequency of dosing	Doses of (males/females) 0/0 (controls), 0.1/0.05, 0.5/0.1, and 0.75/0.2 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	Suspension/0.5% w/v carboxymethylcellulose and 0.1% Tween 80 in water
Species/strain	Rat/Wistar
Number/sex/group	20
Satellite groups	None

Method	
Study design	Males were treated 28 days before mating, throughout mating and until the day before necropsy. Females were treated 14 days before mating, throughout mating and until Day 7 of gestation (inclusive). Animals were paired on the basis of one male and one female from the same group for a maximum of 21 days. The day of mating, confirmed by vaginal smear or presence of a plug, was taken as Day 0 of gestation (G0). Males were sacrificed after approximately 8 weeks of treatment; the testes and epididymides were weighed and an automated sperm analysis was performed. F0 females were subjected to C-section on Day 13 of gestation, and ovary, uterine, and litter parameters were recorded.
Deviation from study protocol affecting interpretation of results	No

Table 10. Observations and Results for CD5789: Fertility Toxicity Study by the Oral Route (Gavage) in the Rat (Segment I), Study RDS.03.SRE.12759

Parameter	Major Findings
Mortality	No unscheduled deaths
Clinical signs	No treatment-related effects
Body weights	No treatment-related effects
Necropsy findings	No treatment-related effects on mating performance or fertility in any group No treatment-related effects on sperm motility or count No treatment-related effects on C-section parameters

5.5.5.2. Embryo-Fetal Development

CD5789: Embryo Toxicity Study by the Oral Route (Gavage) in the Rat (Segment II), Study RDS.03.SRE.12521

Key study findings:

- There were no effects on maternal survival. Dosing at 1 mg/kg/day resulted in reduced mean body weight at termination (Day 20). Mean BW change over days 6 to 18 was significantly reduced at both 0.3 and 1 mg/kg/day.
- At 1 mg/kg/day, treatment-related effects included reduced fetal survival due to increased incidence of both early and late resorptions and reduced mean fetal weight.
- Fetuses from the 0.3 and 1 mg/kg/day groups exhibited substantial external, visceral, and skeletal abnormalities, in relation to dosage. No external or visceral malformations were observed in offspring of animals treated at 0.1 mg/kg/day or less.
- Treatment-related increased incidences of less severe skeletal anomalies and variations were noted at 0.1 mg/kg/day. No toxicologically meaningful effects on skeletal development were observed at 0.03 mg/kg/day.
- 0.1 mg/kg/day ($AUC_{0\text{-}24h}$ =172 ng•h/mL on Day 17) was an apparent NOAEL for maternal toxicity, while 0.03 mg/kg/day ($AUC_{0\text{-}24h}$ =56.8 ng•h/mL on Day 17) was regarded to be a NOAEL for fetal effects.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 11. Methods for CD5789: Embryo Toxicity Study by the Oral Route (Gavage) in the Rat (Segment II), Study RDS.03.SRE.12521

Method	
Dose and frequency of dosing	0, 0.03, 0.1, 0.3, and 1 mg/kg/day, once daily, on days 6 to 17, inclusive, of gestation
Route of administration	Oral gavage
Formulation/vehicle	Suspension/0.5% (w/v) carboxymethylcellulose and 0.1% (w/v) Tween 80 in water for injection
Species/strain	Rat/Sprague-Dawley
Number/sex/group	25 (only females were dosed); F0 females were 10 to 13 weeks old on gestation Day 0, and weighed approximately 200 g
Satellite groups	Yes, six females per group used for TK analysis
Study design	Gestation Day 0 was considered to be the day of confirmed mating. F0 females euthanized and C-sectioned on Day 20 postmating. Fetuses were examined for external, visceral, and skeletal effects
Deviation from study protocol affecting interpretation of results	No

Table 12. Observations and Results for CD5789: Embryo Toxicity Study by the Oral Route (Gavage) in the Rat (Segment II), Study RDS.03.SRE.12521

Parameter	**Major Findings**
Mortality	No unscheduled deaths of F0 animals.
Clinical signs	Four F0 females at 1 mg/kg/day exhibited red/black vaginal discharge on 1 to 3 days between days 15 and 20 of gestation; this may have been associated with fetal resorption. No other remarkable observations.
Body weights	Mean BW was significantly reduced at 1 mg/kg/day in comparison to control from Day 11 to termination (305.0±19.8 versus 384.2±35.0 on Day 20, $p<0.01$); no statistically significant differences were apparent at 0.3 mg/kg/day or below. Mean body weight gain was significantly reduced over selected intervals at 0.3 and 1 mg/kg/day, including the period of dosing (comparing 1 mg/kg/day group to control, mean values of 36.7±12.3 and 96.1±16.2 were observed over days 6 to 18, $p<0.01$).
Necropsy findings C-section data	Mean weight of the gravid uterus was significantly reduced at 1 mg/kg/day (28.8±14.3 g compared to 72.3±23.7 g in controls, $p<0.01$); no significant differences at 0.3 mg/kg/day or below. At 1 mg/kg/day, treatment-related effects included reduced fetal survival (increased postimplantation loss) due to increased incidence of both early and late resorptions and reduced mean fetal weight.

Parameter	Major Findings
Necropsy findings Offspring	All fetuses from the 1 mg/kg/day group exhibited external abnormalities; observations included a short jaw with protruding tongue, reduced eye bulge, exencephaly, malformed limbs (hemimelia/micromelia), spina bifida, anal atresia and acaudia. Similar (but less severe) external malformations were noted in fetuses from the 0.3 mg/kg/day group. No external malformations were observed in offspring of animals treated at 0.1 mg/kg/day or less. All examined fetuses from the 1 mg/kg/day group were found to have multiple abnormalities of the viscera, including abnormalities of the urogenital organs, malpositioned testes, marked dilation of the renal pelvis and/or ureters, and a malformed brain (associated with exencephaly). The majority of these fetuses also had eye abnormalities and a cleft palate. Similar (but less severe) visceral malformations were noted in fetuses from the 0.3 mg/kg/day group. No visceral malformations were observed in offspring of animals treated at 0.1 mg/kg/day or less. All examined fetuses from the 1 mg/kg/day group had a generalized gross disruption of the skeleton, and the majority of fetuses from the 0.3 mg/kg/day group exhibited skeletal malformations, including defects of the mandible, pectoral girdle, pelvis, and limbs. Acrania was also noted. Treatment at 0.3 mg/kg/day was also associated with increased incidences of less severe skeletal anomalies and variations, including reduced ossification of many areas. Treatment-related increased incidences of less severe skeletal anomalies and variations were noted at 0.1 mg/kg/day. Although treatment at 0.03 mg/kg/day was associated with increased incidences of unilateral or bilateral rudimentary 14th ribs and incomplete ossification of the 6th sternebra, these minor effects were not considered to be of substantial toxicological significance.

CD5789: Embryo Toxicity Study by the Oral Route (Gavage) in the Rabbit (Segment II), Study RDS.03.SRE.12520

Key study findings:

- There were no unscheduled deaths of F0 animals at 5 mg/kg/day or less.
- No evidence of maternal toxicity was observed in animals dosed at 5 mg/kg/day or less, including no treatment-related effects on maternal BW, feed consumption, or gross necropsy or C-section parameters.
- A dosage of 5 mg/kg/day affected fetal morphology, including increased incidence of defects of the tail, limbs, urogenital organs, and vertebral column.
- There were no apparent treatment-related fetal effects at 0.5 mg/kg/day.
- 5 mg/kg/day ($AUC_{0\text{-}24h}$ =84.8 ng•h/mL on Day 19) was an apparent NOAEL for maternal toxicity, while 0.5 mg/kg/day ($AUC_{0\text{-}24h}$ =10.4 ng•h/mL on Day 19) was regarded to be a NOAEL for fetal effects.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 13. Methods for CD5789: Embryo Toxicity Study by the Oral Route (Gavage) in the Rabbit (Segment II), Study RDS.03.SRE.12520

Method	
Dose and frequency of dosing	0, 0.5, 5, and 50 mg/kg/day, once daily, on days 6 to 19, inclusive, of gestation
Route of administration	Oral gavage
Formulation/vehicle	Suspension/0.5% (w/v) carboxymethylcellulose and 0.1% (w/v) Tween 80 in water for injection
Species/strain	Rabbit/New Zealand White
Number/sex/group	22 (only females were dosed); F0 females were 17 to 19 weeks old on gestation Day 0 and weighed approximately 3-4 kg.
Satellite groups	Yes, four females per group used for TK analysis.
Study design	Gestation Day 0 was considered to be the day of confirmed mating. F0 females euthanized and C-sectioned on Day 29 postmating. Fetuses were examined for external, visceral, and skeletal effects.
Deviation from study protocol affecting interpretation of results	No

Table 14. Observations and Results for CD5789: Embryo Toxicity Study by the Oral Route (Gavage) in the Rabbit (Segment II), Study RDS.03.SRE.12520

Parameter	Major Findings
Mortality	50 mg/kg/day exceeded the maximum tolerated dosage. Dosing of animals in the 50 mg/kg/day group was stopped on Day 14 or 15 of gestation. Two animals at 50 mg/kg/day were found dead (one on Day 18, one on Day 19), and 12 were sacrificed for "ethical" reasons between Days 14 and 21, in one instance following spontaneous abortion. There were no unscheduled deaths of F0 animals at 5 mg/kg/day or less.
Clinical signs	A dose of 50 mg/kg/day was not tolerated. No treatment-related clinical signs were observed at 5 mg/kg/day or less.
Body weights	There were no treatment-related effects on mean BW or mean BW change at 5 mg/kg/day or less.
Necropsy findings C-section data	Mean weight of the gravid uterus could not be meaningfully assessed for animals at 50 mg/kg/day, due to excessive toxicity. There were no remarkable differences in mean uterine weight at 5 mg/kg/day or below. Fetal data at 50 mg/kg/day cannot be meaningfully analyzed. At 5 mg/kg/day, no statistically significant differences in C-section parameters were observed.
Necropsy findings Offspring	At 5 mg/kg/day, 12 fetuses (6%) from five litters had acaudia (absence of the tail). One of the fetuses with acaudia also had amelia and hemimelia of the left and right hindlimb respectively together with gastroschisis. Less severe anomalies of the tail (short and/or bent) were also noted in 20 out of 22 litters, effecting approximately 40% of the fetuses. At 5 mg/kg/day, a slight increase in the incidence of abnormalities of the urogenital system may have been observed, although it was not clear that this was genuinely a treatment-related effect. These included one fetus described as having had a "gross disruption" of the urogenital system and four fetuses with "malpositioned" or small or misshapen kidneys. At 5 mg/kg/day, 25 fetuses from 8 litters had a malformed vertebral column, typically caudal to the lumbar or sacral vertebrae, including 12 instances of acaudia. An increased incidence of fetuses with less severe anomalies of the vertebral column (e.g., malpositioned, misshapen, bipartite, and fused vertebrae) in the caudal region was also observed. There were no apparent treatment-related gross, visceral, or skeletal fetal effects at 0.5 mg/kg/day.

5.5.5.3. Prenatal and Postnatal Development

CD5789: Pre and Postnatal Development Study by the Oral Route (Gavage) in the Wistar Rat (Segment III), Study RDS.03.SRE.12758

Key study findings:

- There were no effects on any parameter assessed, including survival, clinical signs, body weight gain, physical or neurological development of F1 pups, or reproductive parameters in F1 pups.
- 0.1 mg/kg/day ($AUC_{0\text{-}24h}$ =63 ng•h/mL on postnatal Day 20) was an apparent NOAEL under the conditions of this study.
- Although no toxicity was observed, this study is considered to have adequately challenged the test system, since the systemic exposure achieved was approximately 600 times the maximum systemic exposure observed during clinical use of the product (maximum observed clinical $AUC_{0\text{-}24h}$ =0.106 ng•h/mL).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 15. Methods for CD5789: Pre and Postnatal Development Study by the Oral Route (Gavage) in the Wistar Rat (Segment III), Study RDS.03.SRE.12758

Method	
Dose and frequency of dosing	0, 0.01, 0.03, and 0.1 mg/kg/day, once daily, on Day 6 of gestation until Day 20 postpartum
Route of administration	Oral gavage
Formulation/vehicle	Suspension/0.5% w/v carboxymethylcellulose and 0.1% Tween 80 in water
Species/strain	Rat/Han Wistar
Number/sex/group	25 F0 females; 25 pups of each sex were selected to form the F1 generation (including at least one pup of each gender from each litter). Only F0 females were dosed. F0 females were approximately 10 to 13 weeks old on gestation Day 0 and weighed approximately 200 g.
Satellite groups	Yes, an additional 6 pregnant F0 animals per treatment group (3 in control group) were used for TK purposes.
Study design	F0 females were presumed pregnant when received. F0 females dosed once daily from Day 6 of gestation through Day 20 postpartum. The test material was not administered to F0 males or to F1 animals. F0 females were sacrificed on Day 21 postpartum. F1 animals (pups of F0 animals) of each sex were randomly selected for pairing with a nonsibling from the same treatment group for breeding of the F2 generation (cohabitated at approximately 11 weeks of age). F1 breeder females were sacrificed on gestation Day 13 and C-sectioned. F1 animals were also assessed for effects on developmental landmarks, sensory function, behavior, learning, and memory.
Deviation from study protocol affecting interpretation of results	No

Table 16. Observations and Results for CD5789: Pre- and Postnatal Development Study by the Oral Route (Gavage) in the Wistar Rat (Segment III), Study RDS.03.SRE.12758

Generation	Major Findings
F0 Dams	No treatment-related effects were observed.
F1 Generation	No treatment-related effects were observed.
F2 Generation	No treatment-related effects were observed.

5.5.6. Other Toxicology Studies

5.5.6.1. Acute Skin Irritation Potential

CD5789: Acute Skin Irritation in the Rabbit, Study RDS.03.SRE.12613

When applied to skin of rabbits, formulations containing trifarotene exhibited potential to induce irritation of the skin, including induction of erythema and edema.

5.5.6.2. Acute Eye Irritation Potential

CD5789: Acute Eye Irritation in the Rabbit, Study RDS.03.SRE.12614

When instilled into the "conjunctival sac" of rabbit eyes, formulations containing trifarotene exhibited potential to induce irritation of the ocular tissues, including "chemosis" (graded very slight to marked), slight to moderate redness of the conjunctiva, "clear to whitish purulent discharge," "iris lesion," and corneal opacity (graded moderate).

5.5.6.3. Phototoxicity Potential

CD5789: Photoirritation and Photosensitization by Cutaneous Route in the Guinea Pig, Study RDS.03.SRE.12615

When topically applied to guinea pigs that were subsequently exposed to UV light (approximately 9 joules/cm^2 UVA and 0.08 joule/cm^2 UVB), formulations containing trifarotene exhibited no potential to induce phototoxicity.

5.5.6.4. Sensitization Potential

A Skin Sensitization Study of CD5789 Cream in Guinea Pigs (Buehler Test), Study I-4549

Formulations containing trifarotene exhibited no potential to induce sensitization in a Buehler assay conducted with guinea pigs.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of trifarotene cream (AKLIEF® Cream) 50 µg/g (0.005% w/w) for once daily (QD) topical treatment of acne vulgaris in subjects 9 years of age and older. Two MUsTs evaluated QD topical application of 50 µg/g and 100 µg/g trifarotene cream for 29 days in adult and pediatric subjects with acne vulgaris. Most of the systemic concentrations following repeated QD trifarotene cream 50 µg/g topical application were below or near the limit of quantification (LOQ) of 5 pg/mL in both adult and pediatric subjects. Results from in vitro studies demonstrated that three cytochrome P450 (CYP) enzymes contribute to the overall metabolism of trifarotene. Physiologically-based pharmacokinetic (PBPK) modeling and systemic exposure results from MUsTs suggested a low potential of drug interaction in human with the therapeutic dose of trifarotene cream 50 µg/g. A clinical drug interaction study of trifarotene cream and oral contraceptive together with in vitro results suggest that trifarotene cream is not expected to impact the systemic concentrations of oral contraceptives containing levonorgestrel (LNG) and ethinyl estradiol (EE).

Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 211527 acceptable.

6.2. Summary of Clinical Pharmacology Assessment

Two MUsTs evaluated trifarotene cream 50 µg/g and 100 µg/g using a similar study design. There were 39 adult subjects in Study 40182 and 35 pediatric subjects in Study 18237. Study subjects received QD topical treatment for 29 days and the drug was applied to the face, shoulders, upper back, and upper chest except the neck. The area of drug application is considered as maximal BSA for the indication of acne vulgaris. The total amount of drug applied daily was 2 g in the adult MUsT (Study 40182) and ranged from 1.1 to 2 g in the pediatric MUsT (Study 18237). Plasma levels of trifarotene were detectable in 7 out of 19 adult subjects and in 3 out of 17 pediatric subjects who received trifarotene cream 50 µg/g for 29 days. The C_{max} of plasma trifarotene reached up to 9.6 pg/mL, and AUC_{0-24} was up to 106 pg·h/mL.

Results from in vitro drug-drug interaction (DDI) studies suggest that trifarotene cream 50 µg/g does not inhibit or induce CYP enzymes and it did not inhibit drug transporters. Hence trifarotene cream 50 µg/g is not expected to increase or decrease the systemic exposure of other coadministered drugs that are substrates of CYP enzymes and transporters.

The Applicant conducted a PBPK model to assess the effect of other drugs on the systemic exposure of trifarotene cream 50 µg/g. The results indicated that when trifarotene was coadministered with a hypothetical CYP2C9 and CYP3A4 strong inhibitor, the mean C_{max} and

AUC could increase by approximately 2.3 and 2.9-fold, respectively. The simulated highest systemic concentration of trifarotene still allows for a large safety margin based on nonclinical data.

In vivo DDI study with concomitant administration of an oral contraceptive containing LNG and EE and trifarotene cream 100 µg/g was inconclusive due to limited number of subjects with measurable trifarotene concentration. While the results showed that there was no effect on the systemic exposure of LNG and EE, only 6 of 22 subjects had measurable concentration of trifarotene.

The Applicant conducted a TQT study with trifarotene gel 100 µg/g in healthy adult subjects and found no significant QTc prolongation effect from trifarotene. The systemic exposure of trifarotene following topical application of trifarotene gel 100 µg/g was higher than the systemic exposure observed in MUsTs, and the TQT study result indicates that the therapeutic use of the proposed strength (i.e., 50 µg/g) of trifarotene cream is not likely to cause any QTc prolongation.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics of Trifarotene Under Maximal Use Conditions

A 4-week treatment with approximately 2 g per day of trifarotene cream 50 µg/g under maximal use conditions resulted in low systemic exposure in adult (Study 40182) and pediatric (Study 18237) subjects with acne vulgaris.

Study 40182 (adults) had two treatment cohorts (i.e., trifarotene cream 50 µg/g and trifarotene cream 100 µg/g). Trifarotene cream 50 µg/g treatment cohort (N=19) showed quantifiable systemic exposures in seven subjects on Day 29. The C_{max} ranged from 5.0 to 9.6 pg/mL and AUC ranged from 75.2 to 103.6 pg·h/mL. Trifarotene cream 100 µg/g treatment cohort (N=18) showed quantifiable systemic exposures in 11 subjects by Day 29. The C_{max} ranged from 5.0 to 31.3 pg/mL and AUC ranged from 78.7 to 243.9 pg·h/mL. Systemic concentrations appear to be at or near steady state after 2 weeks of topical treatment of trifarotene cream.

A MUsT (Study 18237) in pediatric subjects aged 10 to 17 years inclusive also had two cohorts: Trifarotene cream 50 µg/g and trifarotene cream 100 µg/g. Trifarotene cream 50 µg/g cohort (N=18) demonstrated quantifiable systemic exposures only in three subjects and on Day 29, the C_{max} ranged between 7 and 9 pg/mL and AUC_{0-24} ranged between 89 and 106 pg·h/mL. Trifarotene cream 100 µg/g treatment cohort (N=17) showed systemic exposures in 11 subjects and the C_{max} ranged between 5 and 52 pg/mL and AUC_{0-24} ranged between 68 and 547 pg·h/mL. Overall, systemic exposures of trifarotene in adult and pediatric subjects with acne vulgaris following topical treatment of trifarotene cream 50 µg/g were low. Two subjects (one from each cohort) were terminated early from the study due personal reasons.

Metabolism of Trifarotene

In vitro Study 31111 was conducted to identify CYP enzymes involved in the metabolism of trifarotene and its metabolites. Study results demonstrated that CYP2C9 was the primary metabolizing isozyme of trifarotene accounting for up to 67% of trifarotene metabolism and that CYP2C8 and CYP3A4 accounted for 16% and 17% of trifarotene metabolism, respectively.

The Applicant identified five metabolites including three metabolites (CD09986, CD06700, and CD06530) that are pharmacologically active in in vitro assays. None of three active metabolites produced quantifiable plasma levels in subjects with acne vulgaris who received trifarotene cream 50 µg/g in MUsTs.

Effect of Other Drugs on the Systemic Exposure of Trifarotene Cream 50 µg/g

The Applicant used PBPK modeling to assess the potential effect of other drugs (including hypothetical CYP2C9 and CYP3A4 strong inhibitors) on the exposure of trifarotene. The PBPK modeling predicted that C_{max} and AUC of trifarotene could increase by 2.3- and 2.9-fold, respectively, if co-administered with strong CYP2C9 and CYP3A4 inhibitor. The simulated highest C_{max} of trifarotene was markedly lower than the safety margin of trifarotene cream 50 µg/g.

Effect of Trifarotene Cream 50 µg/g on Other Drugs

Results of in vitro drug-drug interaction studies indicated that trifarotene has an inhibitory activity to two CYP enzymes (CYP2C8 and CYP2C9) and two transporters (OAP1B1and OAP1B3) with IC_{50} ranging from 1.65 to 7.8µM, which is notably higher than observed systemic exposure of 0.00002µM following administration of trifarotene cream 50 µg/g in human under maximal use conditions. Trifarotene cream 50 µg/g did not inhibit CYP1A2, 2B6, 2C19, 2D6 and 3A4, and did not induce CYP1A2, 2B6, and 3A4. Trifarotene also did not inhibit multi-antimicrobial extrusion protein (MATE), organic anion transporter (OAT), organic cation transporter (OCT), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), bile salt export pump (BSEP), or MRP drug transporters.

Clinical DDI Study With Oral Contraceptive Containing Levonorgestrel and Ethinyl Estradiol

The Applicant conducted a clinical DDI study of trifarotene cream 100 µg/g with an oral contraceptive containing LNG 0.15 mg and EE 0.03 mg. The results showed that there was no effect on the systemic exposure of LNG and EE. However, only 6 out of 22 subjects presented quantifiable systemic exposure of trifarotene, which does not represent adequate number of subjects with quantifiable trifarotene systemic concentrations to permit a definitive conclusion.

As noted above results from in vitro DDI studies suggest that trifarotene cream 50 µg/g does not induce CYP enzymes. The totality of evidence indicates that trifarotene cream 50 µg/g is not expected to affect the circulating concentrations of oral hormonal contraceptives containing LNG and EE.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is to apply a thin layer of trifarotene cream 50 µg/g once daily to affected areas via topical route.

Therapeutic Individualization

The Applicant did not conduct studies for therapeutic individualization of the proposed trifarotene cream 50 µg/g product and such assessment is not warranted.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Maximal Usage PK Study

Trifarotene (also known as CD5789), a retinoid acid receptor γ agonist, was developed as a topical cream formulation for treatment of acne vulgaris in patients 9 years and older.

Each of two MUsTs (one in adults and one in pediatric subjects) evaluated trifarotene cream 50 µg/g and trifarotene cream 100 µg/g following QD topical application for 4 weeks. Systemic exposures of trifarotene following trifarotene cream 50 µg/g topical treatment were lower compared to trifarotene systemic exposure following trifarotene cream 100 µg/g topical treatment (Table 17). A 4-week topical application of the to-be-marketed trifarotene 50 µg/g cream formulation demonstrated measurable trifarotene levels in 7 out of 19 adult subjects and 3 out of 17 pediatric subjects, and the highest systemic concentration was 9.6 pg/mL in adults and 9 pg/mL in pediatrics.

The 4-week topical application of trifarotene cream 100 µg/g resulted in measurable systemic levels of trifarotene in 11 out of 18 adult subjects and 11 out of 16 pediatric subjects, and the systemic exposures of trifarotene were higher in trifarotene cream 100 µg/g cohort than in 50 µg/g cohort. The pediatric MUsT (Study 18237) did not have any subjects at age 9 years old and had only one subject at ages 10 and 11 years each due to a difficulty of recruiting pediatric subjects with acne vulgaris with disease within the upper range of severity.

Table 17. Summary of Trifarotene PK Parameters on Day 29, Study 40182 (Adult Subjects)

		CD5789 50 µg/g				CD5789 100 µg/g			
		C_{max} (pg/mL)	T_{max} (h)	AUC_{0-24h} (pg.h/mL)	AUC_{0-t} (pg.h/mL)	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-24h} (pg.h/mL)	AUC_{0-t} (pg.h/mL)
Day 29	Mean ± SD	NR	NR	NR	NR	10.8±7.7	4.4±1.2	118.7±53.0	67.1±60.7
	Geometric mean	NR	NR	NR	NR	8.8	NR	109.7	47.8
	N (N quantifiable)	19 (7)	19 (7)	19 (7)	19 (7)	18 (11)	18 (11)	18 (11)	18 (11)
	Min-Max	<5.0-9.6	3.9-4.0	75.2-103.6	20.2-41.2	<5.0-31.3	4.0-8.0	78.7-243.9	21.3-208.7
	CV (%)	NR	NR	NR	NR	71	28	45	91

SD = standard deviation; Min = minimum; Max = maximum; NR = non-reportable (i.e., when strictly less than 50 % of the data are quantifiable)
Abbreviations used for the PK parameters are given in the List of Abbreviations and Definitions of Terms
For descriptive statistics calculations, BLQ data (<5 pg/mL) were replaced by the LOQ for C_{max} (i.e., 5 pg/mL) and by the lowest AUC value (i.e., 21.3 and 78.7 pg.h/mL for the Trifarotene 100 µg/g Cream AUC_{0-t} and AUC_{0-24h}, respectively
Data Source: Table 15, RD.03.SRE.40182

Table 18. Summary of Trifarotene PK Parameters on Day 29, Study 18237 (Pediatric Patients)

		CD5789 50 µg/g cream				CD5789 100 µg/g cream			
		C_{max} (pg/mL)	T_{max} (h)	AUC_{0-24h} (pg.h/mL)	AUC_{0-t} (pg.h/mL)	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-24h} (pg.h/mL)	AUC_{0-t} (pg.h/mL)
Day 29	Mean ± SD	N.R.	N.R.	N.R.	N.R.	12 ± 12	3.5 ± 1.3	137 ± 119	90 ± 133
	N (N quantifiable)	17 (3)	17 (3)	17 (3)	17 (3)	16 (11[a])	11	16 (11)	16 (11)
	Min - Max	7 - 9	4 - 4	89 - 106	22 - 41	5 - 52	2 – 6	68 - 547	15 - 547
	CV (%)	N.R.	N.R.	N.R.	N.R.	98%	37%	87%	148%

SD = standard deviation; Min = minimum; Max = maximum; CV = coefficient of variation; NR = non-reportable (i.e., when less than 50 % of the data were quantifiable)
Abbreviations used for the PK parameters are given in the List of Abbreviations and Definitions of Terms
For descriptive statistics calculations, BLQ data (<5 pg/mL) were replaced by the LOQ for C_{max} (i.e., 5 pg/mL) and by the lowest AUC value (15 pg.h/mL and 68 pg.h/mL for AUC_{0-t} and AUC_{0-24h}, respectively)
a) Seven subjects had quantifiable values at both time points.
Data Source: Table 9, RD.06.SRE.18237

Thorough QT Study

One TQT study (Study 40196) used supratherapeutic dose (approximately 6 times higher dose compared to the one used in the maximal usage study) of trifarotene 100 µg/g in a gel formulation. A daily dose of 12 g of trifarotene gel was applied on a healthy skin surface of 6,000 cm^2 for 2 weeks to achieve supratherapeutic exposure.

The results indicated that the systemic exposure of trifarotene following application of trifarotene gel 100 µg/g were at least 3.4-fold higher than that achievable with the to-be-marketed cream formulation (50 µg/g) under maximal use conditions. Quantifiable levels of trifarotene were measured with a mean ± standard deviation (SD) C_{max} of 33.2±33.6 pg/mL (highest C_{max}: 187 pg/mL). The mean ± SD AUC_{0-24h} value was 440±351 pg·h/mL and the mean T_{max} value was 4.2 hours. Based on the QTc double-delta data, there was no significant QT/QTc prolongation with trifarotene at the supratherapeutic dose. It is noted that this study was conducted with a different dosage form (i.e., gel) compared to the to-be-marketed cream formulation. However, findings of this study that it produced a higher exposure will provide support to the to-be-marketed cream formulation.

In Vitro Metabolism and In Vitro DDI Studies

The Applicant conducted a total of six in vitro DDI studies to assess the metabolism of trifarotene and drug interaction potential of trifarotene. The results of the in vitro metabolism

study indicated that 3 CYP enzymes are mainly responsible for trifarotene metabolism: CYP2C9 (67%), CYP2C8 (16%), and CYP3A4 (17%). There were five metabolites identified in vitro and three of them (CD09986, CD06700, and CD06530) were pharmacologically active in the RAR alpha, beta and gamma transactivation assays. In vivo results from the MUsT in adult subjects and pediatric subjects receiving trifarotene cream 50 µg/g demonstrated that plasma levels of three active metabolites were below the LOQ of 10 pg/mL.

In vitro DDI study assessed the potential of trifarotene to inhibit or induce CYP enzymes and also assessed the potential of trifarotene to inhibit drug transporters.

Trifarotene did not increase the CYP activities and mRNA levels at concentrations up to 3µM (equivalent to 1.4 µg/mL). Hence trifarotene cream 50 µg/g is not expected to induce CYP1A2, 2B6 and 3A4.

Trifarotene is not expected to inhibit CYP1A2, 2B6, 2C19, 2D6 and 3A4. There was reversible inhibitory activity of trifarotene on CYP2C8 (IC_{50}=7.8µM, Ki =3.7µM) and CYP2C9 (IC_{50}=3.9µM, Ki =0.9µM).

Trifarotene also did not inhibit MATE, OAT, OCT, P-gp, BSEP, or MPR drug transporters. Trifarotene inhibited the OATP1B1 and OATP1B3 uptake transporters with IC_{50} ranging from 1.65 to 2.14µM. Trifarotene IC_{50} for BCRP efflux transporter was 2.78µM which is approximately 140,000-fold higher than the C_{max} of trifarotene (9.6 pg/mL equivalent to 0.00002µM) measured in a maximal usage PK study (Study 40182).

Overall, the in vitro DDI studies showed that the potential for trifarotene to inhibit CYP enzymes and transporters was observed at high concentrations, with IC_{50} values of 1.65µM or higher. Based on low systemic exposure of trifarotene following topical application of trifarotene cream 50 µg/g, there is a low potential for trifarotene to inhibit or induce metabolic enzymes or transporters under clinical use conditions.

PBPK Modeling to Address Effect of Other Drugs on Trifarotene

A PBPK model was developed to assess a potential DDI substrate of trifarotene with fluconazole 400 mg, a moderate inhibitor of CYP2C9 and CYP3A4 as in vitro study indicated that CYP2C9 and CYP3A4 account for 84% of trifarotene metabolism The PBPK model predicted that mean C_{max} and AUC of trifarotene could increase by 1.17- and 1.19-fold, respectively when a moderate inhibitor is co-administered. A simulation with a strong CYP inhibitor, a worst-case scenario, predicted that mean C_{max} and AUC could increase by 2.3- and 2.9-fold, respectively. Nonetheless, simulated highest systemic exposure of trifarotene appeared to still be low with a large safety margin for trifarotene cream 50 µg/g under clinical use conditions. It should be noted that even under the worst-case scenario, the predicted increase in systemic exposure is not expected to induce any CYP enzymes.

Clinical DDI Study With Oral Contraceptive Containing LNG and EE

An in vivo DDI Study 103918 assessed the potential effect of trifarotene on the systemic levels of an oral contraceptive containing LNG 0.15 mg and EE 0.03 mg. A total of 22 healthy female subjects (age 19 to 35 years, inclusive) received once daily topical application of 2 g trifarotene cream 100 µg/g to the face, shoulders, upper chest and upper back for 14 days. Repeated topical application of trifarotene cream 100 µg/g resulted in quantifiable systemic exposure in 6 out of 22 subjects with the C_{max} ranged from 5.08 pg/mL to 10.76 pg/mL and the AUC_{0-t} ranged from 39.41 pg·h/mL to 97.47 pg·h/mL. The systemic levels observed were comparable to those observed in subjects with acne vulgaris that applied trifarotene cream 50 µg/g under maximal use conditions. All 22 subjects presented quantifiable LNG and EE plasma concentrations.

The ratios of the geometric least square means and their 90% confidence intervals (CIs) for systemic exposure parameters (C_{max} and AUC_{0-t}) for LNG and EE showed that the 90% CIs of these ratios were between 0.80 and 1.25 suggesting that topical application of trifarotene cream 100 µg/g with an oral contraceptive containing LNG and EE does not affect the systemic levels of LNG or EE. However, the observed quantifiable trifarotene concentrations in only six subjects do not represent adequate number of subjects to permit a definitive conclusion.

Results from in vitro DDI studies indicated that trifarotene cream 50 µg/g does not induce CYP enzymes. The totality of evidence suggests that trifarotene cream 50 µg/g is not expected to affect the circulating concentrations of oral hormonal contraceptives containing LNG and EE.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

No. For topical product, PK assessed under maximal use conditions supports systemic safety rather than efficacy.

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

Yes. The Applicant evaluated the once daily topical application of the product in subjects aged 10 years and older with acne vulgaris in two MUsTs and three phase 3 trials.

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

No. The effect of intrinsic factors on the PK of trifarotene cream was not evaluated due to quantifiable concentrations in very few subjects. Any further analysis of available data would not be fruitful.

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

Food-drug interactions are not applicable for topical products. Results of in vitro metabolism and enzyme and transporter inhibition and induction assays, a clinical drug interaction study with an oral contraceptive, and PBPK modeling support a low potential for DDI at clinically relevant doses.

Question on clinically relevant specifications

Not applicable.

7. Sources of Clinical Data and Review Strategy

7.1. Clinical Studies

Below is the table of clinical trials evaluated to determine approvability of trifarotene 50 ug/g cream for the proposed indication.

Table 19. Clinical Trials Relevant to This NDA

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Centers and Countries
Controlled Studies to Support Efficacy and Safety								
Phase 3 efficacy and safety	18251	Multicenter, randomized, double-blind, parallel-group, vehicle-controlled	Once daily application per evening per topical	Absolute change in mean inflammatory lesion count. Absolute change in mean noninflammatory lesion count. Percentage of subjects who achieved an IGA score of *clear* or *almost clear* and at least two-grade improvement from baseline on face. Percentage of subjects who achieved an PGA score of *clear* or *almost clear* and at least two-grade improvement from baseline on the trunk.	12 weeks	N=1,208 CD5789 50 µg/g cream (N=612), vehicle cream (N=596)	Subjects ≥9 years old with moderate facial and truncal acne vulgaris (IGA =3, ≥20 inflammatory lesions and ≥25 noninflammatory lesions on the face; PGA =3, ≥20 inflammatory lesions and ≥20 but no more than 100 noninflammatory lesions on the trunk). Moderate truncal acne vulgaris was optional for children aged 9–11 years.	119 centers in United States, Canada, Puerto Rico, and Europe with 117 actually enrolling subjects

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Centers and Countries
Phase 3 efficacy and safety	18252	Multicenter, randomized, double-blind, parallel-group, vehicle-controlled	Once daily application per evening per topical	Absolute change in mean inflammatory lesion count. Absolute change in mean noninflammatory lesion count. Percentage of subjects who achieved an IGA score of *clear* or *almost clear* and at least two-grade improvement from baseline on face. Percentage of subjects who achieved a PGA score of *clear* or *almost clear* and at least two-grade improvement from baseline on trunk.	12 weeks	N=1,212 CD5789 50 µg/g cream (N=602), vehicle cream (N=610)	Subjects ≥9 years old with moderate facial and truncal acne vulgaris (IGA =3, ≥20 inflammatory lesions and ≥25 noninflammatory lesions on the face; PGA =3, ≥20 inflammatory lesions and ≥20 but no more than 100 noninflammatory lesions on the trunk). Moderate truncal acne vulgaris was optional for children aged 9-11 years.	81 centers: United States, Europe, and Russia
Studies to Support Safety								
Long-term safety	18250	Multicenter, open-label, single-arm	Once daily application per evening per topical	To evaluate the safety of CD5789 50 µg/g cream in the long-term treatment (up to 52 weeks) of subjects with moderate acne vulgaris. Efficacy was evaluated as a secondary objective.	52 weeks	N=455 CD5789 50 µg/g cream (n=453), 52 weeks (up to 364 days)	Subjects ≥9 years old with moderate facial and truncal acne vulgaris (IGA =3, ≥20 inflammatory lesions and ≥25 noninflammatory lesions on the face; PGA =3, ≥20 inflammatory lesions and ≥20 noninflammatory lesions on upper back, shoulders, and anterior chest). Moderate truncal acne vulgaris was optional for children aged 9-11 years.	32 centers: 18 in Europe and 14 in United States

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Centers and Countries
Dermal safety	40208	Single-center; randomized; vehicle- and negative-controlled; evaluator-blinded; intra-individual comparison	One application per Day 1	To determine potential of CD5789 cream at 50 µg/g and 100 µg/g to induce phototoxic (photo-irritation) reaction in healthy subjects.	4 days	N=35 CD5789 50 µg/g cream, CD5789 100 µg/g cream, CD5789 vehicle cream, white petrolatum ointment	Healthy subjects aged 18-65 years	
Dermal safety	40209	Single-center; randomized; vehicle-, negative- and positive-controlled; evaluator-blinded, intra-individual comparison	Daily application on back under semi-occlusive conditions, 6 days/week for 3 consecutive days (total of 18 applications)	To determine cutaneous cumulative irritation potential of CD5789 cream at 50 µg/g and 100 µg/g following repeated applications on skin of healthy subjects.	22 days	N=35 CD5789 50 µg/g cream, CD5789 100 µg/g cream, CD5789 vehicle cream, white petrolatum ointment, SLS 0.25% solution	Healthy subjects aged 18-65 years	

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Centers and Countries
Dermal safety	40189	Single-center, randomized, vehicle- and negative-controlled, evaluator blinded, intra-individual comparison	See Section 8.2.1	To determine photosensitization potential of CD5789 cream at various concentrations (25 and 100 µg/g) and corresponding vehicle cream after repeated applications.	Induction phase: 3 weeks	N=55 CD5789 25 µg/g cream, CD5789 100 µg/g cream, CD5789 vehicle cream, white petrolatum ointment	Healthy subjects aged 18-65 years	
Dermal safety	40190	Single-center, randomized, vehicle- and negative-controlled, evaluator-blinded, intra-individual comparison	See Section 8.2.1	To determine sensitization potential of CD5789 cream at 25 and 100 µg/g and corresponding vehicle cream after repeated applications.	Induction phase: 3 weeks	N=240 CD5789 25 µg/g cream, CD5789 100 µg/g cream, CD5789 vehicle cream, white petrolatum ointment	Healthy subjects aged 18-65 years	

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Centers and Countries
Other Studies Pertinent to Review of Efficacy or Safety (e.g., clinical pharmacological studies)								
Cardiac safety (TQTc study)	40196	Period 1: single-center, open-label Period 2: single-center, randomized, double-blind, vehicle- and positive-controlled, parallel group	Period 1: N=5 CD5789 100 µg/g gel Period 2: N=180 vehicle gel+ moxifloxacin (n=60), vehicle gel+placebo capsule (n=60), CD5789 100 µg/g gel+placebo capsule (n=60)	Period 1: To assess optimal treatment duration to be used in Period 2 based on systemic exposure and the associated local tolerance of CD5789 after repeated once daily topical application over 2 weeks in healthy subjects treated by 12 g/day of CD5789 topical gel at 100 µg/g on 6,000 cm^2 body surface area. Period 2: To evaluate the effect of CD5789 at supratherapeutic dose after repeated topical applications, on ventricular repolarization compared with its vehicle, specifically on the QTcF from surface ECG, in healthy subjects.	Period 1: 14 days Period 2: 15 days	Period 1: N=5 Period 2: N=180	Healthy subjects aged 18-65 years	
MUsT adult PK	40182	Multicenter, randomized, double-blind, parallel group		To assess systemic exposure of CD5789 under maximal use conditions, after repeated once daily topical application of CD5789 50 µg/g and 100 µg/g cream in subjects with severe acne vulgaris over 4 weeks.	29 days	N=39 CD5789 50 µg/g cream (n=21), CD5789 100 µg/g cream (n=18)	Subjects aged 18-35 years with severe facial acne vulgaris (IGA =4 with at least 30 noninflammatory lesions and at least 40 inflammatory lesions)	6 centers: 5 in Europe and 1 in United States

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	Centers and Countries
MUsT pediatric PK	18237	Multicenter, randomized, double-blind, parallel group		To assess systemic exposure of CD5789 under maximal use conditions, after repeated once daily topical application of CD5789 50 µg/g and 100 µg/g cream in subjects aged 9-17 years with severe acne vulgaris over 4 weeks.	29 days	N=35 CD5789 50 µg/g cream (n=18), CD5789 100 µg/g cream (n=17)	Subjects aged 9-17 years with facial acne vulgaris (IGA of at least 3 for 9- to 11-year-old subjects; IGA of 4 for 12- to 17-year-old subjects)	3 centers in United States

Abbreviations: IGA = Investigator Global Assessment; PGA = Physician Global Assessment; MUsT = maximal usage trial; NCT = national clinical trial; QTcF = Fridericia's corrected QT-interval; SLS = sodium lauryl sulfate; TQTc = thorough QTc

7.2. Review Strategy (Clinical Plus Statistical)

Data Sources

The data sources used for the evaluation of the efficacy and safety of trifarotene, 0.005% cream included the Applicant's clinical study reports, datasets, line listings, 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.[4]

Data and Analysis Quality

The databases for the study required minimal data management prior to performing analyses. The original submission included statistical programs for generating multiple imputations for missing data.

[4] The analysis datasets used in this review are archived at \\cdsesub1\evsprod\NDA211527\0001\m5\datasets.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

The Applicant conducted two-identically designed, multicenter, randomized, double-blind, vehicle-controlled trials (RD.03.SRE.18251 and RD.03.SRE.18252, hereinafter referred to as Studies 18251 and 18252) comparing trifarotene cream 50µg/g versus its vehicle applied once daily in the evening for 12 weeks for the treatment of subjects with moderate facial and truncal acne vulgaris. Study 18251 was conducted in Canada; the United States including Puerto Rico; and the European Union (Germany and Hungary). Study 18252 was conducted in the United States, the European Union (Czech Republic, Hungary, Poland, Romania, Spain), Russia, and Ukraine.

The protocols define the following inflammatory lesions:

- **Papule:** A small, red, solid elevation less than 0.5 cm in diameter
- **Pustule:** A small, circumscribed elevation of the skin that contains yellow-white exudates

The protocols define the following noninflammatory lesions:

- **Open comedone:** A pigmented dilated pilosebaceous orifice (blackhead)
- **Closed comedone:** A tiny white papule (whitehead)

The protocols list the following key inclusion criteria:

- Male or female, 9 years of age and older at the screening visit
- Facial acne:
  - Severity grade of 3 (moderate) on the IGA scale at screening and baseline
  - A minimum of 20 inflammatory lesions and 25 noninflammatory lesions on the face at screening and baseline
- Truncal acne (optional criteria for subjects between 9 and 11 years of age)**:**
  - Severity grade of 3 (moderate) on the PGA scale at screening and baseline visits on trunk (shoulders, upper back, and upper anterior chest) reachable for self-application of study drug by the subject
  - A minimum of 20 inflammatory lesions and 20 noninflammatory lesions but no more than 100 noninflammatory lesion counts on the trunk (shoulders, upper back, and upper anterior chest) reachable to self-application of study drug by the subject at screening and baseline

The protocols also list the following key exclusion criteria:

- The subject has severe forms of acne (e.g., acne conglobata, acne fulminans) or secondary acne form (e.g., chloracne, drug-induced acne, etc.)
- The subject has more than one nodule on the face or on the trunk at screening and baseline
- The subject has any acne cyst on the face or on the trunk at screening and baseline

The IGA of facial acne and PGA of truncal acne are presented in Table 20 and Table 21, respectively.

Table 20. Investigator Global Assessment of Facial Acne

Investigator's Global Assessment Scale (IGA) Face		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

Source: Applicant's figure on p. 79 of Protocol 18251

Table 21. Physician Global Assessment of Truncal Acne

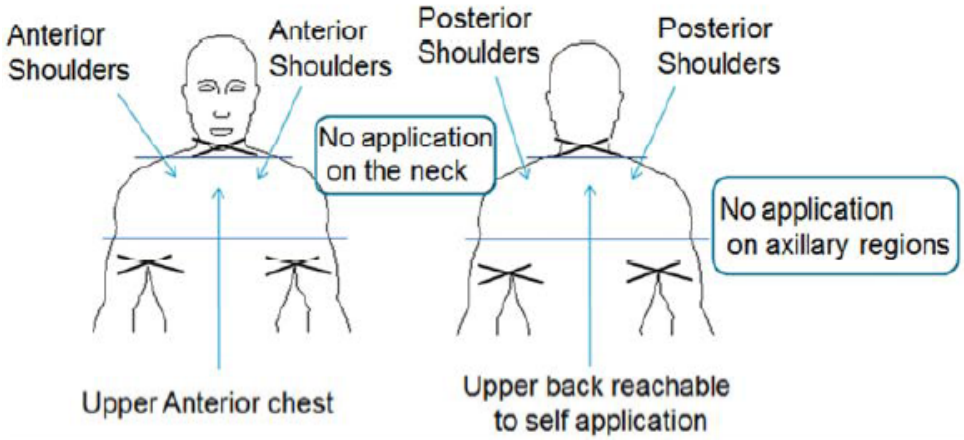
Physician Global Assessment Scale (PGA) Trunk		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

Source: Applicant's figure on p. 80 of Protocol 18251

The protocols specify that subjects were to be randomized using an Interactive Response Technology (IRT) system in a 1:1 ratio within a block to trifarotene or vehicle with randomization stratified by clinical trial center. However, the clinical study reports (CSRs) state that during the study, the Applicant learned that the randomization was implemented without the stratification for center. According to the CSRs, the IRT system was reset on December 22, 2016, to stratify randomization based on center. In Study 18251, a total of 534 (44%) subjects were randomized before this date, and 674 (56%) subjects were randomized after this date. In Study 18252, 968 (80%) subjects were randomized before December 22, 2016, and 244 (20%) subjects were randomized after this date. Sensitivity analyses exploring the impact of the change in randomization is presented in Section 8.1.4.

The protocols state that subjects were instructed to apply the study drug on the face (i.e., chin, right and left cheek, nose, and forehead) and trunk (i.e., right and left upper back, right and left shoulders, and right and left upper anterior chest reachable to self-application by the subject as depicted in Figure 2) once daily in the evening after washing and drying with the objective to cover these areas with a thin layer of study drug, even on areas with no clinically evident acne. Subjects were evaluated during study visits at baseline and Weeks 1, 2, 4, 8, and 12.

Figure 2. Trunk Application Area



Source: Applicant's figure on p. 60 of Protocol 18251

The statistical analysis plans (SAPs) list the following three co-primary endpoints which were evaluated on the face:

- Success rate, defined as the percentage of subjects who achieve an IGA score of 1 (almost clear) or 0 (clear) and at least a two-grade improvement from baseline at Week 12
- Absolute change in facial inflammatory lesion count from baseline to Week 12
- Absolute change in facial noninflammatory lesion count from baseline to Week 12

The SAPs list the following three co-secondary endpoints which were evaluated on the trunk:

- Percentage of subjects who achieve a PGA score of 1 (almost clear) or 0 (clear) and at least a two-grade improvement from baseline at Week 12
- Absolute change in truncal inflammatory lesion count from baseline to Week 12
- Absolute change in truncal noninflammatory lesion count from baseline to Week 12

The SAPs list the following supportive endpoints related to lesion counts:

- Percent change in facial noninflammatory lesion counts from baseline to Week 12
- Percent change in facial inflammatory lesion counts from baseline to Week 12
- Percent change in truncal noninflammatory lesion counts from baseline to Week 12
- Percent change in truncal inflammatory lesion counts from baseline to Week 12

8.1.2. Statistical Methodologies

The SAPs define the following analysis populations:

- The intention-to-treat (ITT) population includes any subjects who are randomized. Subjects in the ITT population are analyzed according to randomized treatment.
- The intention-to-treat on the trunk (ITTT) population includes any subjects in the ITT population with moderate truncal acne at the baseline visit. This excludes children between 9 and 11 years old who did not have a PGA score of 3, at least 20 inflammatory lesions on the trunk, and at least 20 noninflammatory lesions on the trunk. Subjects in the ITTT population are analyzed according to randomized treatment.
- The safety population (SAF) is defined as subjects in the ITT population who applied/were administered the study medicine at least once.
- The safety population for local tolerability on the trunk (SAFT) is defined as subjects in the SAF population who also applied/were administered study medication on the trunk at least once.
- The per-protocol (PP) population is defined as subjects in the ITT population who have no major protocol deviations. The SAPs state that potential major protocol deviations include:
  - Entrance criterion deviations
  - Noncompliance
    - Subjects who have dosing deviations more than 30% of the planned 84 doses
    - Subjects who miss doses for 5 or more consecutive days just prior to the last visit
  - Prohibited medications: Subjects who have taken interfering concomitant therapies during treatment
  - Administrative error
    - Accidental unblinding
    - Medication dispensing errors
    - Lesion counts and IGA/PGA performed by a nonapproved evaluator
- The per-protocol population on the trunk (PPT) is defined as any subjects in the PP population with moderate truncal acne at the baseline visit.

The final list of major protocol deviation criteria and subjects who have any major protocol deviations were documented in a blind review memo before database lock.

The SAPs specify that the ITT population is used for all efficacy endpoints on the face and the ITTT population is used for all efficacy endpoints on the trunk. Safety analyses using the SAF and SAFT will follow similarly. The SAPs state that the PP and PPT populations will be used for supportive efficacy analyses.

The SAPs specify a strategy to pool small centers (i.e., centers that randomized less than eight subjects) for the analysis. The pooled centers are referred to as “analysis centers.” First, centers

are sorted by country, number of randomized subjects (descending), and center number (ascending). The largest of the small centers is combined with the smallest of the small centers within the same country. If the pooled center has less than eight subjects, it will continue to be combined with the smallest available site until there are at least eight subjects or no sites remain. After all possible pooling, if there are remaining small sites that cannot be pooled into an analysis center with at least eight subjects, these sites will be pooled into the analysis center from the last iteration of the pooling (even if that analysis center is not the smallest). If there was no other pooling done in that country, the sites will be pooled with the smallest site in the country. If no other sites are available in the country, the site will remain with fewer than eight subjects.

The SAPs specify analyzing the co-primary endpoints using the ITT population with multiple imputation (MI) to handle missing data. Success on the IGA and PGA at Week 12 was analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The SAPs specify assessing the treatment-by-analysis center interaction using the pairwise Breslow Day test for homogeneity of the odds ratio across analysis centers at Week 12 using an alpha level of 0.10 and assessing the consistency of the treatment effect across analysis centers using plots and descriptive statistics.

The SAPs state that the change from baseline in facial and truncal lesion counts are analyzed separately by type (i.e., inflammatory and noninflammatory) using an analysis of covariance (ANCOVA) model including factors for baseline count, analysis center, and treatment. The SAPs specify assessing the treatment-by-analysis center interaction in this model using an alpha level of 0.10 and assessing the consistency of the treatment effect across analysis centers using descriptive statistics and using graphical methods.

The SAPs state that if superiority of trifarotene is established for the co-primary endpoints, then the co-secondary endpoints are tested with trifarotene declared superior to vehicle if all co-secondary endpoints results in a two-sided p-value less than 0.05. There was no adjustment for multiplicity for the supportive endpoints.

Missing Data and Sensitivity Analyses

The SAPs dated October 5, 2015, for Studies 18251 and 18252 specified that the primary method of imputation for missing data would be MI using the missing at random (MAR) assumption. The seed numbers and number of planned imputations (i.e., 5) were specified. The SAP addendums dated December 8, 2017 for Study 18251 and October 23, 2017 for Study 18252 provide further details on the imputation strategies. Apart from the number of imputations (i.e., 50 instead of 5) and the addition of a categorical MI sensitivity analysis for the IGA/PGA endpoints, the analyses envisioned in the SAPs dated October 5, 2015 did not change.

The SAPs specify that the Markov Chain Monte Carlo method is used to create monotonic data. Subsequently, a linear regression model is used for missing lesion count data, and a logistic regression model is used for ordinal IGA/PGA scores with treatment and non-missing data from earlier timepoints included as covariates in the model. IGA/PGA scores at prior timepoints (i.e., the covariates in the model) except for baseline are treated as continuous data for the primary analysis. IGA/PGA success is calculated from the imputed IGA/PGA scores. Results are combined using Proc MIANALYZE in SAS. The SAPs dated October 5, 2015, planned to create five imputed datasets. The SAP addendums dated December 8, 2017 for Study 18251 and October 23, 2017 for Study 18252 specified using 50 imputed datasets.

Sensitivity analyses listed in the SAP for the co-primary (secondary) endpoints specify analyzing the following:

- PP(T) population using MI to handle missing data under the MAR assumption
- ITT(T) population using MI based on a pattern-mixture model under the missing not at random (MNAR) assumption for the missing data by using the profiles from vehicle subjects with observed data to impute missing data
- ITT(T) population using last observation carried forward (LOCF) to handle missing data
- ITT(T) population assuming subjects with missing IGA data at Week 12 are failures (missing as failure [MAF]), and subjects with missing lesion counts at Week 12 are assigned the median change in lesion count from subjects who were failures on the IGA within the same treatment group

The SAP addendums also add an additional sensitivity analysis that repeats the MI process treating prior IGA/PGA scores as categorical covariates instead of continuous covariates, specify a procedure for checking if any covariates cause convergence issues, and provide sample code of all MI analyses.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Study 18251 enrolled and randomized 1,208 subjects, 612 to trifarotene and 596 to vehicle, from 117 centers in the United States, Canada, Germany, Hungary, and Puerto Rico. Study 18252 enrolled and randomized 1,212 subjects, 602 to trifarotene and 610 to vehicle, from 81 centers in the United States, Russia, Poland, Hungary, Ukraine, Romania, Czech Republic, and Spain. Table 22 presents the reasons for subject discontinuation from the studies as classified by the Applicant. The proportion of subjects who discontinued overall were similar across treatment arms in both trials; however, more subjects in the trifarotene groups discontinued due to adverse events than those in the vehicle groups.

Table 22. Disposition of Subjects Enrolled, Studies 18251 and 18252

	Study 18251		Study 18252	
ITT Population	Trifarotene N=612	Vehicle N=596	Trifarotene N=602	Vehicle N=610
Discontinued	72 (11.8%)	61 (10.2%)	44 (7.3%)	37 (6.1%)
Lack of efficacy	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Adverse event(s)	14 (2.3%)	1 (0.2%)	9 (1.5%)	1 (0.2%)
Withdrawal by subject	39 (6.4%)	32 (5.4%)	18 (3.0%)	21 (3.4%)
Protocol violation(s)	3 (0.5%)	1 (0.2%)	4 (0.7%)	1 (0.2%)
Lost to follow-up	13 (2.1%)	23 (3.9%)	9 (1.5%)	11 (1.8%)
Pregnancy	0	2 (0.3%)	1 (0.2%)	1 (0.2%)
Other	2 (0.3%)	1 (0.2%)	3 (0.5%)	1 (0.2%)

Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: ITT = intention-to-treat

Table 23 presents the demographic characteristics for the subjects enrolled in Studies 18251 and 18252. Subject demographics were generally balanced across treatment groups within trials. The breakdown of subjects' race, ethnicity, and region differed between the studies, likely due to the differing countries in which each study was conducted. Study 18251 had a higher proportion of subjects who were Hispanic and nonwhite, while over 90% of subjects in Study 18252 were white.

Approximately half of subjects in both studies were less than 18 years of age. Study 18251 enrolled one 9-year-old subject who was assigned to trifarotene and four 10-year-old subjects who were assigned to vehicle. The minimum age among the subjects enrolled in Study 18252 was 11-years of age.

Table 23. Demographic Characteristics of Subjects Enrolled, Studies 18251 and 18252

	Study 18251		Study 18252	
ITT Population	Trifarotene N=612	Vehicle N=596	Trifarotene N=602	Vehicle N=610
Age				
Mean (SD)	19.6 (6.9)	19.3 (5.9)	19.6 (6.2)	19.9 (6.4)
Median	17	18	18	18
Range	9, 58	10, 50	11, 49	11, 46
9–11 years	10 (1.6%)	9 (1.5%)	9 (1.5%)	6 (1.0%)
12–17 years	304 (49.7%)	269 (45.1%)	267 (44.4%)	288 (47.2%)
≥18 years	298 (48.7%)	318 (53.4%)	326 (54.2%)	316 (51.8%)
Sex				
Male	307 (50.2%)	272 (45.6%)	245 (40.7%)	272 (44.6%)
Female	305 (49.8%)	324 (54.4%)	357 (59.3%)	338 (55.4%)
Race				
White	508 (83.0%)	484 (81.2%)	565 (93.9%)	554 (90.8%)
Black or African American	47 (7.7%)	49 (8.2%)	27 (4.5%)	42 (6.9%)
Asian	23 (3.8%)	32 (5.4%)	2 (0.3%)	6 (1.0%)
American Indian or Alaska Native	11 (1.8%)	5 (0.8%)	1 (0.2%)	2 (0.3%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Multiple	8 (1.3%)	10 (1.7%)	2 (0.3%)	2 (0.3%)
Other	14 (2.3%)	15 (2.5%)	5 (0.8%)	3 (0.5%)
Ethnicity				
Hispanic or Latino	135 (22.1%)	148 (24.8%)	60 (10.0%)	62 (10.2%)
Not Hispanic or Latino	477 (77.9%)	448 (75.2%)	542 (90.0%)	548 (89.8%)

ITT Population	Study 18251 Trifarotene N=612	Study 18251 Vehicle N=596	Study 18252 Trifarotene N=602	Study 18252 Vehicle N=610
Skin phototype				
Type I	31 (5.1%)	34 (5.7%)	36 (6%)	37 (6.1%)
Type II	197 (32.2%)	182 (30.5%)	274 (45.5%)	249 (40.8%)
Type III	233 (38.1%)	227 (38.1%)	233 (38.7%)	248 (40.7%)
Type IV	97 (15.8%)	91 (15.3%)	33 (5.5%)	38 (6.2%)
Type V	43 (7.0%)	48 (8.1%)	14 (2.3%)	19 (3.1%)
Type VI	11 (1.8%)	14 (2.3%)	12 (2%)	19 (3.1%)
Region				
United States	407 (66.5%)	395 (66.3%)	124 (20.6%)	154 (25.2%)
Canada	70 (11.4%)	69 (11.6%)	NA	NA
Other	135 (22.1%)	132 (22.1%)	478 (79.4%)	456 (74.8%)

Source: Reviewer's analysis (similar to Applicant's analysis)
Applicant coded Puerto Rico as European Union/Other in Study 18251
Abbreviations: ITT = intention-to-treat; SD = standard deviation

Table 24 presents the baseline disease characteristics of subjects randomized in Studies 18251 and 18252 (i.e., the ITT population). All subjects had moderate facial acne (i.e., an IGA score of 3) at baseline, and approximately 99% of subjects had moderate truncal acne (i.e., a PGA score of 3) at baseline. Baseline disease characteristics were similar for the ITTT population used to analyze truncal acne and are presented in Table 88 in the Appendix in Section 18.6.

In Study 18251, five subjects (two assigned to trifarotene and three assigned to vehicle) had a noninflammatory lesion count less than the inclusion criteria of 25, with counts between 21 and 24. Three subjects (two assigned to trifarotene and one assigned to vehicle) had a trunk noninflammatory lesion count greater than 100, with counts between 106 and 125. In Study 18252, two subjects (one assigned to each treatment) had an inflammatory lesion count less than the inclusion criteria of 20; one subject had 10 inflammatory lesions, and the other with 7 inflammatory lesions. Four subjects (two assigned to each treatment) had a trunk noninflammatory lesion count greater than 100, with counts between 101 and 260.

Table 24. Baseline Disease Characteristics of ITT Subjects Enrolled, Studies 18251 and 18252

ITT Population	Study 18251 Trifarotene N=612	Study 18251 Vehicle N=596	Study 18252 Trifarotene N=602	Study 18252 Vehicle N=610
IGA (face)				
Moderate (3)	612 (100%)	596 (100%)	602 (100%)	610 (100%)
Inflammatory lesions (face)				
Mean (SD)	35 (13)	35 (14)	36 (12)	37 (15)
Median	31	31	33	34
Range	20, 131	20, 113	10, 110	7, 200
Noninflammatory lesions (face)				
Mean (SD)	54 (29)	53 (26)	51 (26)	51 (26)
Median	46	45	43	44
Range	22, 225	21, 191	25, 232	25, 305

	Study 18251		Study 18252	
ITT Population	Trifarotene N=612	Vehicle N=596	Trifarotene N=602	Vehicle N=610
PGA (trunk)				
Clear (0)	9 (1.5%)	8 (1.3%)	3 (0.5%)	1 (0.2%)
Almost Clear (1)	1 (0.2%)	2 (0.3%)	1 (0.2%)	0
Mild (2)	2 (0.3%)	1 (0.2%)	0	0
Moderate (3)	600 (98%)	585 (98%)	598 (99%)	609 (99.8%)
Inflammatory lesions (trunk)	N=611	N=595		
Mean (SD)	37 (18)	36 (17)	39 (16)	39 (17)
Median	32	31	35	34
Range	0, 140	0, 115	0, 100	0, 220
Noninflammatory lesions (trunk)	N=611	N=595		
Mean (SD)	46 (22)	48 (22)	46 (20)	46 (20)
Median	42	43	42	42.5
Range	0, 125	0, 107	0, 180	0, 260

Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: ITT = intention-to-treat; IGA = Investigator Global Assessment; PGA = Physician Global Assessment; SD = standard deviation

8.1.4. Results for Primary and Secondary Endpoints

Table 25 presents the percentage of subjects with missing IGA/PGA assessments at each study visit. The amount of missing data at each visit for facial lesion counts and trunk lesion counts were similar. Missing data were generally balanced across the treatment groups with Study 18251 having more missing data than Study 18252.

Table 25. Missing IGA/PGA Assessments by Visit for ITT Population, Studies 18251 and 18252

	Study 18251		Study 18252	
ITT Population	Trifarotene N=612	Vehicle N=596	Trifarotene N=602	Vehicle N=610
Week 1	28 (4.6%)	29 (4.9%)	7 (1.2%)	13 (2.1%)
Week 2	34 (5.6%)	33 (5.5%)	14 (2.3%)	13 (2.1%)
Week 4	30 (4.9%)	23 (3.9%)	15 (2.5%)	15 (2.5%)
Week 8	55 (9.0%)	46 (7.7%)	31 (5.1%)	32 (5.2%)
Week 12	69 (11.3%)	57 (9.6%)	39 (6.5%)	37 (6.1%)

Source: Reviewer's analysis
Abbreviations: ITT = intention-to-treat; IGA = Investigator Global Assessment; PGA = Physician Global Assessment

Table 26 and Table 27 present the results of the co-primary endpoints evaluated on the face and the co-secondary endpoints evaluated on the trunk. All endpoints were statistically significant with p-values less than or equal to 0.001. The treatment effect observed in Study 18252 was generally larger than the treatment effect observed in Study 18251.

Table 26. Results for Co-primary Endpoints (Face) at Week 12 for ITT Population, Studies 18251 and 18252

	Study 18251			Study 18252		
	Trifarotene N=612	Vehicle N=596	Trt Effect (p-value)	Trifarotene N=602	Vehicle N=610	Trt Effect (p-value)
IGA success (face)	29.4%	19.5%	9.8% (<0.001)	42.3%	25.7%	16.6% (<0.001)
Inflammatory lesions						
Baseline mean	34.7	34.8		36.1	37.0	
Week 12 mean	15.7	19.3		12.0	17.6	
Change, LS mean	-19.0	-15.4	-3.6 (<0.001)	-24.2	-18.7	-5.6 (<0.001)
Noninflammatory lesions						
Baseline mean	54.0	52.8		50.6	51.2	
Week 12 mean	28.0	34.5		20.6	28.9	
Change, LS mean	-25.0	-17.9	-7.1 (<0.001)	-30.1	-21.6	-8.5 (<0.001)

Source: Reviewer's analysis (similar to Applicant's analysis)
Missing data imputed using multiple imputation. Means and LS means combined from 50 imputed datasets. P-value for IGA success calculated from Cochran-Mantel-Haenszel test stratified by analysis center. P-value for change in lesion counts calculated from an analysis of covariance model including factors for baseline count, analysis center, and treatment. The SE for the mean inflammatory lesion counts was approximately 0.6, and SE for the mean noninflammatory lesion counts was approximately 1.0.
Abbreviations: SE = standard error; LS = least square; IGA = Investigator Global Assessment; Trt = treatment

Table 27. Results for Co-secondary Endpoints (Trunk) at Week 12 for ITTT Population, Studies 18251 and 18252

	Study 18251			Study 18252		
	Trifarotene N=600	Vehicle N=585	Trt Effect (p-value)	Trifarotene N=598	Vehicle N=609	Trt Effect (p-value)
PGA success (trunk)	35.7%	25.0%	10.7% (<0.001)	42.6%	29.9%	12.7% (<0.001)
Inflammatory lesions						
Baseline mean	37.5	36.2		39.3	39.1	
Week 12 mean	15.9	17.9		13.5	18.8	
Change, LS mean	-21.4	-18.8	-2.5 (<0.001)	-25.5	-19.8	-5.7 (<0.001)
Noninflammatory lesions						
Baseline mean	47.0	48.3		46.4	45.8	
Week 12 mean	24.5	29.4		20.5	24.5	
Change, LS mean	-21.9	-17.8	-4.1 (0.001)	-25.9	-20.8	-5.0 (<0.001)

Source: Reviewer's analysis (same as Applicant's analysis)
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets. P-value for PGA success calculated from Cochran-Mantel-Haenszel test stratified by analysis center. P-value for change in lesion counts calculated from an analysis of covariance model including factors for baseline count, analysis center, and treatment. The SE for the mean inflammatory lesion counts was approximately 0.6, and SE for the mean noninflammatory lesion counts was approximately 1.0.
Abbreviations: ITTT = intention-to-treat on the trunk; SE = standard error; LS = least square; PGA = Physician Global Assessment; Trt = treatment

Table 28 presents the sensitivity analyses described in Section 8.1.2. All sensitivity analyses were consistent with the primary analysis. Sensitivity analyses for the co-secondary endpoints were also consistent with the primary analysis and are presented in Table 89 in the Appendix in Section 18.6.

Table 28. Sensitivity Analyses of Co-primary Endpoints (Face) at Week 12, Studies 18251 and 18252

	Study 18251			Study 18252		
	Trifarotene N=612	Vehicle N=596	Trt Effect (p-value)	Trifarotene N=602	Vehicle N=610	Trt Effect (p-value)
IGA success (face)						
ITT population						
Primary–MI	29.4%	19.5%	9.8% (<0.001)	42.3%	25.7%	16.6% (<0.001)
MI (MNAR)	28.6%	19.5%	9.2% (<0.001)	41.7%	25.6%	16.1% (<0.001)
LOCF	26.8%	18.1%	8.7% (<0.001)	40.4%	24.4%	15.9% (<0.001)
MAF	26.3%	18.1%	8.2% (<0.001)	40.0%	24.3%	15.8% (<0.001)
MI (categorical)	29.3%	19.5%	9.9% (<0.001)	42.3%	25.6%	16.7% (<0.001)
Per-protocol population	*N=514*	*N=507*		*N=490*	*N=544*	
MI	29.1%	18.5%	10.6% (<0.001)	43.2%	26.8%	16.4% (<0.001)
Inflammatory lesions, LS mean						
ITT population						
Primary–MI	-19.0	-15.4	-3.6 (<0.001)	-24.2	-18.7	-5.6 (<0.001)
MI (MNAR)	-18.8	-15.4	-3.4 (<0.001)	-24.1	-18.7	-5.4 (<0.001)
LOCF	-18.3	-14.7	-3.5 (<0.001)	-23.7	-18.0	-5.6 (<0.001)
MAF	-19.2	-15.5	-3.7 (<0.001)	-24.2	-18.5	-5.7 (<0.001)
Per-protocol population	*N=514*	*N=507*		*N=490*	*N=544*	
MI	-19.7	-15.8	-3.9 (<0.001)	-25.1	-19.5	-5.7 (<0.001)
Noninflammatory lesions, LS mean						
Primary–MI (ITT)	-25.0	-17.9	-7.1 (<0.001)	-30.1	-21.6	-8.5 (<0.001)
MI (MNAR, ITT)	-24.6	-17.7	-6.9 (<0.001)	-29.8	-21.5	-8.3 (<0.001)
LOCF	-23.7	-16.9	-6.9 (<0.001)	-29.1	-20.5	-8.6 (<0.001)
MAF	-25.4	-18.4	-7.0 (<0.001)	-29.7	-21.3	-8.4 (<0.001)
Per-protocol population	*N=514*	*N=507*		*N=490*	*N=544*	
MI	-26.6	-19.0	-7.6 (<0.001)	-30.9	-22.4	-8.5 (<0.001)

Source: Reviewer's analysis (similar to Applicant's analysis).
LS means presented for lesion counts. Missing data imputed using multiple imputation, and results for LS means combined from 50 imputed datasets. P-value for IGA success calculated from Cochran-Mantel-Haenszel test stratified by analysis center. P-value for change in lesion counts calculated from an analysis of covariance model including factors for baseline count, analysis center, and treatment. LOCF results differ from Applicant's, as the clinical study report states that baseline data were not carried forward to impute the missing observations. As the statistical analysis plan does not mention this, reviewer applied LOCF to ITT population.
Abbreviations: LS = least square; ITT = intention-to-treat; IGA = Investigator Global Assessment; MI = multiple imputation; MAF = missing as failure; MNAR = missing not at random; LOCF = last observation carried forward; Trt = treatment

Supportive Endpoints

The SAPs specified as supportive endpoints the percent change in facial and truncal inflammatory and noninflammatory lesion counts from baseline to Week 12. The results of these endpoints are reported in Table 29.

Table 29. Results for Percent Change From Baseline in Lesion Counts at Week 12, Studies 18251 and 18252

	Study 18251			Study 18252		
	Trifarotene	**Vehicle**	**Trt Effect**	**Trifarotene**	**Vehicle**	**Trt Effect**
Facial lesions, ITT population	N=612	N=596		N=602	N=610	
Inflammatory lesions						
Percent change, mean (SE)	-54.4 (1.4)	-44.8 (1.6)	-9.6	-66.2 (1.3)	-51.2 (1.5)	-14.9
Noninflammatory lesions						
Percent change, mean (SE)	-49.7 (1.4)	-35.7 (1.8)	-14.0	-57.7 (1.3)	-43.9 (1.5)	-13.8
Truncal lesions, ITTT population	N=600	N=585		N=598	N=609	
Inflammatory lesions						
Percent change, mean (SE)	-57.4 (1.5)	-50.0 (1.6)	-7.4	-65.4 (1.4)	-51.1 (2.2)	-14.3
Noninflammatory lesions						
Percent change, mean (SE)	-49.1 (1.7)	-40.3 (1.9)	-8.9	-55.2 (1.5)	-45.1 (1.6)	-10.1

Source: Reviewer's analysis (same results as Applicant's analysis)
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets
Abbreviations: ITT = intention-to-treat; ITTT = intention-to-treat on the trunk; SE = standard error; Trt = treatment

Randomization Issue

As discussed in Section 8.1.1, the CSRs state that stratification by center was mistakenly not implemented in the randomization scheme for the first part of the studies. On December 22, 2016, the Applicant reset the IRT system to stratify randomization by center. In Study 18251, a total of 534 (44%) subjects were randomized before this date, and 674 (56%) subjects were randomized after this date. In Study 18252, 968 (80%) subjects were randomized before December 22, 2016, and 244 (20%) subjects were randomized after this date.

To explore possible impacts of the change in randomization, results for the co-primary endpoints are presented in Table 30, Table 31, and Table 32 for the subsets of subjects randomized prior to December 22, 2016, and those randomized after. While efficacy appears to be larger after the randomization change in Study 18251, this trend is not observed in Study 18252. Overall, the mistake and change in the implementation of randomization does not impact the final conclusions of efficacy of trifarotene compared to vehicle.

Table 30. IGA Success at Week 12 for Subjects Randomized Before and After Change in Randomization Scheme

	Study 18251			Study 18252		
	Trifarotene	Vehicle	Trt Effect	Trifarotene	Vehicle	Trt Effect
Overall	N=612	N=596		N=602	N=610	
	29.4%	19.5%	9.8%	42.3%	25.7%	16.6%
Before	N=267	N=267		N=484	N=484	
	26.2%	20.0%	6.2%	43.3%	26.1%	17.2%
After	N=345	N=329		N=118	N=126	
	31.4%	18.9%	12.5%	38.5%	23.8%	14.8%

Source: Reviewer's analysis
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets
Abbreviations: Trt = treatment; IGA = Investigator Global Assessment

Table 31. Inflammatory Facial Lesion Count Results for Subjects Randomized Before and After Change in Randomization Scheme

	Study 18251			Study 18252		
	Trifarotene	Vehicle	Trt Effect	Trifarotene	Vehicle	Trt Effect
Overall	N=612	N=596		N=602	N=610	
Baseline mean	34.7	34.8		36.1	37.0	
Change, mean (SE)	-19.0 (0.6)	-15.6 (0.6)	-3.4	-24.2 (0.6)	-19.4 (0.7)	-4.8
Change, LS mean (SE)	-19.0 (0.5)	-15.4 (0.5)	-3.6	-24.2 (0.5)	-18.7 (0.5)	-5.5
Before	N=267	N=267		N=484	N=484	
Baseline mean	34.4	34.0		35.6	36.1	
Change, mean (SE)	-18.3 (0.8)	-15.8 (0.8)	-2.5	-23.9 (0.7)	-18.9 (0.7)	-5.0
Change, LS mean (SE)	-18.0 (0.8)	-15.8 (0.8)	-2.2	-23.8 (0.6)	-18.3 (0.6)	-5.5
After	N=345	N=329		N=118	N=126	
Baseline mean	34.9	35.5		38.2	40.6	
Change, mean (SE)	-19.6 (0.8)	-15.5 (0.9)	-4.1	-25.2 (1.4)	-21.6 (1.7)	-3.6
Change, LS mean (SE)	-19.8 (0.9)	-15.1 (0.9)	-4.7	-27.6 (1.6)	-21.7 (1.5)	-5.9

Source: Reviewer's analysis
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets
Abbreviations: Trt = treatment; SE = standard error; LS = least square

Table 32. Noninflammatory Facial Lesion Count Results for Subjects Randomized Before and After Change in Randomization Scheme

	Study 18251			Study 18252		
	Trifarotene	Vehicle	Trt Effect	Trifarotene	Vehicle	Trt Effect
Overall	N=612	N=596		N=602	N=610	
Baseline mean	54.0	52.8		50.6	51.2	
Change, mean (SE)	-26.0 (0.9)	-18.3 (1.0)	-7.7	-30.0 (1.0)	-22.3 (0.8)	-7.7
Change, LS mean (SE)	-25.0 (0.9)	-17.9 (0.9)	-7.1	-30.1 (0.7)	-21.6 (0.7)	-8.5
Before	N=267	N=267		N=484	N=484	
Baseline mean	50.8	49.0		48.8	49.8	
Change, mean (SE)	-23.4 (1.5)	-17.7 (1.5)	-5.7	-28.9 (1.1)	-21.3 (0.9)	-7.6
Change, LS mean (SE)	-21.2 (1.5)	-16.9 (1.4)	-4.3	-29.4 (0.8)	-20.6 (0.8)	-8.8
After	N=345	N=329		N=118	N=126	
Baseline mean	56.5	55.9		58.1	56.5	
Change, mean (SE)	-28.1 (1.2)	-18.9 (1.3)	-9.2	-34.6 (2.4)	-26.4 (1.7)	-8.2
Change, LS mean (SE)	-27.8 (1.3)	-19.2 (1.4)	-8.6	-34.3 (1.9)	-26.3 (1.8)	-8.0

Source: Reviewer's analysis
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets
Abbreviations: Trt = treatment; SE = standard error; LS = least square

Face Versus Trunk: Exploratory Analysis

It is of interest to investigate how the treatment response on one region (i.e., the face) is associated with the treatment response on the other region (i.e., the trunk) as most subjects who were enrolled in the studies had moderate acne on both regions, and the assessment of efficacy for acne is based on the face. Table 33 presents a cross-tabulation of IGA and PGA success for the ITTT population, i.e., subjects with both moderate facial acne and moderate truncal acne. The IGA and PGA binary response outcomes were the same (i.e., the subject achieved success on both scales or failed to achieve success on both scales) for approximately 77 to 87% of subjects.

Study 18252 had higher IGA response rates than Study 18251 (see Table 26), and Table 33 shows that Study 18252 also had higher agreement between the response rates on the face and trunk than in Study 18251. In Study 18252, approximately 43% of subjects in the trifarotene arm were IGA/PGA responders for each of the face and trunk regions: 35% of subjects achieved treatment success on both regions and the remaining 8% achieved success on only one region and not the other. In Study 18251, 29%/36% of subjects in the trifarotene arm were IGA/PGA responders: 21% of subjects achieved treatment success on both regions, 8% of subjects achieved success only on the face, and 15% of subjects achieved success only on the trunk.

Table 33. IGA vs. PGA Success at Week 12 (ITTT Population)

	Study 18251				Study 18252			
	Trifarotene N=600		Vehicle N=585		Trifarotene N=598		Vehicle N=609	
	IGA		IGA		IGA		IGA	
PGA	Failure	Success	Failure	Success	Failure	Success	Failure	Success
Failure	56%	8%	70%	5%	50%	8%	66%	5%
Success	15%	21%	11%	14%	8%	35%	9%	21%
Agree	77%		84%		84%		87%	
Disagree	23%		16%		16%		13%	

Source: Reviewer's analysis based on the ITTT population
Missing data were imputed with multiple imputation, and results combined from 50 imputed datasets
Abbreviations: ITTT = intention-to-treat on the trunk; IGA = Investigator Global Assessment; PGA = Physician Global Assessment

8.1.5. Findings in Special/Subgroup Populations

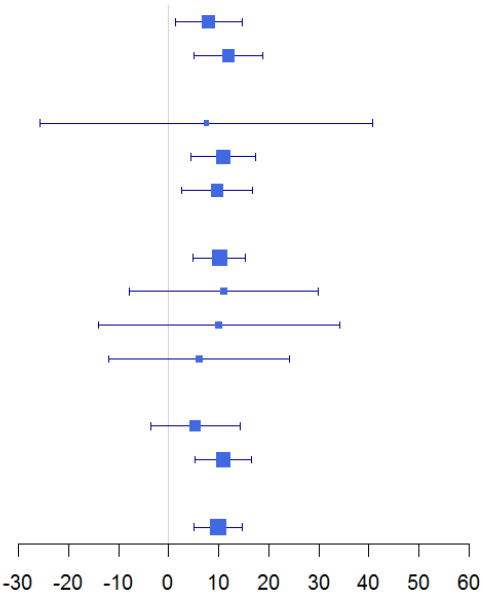
8.1.5.1. Sex, Race, Age, and Ethnicity

Figure 3 and Figure 4 present the efficacy results for the IGA success endpoint at Week 12 (i.e., the percentage of subjects with an IGA score of 0 or 1 and at least a two-grade reduction from baseline) by sex, age group, race, and ethnicity in Studies 18251 and 18252 respectively. Figure 5, Figure 6, Figure 7, and Figure 8 present the efficacy results for the change from baseline in inflammatory and noninflammatory lesions at Week 12 by sex, age group, race, and ethnicity in Studies 18251 and 18252 respectively.

In Study 18252, black subjects in the vehicle arm had a higher IGA response rate and larger decrease in noninflammatory lesions than black subjects in the trifarotene arm; however, this effect was not observed for inflammatory lesions, nor observed in Study 18251. The observation of reversed treatment effect in the subgroup of black subjects in Study 18252 may be attributed to the small, imbalanced sample size in this subgroup (27 subjects in the treatment arm and 42 subjects in the vehicle arm) and/or may be due to chance by examining many subgroups. This is supported by the lack of replication of this trend in Study 18251, which had a larger number of black subjects.

Figure 3. IGA Treatment Effect at Week 12 by Sex, Age Group, Race, and Ethnicity, Study 18251

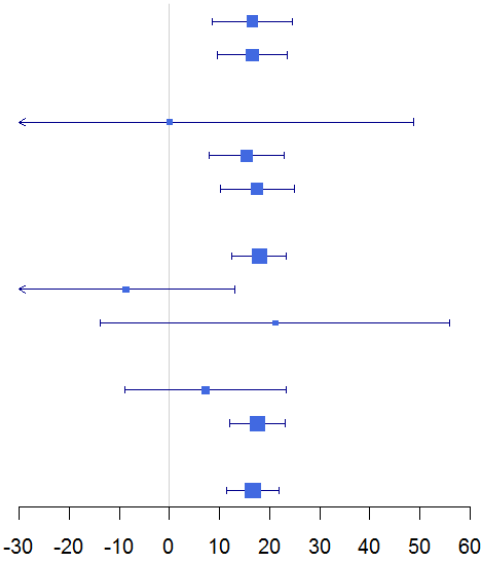
Subgroups	(n[T], n[V])	Trifarotene	Vehicle	Difference
Sex				
Male	(307, 272)	25.9%	17.9%	8%
Female	(305, 324)	32.8%	20.9%	11.9%
Age				
9-11 Years	(10, 9)	20.4%	12.9%	7.5%
12-17 Years	(304, 269)	25.6%	14.7%	10.9%
>=18 Years	(298, 318)	33.5%	23.8%	9.7%
Race				
White	(508, 484)	28.8%	18.7%	10.1%
Black or African American	(47, 49)	40.1%	29.1%	11%
Asian	(23, 32)	32.9%	22.9%	10%
Other	(34, 31)	19.9%	13.8%	6.1%
Ethnicity				
Hispanic or Latino	(135, 148)	20.5%	15.2%	5.3%
Not Hispanic or Latino	(477, 448)	31.9%	21%	10.9%
Overall	(612, 596)	29.4%	19.5%	9.9%



Source: Reviewer's analysis (similar to Applicant's analysis)
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.
Abbreviation: IGA = Investigator Global Assessment

Figure 4. IGA Treatment Effect at Week 12 by Sex, Age Group, Race, and Ethnicity, Study 18252

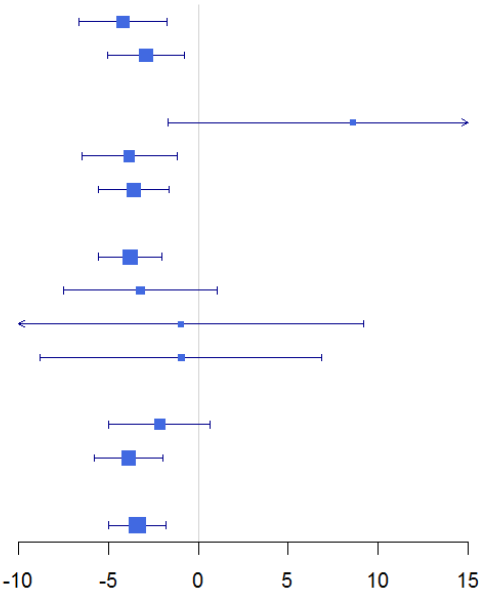
Subgroups	(n[T], n[V])	Trifarotene	Vehicle	Difference
Sex				
Male	(245, 272)	40.1%	23.6%	16.5%
Female	(357, 338)	43.8%	27.3%	16.5%
Age				
9-11 Years	(9, 6)	33.3%	33.3%	0%
12-17 Years	(267, 288)	35.8%	20.4%	15.4%
>=18 Years	(326, 316)	47.8%	30.3%	17.5%
Race				
White	(565, 554)	43.2%	25.3%	17.9%
Black or African American	(27, 42)	25.3%	34%	-8.7%
Other	(10, 14)	35.4%	14.3%	21.1%
Ethnicity				
Hispanic or Latino	(60, 62)	32.9%	25.7%	7.2%
Not Hispanic or Latino	(542, 548)	43.3%	25.7%	17.6%
Overall	(602, 610)	42.3%	25.7%	16.6%



Source: Reviewer's analysis (similar to Applicant's analysis)
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.
Abbreviation: IGA = Investigator Global Assessment

Figure 5. Change From Baseline in Inflammatory Lesion Count at Week 12 by Sex, Age Group, Race, and Ethnicity, Study 18251

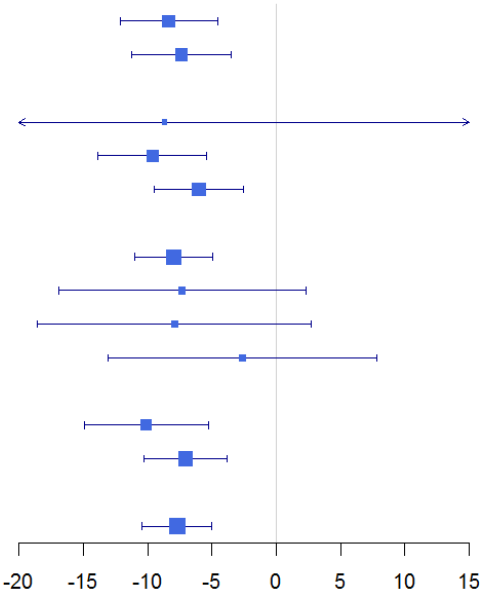
Subgroups	(n[T], n[V])	Trifarotene	Vehicle	Difference
Sex				
Male	(307, 272)	-18.6	-14.4	-4.2
Female	(305, 324)	-19.5	-16.5	-2.9
Age				
9-11 Years	(10, 9)	-10.4	-19	8.6
12-17 Years	(304, 269)	-18.7	-14.8	-3.8
>=18 Years	(298, 318)	-19.7	-16.1	-3.6
Race				
White	(508, 484)	-19.2	-15.4	-3.8
Black or African American	(47, 49)	-19.7	-16.5	-3.2
Asian	(23, 32)	-18.1	-17.1	-1
Other	(34, 31)	-16.9	-15.9	-1
Ethnicity				
Hispanic or Latino	(135, 148)	-18.7	-16.6	-2.2
Not Hispanic or Latino	(477, 448)	-19.1	-15.3	-3.9
Overall	(612, 596)	-19	-15.6	-3.4



Source: Reviewer's analysis (similar to Applicant's analysis)
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

Figure 6. Change From Baseline in Noninflammatory Lesion Count at Week 12 by Sex, Age Group, Race, and Ethnicity, Study 18251

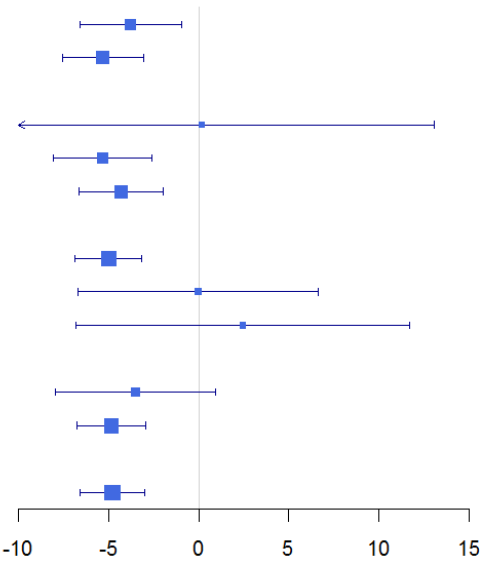
Subgroups	(n[T], n[V])	Trifarotene	Vehicle	Difference
Sex				
Male	(307, 272)	-24.7	-16.4	-8.4
Female	(305, 324)	-27.3	-19.9	-7.4
Age				
9-11 Years	(10, 9)	-16.2	-7.5	-8.7
12-17 Years	(304, 269)	-26.5	-16.8	-9.6
>=18 Years	(298, 318)	-25.9	-19.9	-6
Race				
White	(508, 484)	-26.6	-18.6	-8
Black or African American	(47, 49)	-28.7	-21.4	-7.3
Asian	(23, 32)	-19.3	-11.4	-7.9
Other	(34, 31)	-18.4	-15.7	-2.6
Ethnicity				
Hispanic or Latino	(135, 148)	-28.9	-18.8	-10.1
Not Hispanic or Latino	(477, 448)	-25.2	-18.2	-7
Overall	(612, 596)	-26	-18.3	-7.7



Source: Reviewer's analysis (similar to Applicant's analysis)
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

Figure 7. Change From Baseline in Inflammatory Lesion Count at Week 12 by Sex, Age Group, Race, and Ethnicity, Study 18252

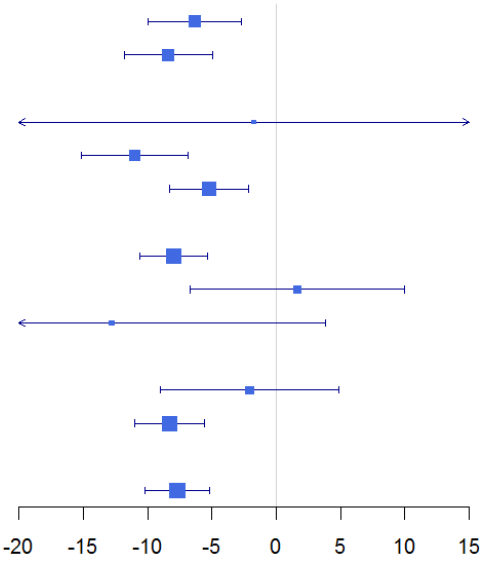
Subgroups	(n[T], n[V])	Trifarotene	Vehicle	Difference
Sex				
Male	(245, 272)	-22.8	-19	-3.8
Female	(357, 338)	-25.1	-19.8	-5.3
Age				
9-11 Years	(9, 6)	-16.3	-16.5	0.2
12-17 Years	(267, 288)	-24	-18.7	-5.3
>=18 Years	(326, 316)	-24.5	-20.2	-4.3
Race				
White	(565, 554)	-24.6	-19.6	-5
Black or African American	(27, 42)	-17.2	-17.1	0
Other	(10, 14)	-17.9	-20.3	2.4
Ethnicity				
Hispanic or Latino	(60, 62)	-18.8	-15.2	-3.5
Not Hispanic or Latino	(542, 548)	-24.8	-19.9	-4.9
Overall	(602, 610)	-24.2	-19.4	-4.8



Source: Reviewer's analysis (similar to Applicant's analysis)
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

Figure 8. Change From Baseline in Noninflammatory Lesion Count at Week 12 by Sex, Age Group, Race, and Ethnicity, Study 18252

Subgroups	(n[T], n[V])	Trifarotene	Vehicle	Difference
Sex				
Male	(245, 272)	-27.1	-20.8	-6.3
Female	(357, 338)	-32	-23.6	-8.4
Age				
9-11 Years	(9, 6)	-14.2	-12.5	-1.7
12-17 Years	(267, 288)	-33.8	-22.8	-11
>=18 Years	(326, 316)	-27.3	-22.1	-5.2
Race				
White	(565, 554)	-30.4	-22.4	-8
Black or African American	(27, 42)	-20.6	-22.3	1.6
Other	(10, 14)	-31.6	-18.8	-12.8
Ethnicity				
Hispanic or Latino	(60, 62)	-26.1	-24	-2.1
Not Hispanic or Latino	(542, 548)	-30.4	-22.2	-8.3
Overall	(602, 610)	-30	-22.3	-7.7



Source: Reviewer's analysis (similar to Applicant's analysis)
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

8.1.5.2. Center/Country

Study 18251 enrolled and randomized 1,208 subjects from 117 centers and Study 18252 enrolled and randomized 1,212 subjects from 81 centers. The SAPs specify analyzing the treatment-by-analysis center interaction using the Breslow Day test for the IGA success rate endpoint and assessing the treatment-by-analysis center interaction in the ANCOVA model for the lesion count endpoints using an alpha level of 0.1. The center by treatment interaction was statistically significant at the 0.1 level for IGA success endpoint at Week 12 in Study 18251 and all of the co-primary endpoints in Study 18252. Therefore, efficacy by center was further explored through plots and descriptive statistics. In the Appendix, Figure 27 through Figure 32 present the results for the co-primary endpoints by site for Studies 18251 and 18252. Only sites that enrolled more than 12 subjects are included in the figures for ease of view. The sites are ordered from that with the largest sample size on the left side of the figures to those with the smallest sample sizes on the right. It should be noted that in Study 18251, 44% of subjects and in Study 18252, 80% of subjects were enrolled before randomization was stratified by site, so randomization is not necessarily preserved for the treatment comparisons within a site.

There is variation in efficacy by site as seen in the figures and evident from the significant treatment by center interaction effect; however, it does not appear that any single site or a few sites drove the overall efficacy results. The large number of sites and small number of subjects per treatment arm in most sites likely describes the large variation. The sites with higher numbers of subjects per treatment arm (e.g., 15 or higher) tended to have more consistent treatment effects with the observed overall treatment effect .

Due to the significant treatment by center interaction terms, the Agency further examined efficacy by country. All subjects enrolled with an IGA score of 3 (i.e., moderate). Table 34 and Table 35 present the baseline lesion counts by country for Studies 18251 and 18252 respectively. Figure 9, Figure 10, and Figure 11 present the results of the co-primary endpoints by country in Study 18251; similarly, Figure 12, Figure 13, and Figure 14 present the results of the co-primary endpoints by country in Study 18252. There were larger observed treatment effects across the co-primary endpoints in subjects from Hungary in Study 18251 compared to the other countries in the study. Similarly, a large treatment effect was observed in subjects from Poland, Russia, Ukraine, and Hungary in Study 18252 compared to the other countries in the studies.

For subjects in the US, the treatment effect for IGA success and change from baseline in inflammatory lesion count was consistent across both trials. For the change from baseline in noninflammatory lesion count, the treatment effect was larger in Study 18251 than Study 18252, though the number of subjects from the US was much larger in Study 18251.

Table 34. Baseline Lesion Count by Country, Study 18251

		Inflammatory Lesions		Noninflammatory Lesions	
ITT Population	Number of Centers 117	Trifarotene N=612	Vehicle N=596	Trifarotene N=612	Vehicle N=596
USA	81	N=407	N=395	N=407	N=395
Mean (SD)		34 (13)	34 (13)	51 (28)	49 (24)
Min, max		20, 131	20, 113	22, 225	21, 191
Canada	13	N=70	N=69	N=70	N=69
Mean (SD)		34 (14)	32 (10)	46 (24)	45 (18)
Min, max		21, 94	20, 63	25, 185	25, 105
Germany	10	N=64	N=60	N=64	N=60
Mean (SD)		38 (14)	41 (15)	76 (31)	75 (26)
Min, max		21, 92	20, 82	33, 183	30, 153
Hungary	9	N=44	N=44	N=44	N=44
Mean (SD)		36 (12)	37 (15)	57 (26)	55 (27)
Min, max		21, 70	20, 85	25, 230	26, 125
Puerto Rico	4	N=27	N=28	N=27	N=28
Mean (SD)		41 (15)	42 (18)	58 (21)	71 (33)
Min, max		20, 75	20, 100	25, 108	27, 159

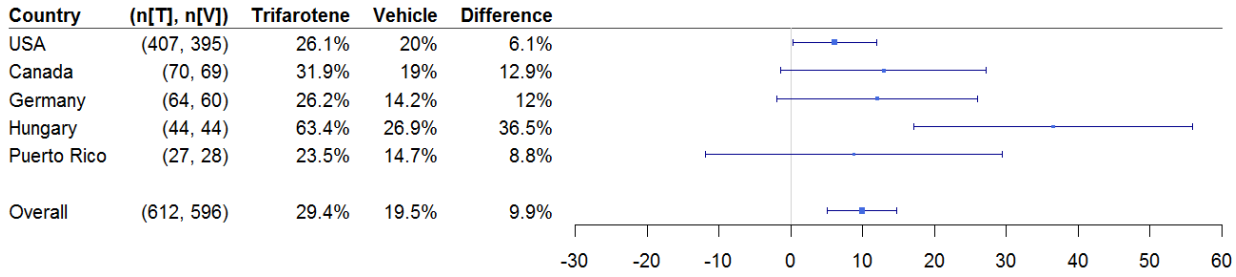
Source: Reviewer's analysis
Abbreviations: ITT = intention-to-treat; SD = standard deviation

Table 35. Baseline Lesion Count by Country, Study 18252

		Inflammatory Lesions		Noninflammatory Lesions	
	Number of Centers	Trifarotene	Vehicle	Trifarotene	Vehicle
ITT Population	81	N=602	N=610	N=602	N=610
USA	28	N=124	N=154	N=124	N=154
Mean (SD)		33 (12)	33 (14)	50 (23)	54 (34)
Min, max		20, 110	20, 165	25, 155	25, 305
Russia	7	N=100	N=81	N=100	N=81
Mean (SD)		37 (11)	38 (11)	42 (19)	44 (18)
Min, max		21, 79	20, 73	25, 118	25, 151
Poland	14	N=92	N=96	N=92	N=96
Mean (SD)		38 (16)	40 (17)	64 (35)	64 (28)
Min, max		20, 101	20, 94	26, 232	27, 159
Hungary	7	N=74	N=66	N=74	N=66
Mean (SD)		35 (12)	39 (23)	55 (35)	51 (25)
Min, max		20, 85	20, 200	25, 225	25, 154
Ukraine	8	N=71	N=74	N=71	N=74
Mean (SD)		37 (10)	38 (11)	46 (17)	45 (16)
Min, max		22, 72	23, 66	25, 98	26, 94
Romania	5	N=64	N=65	N=64	N=65
Mean (SD)		41 (12)	43 (13)	50 (15)	52 (17)
Min, max		20, 70	20, 81	25, 85	25, 95
Czech Republic	8	N=63	N=60	N=63	N=60
Mean (SD)		33 (10)	33 (11)	41 (17)	40 (17)
Min, max		20, 77	21, 78	25, 91	25, 130
Spain	4	N=14	N=14	N=14	N=14
Mean (SD)		29 (11)	29 (9)	71 (34)	53 (20)
Min, max		10, 50	7, 41	35, 165	28, 114

Source: Reviewer's analysis
Abbreviations: ITT = intention-to-treat; SD = standard deviation

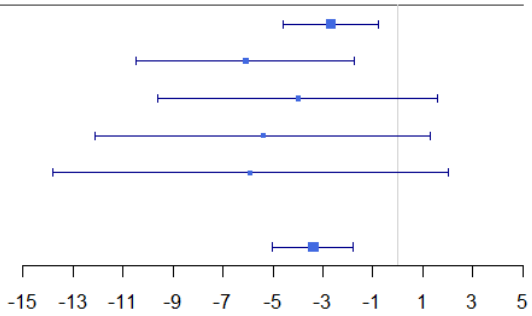
Figure 9. IGA Treatment Effect at Week 12 by Country, Study 18251



Source: Reviewer's analysis
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets
Abbreviation: IGA = Investigator Global Assessment

Figure 10. Change From Baseline in Facial Inflammatory Lesion Count at Week 12 by Country, Study 18251

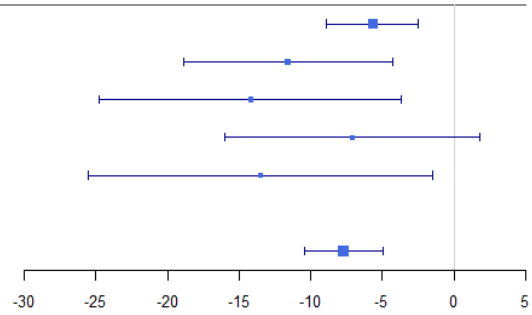
Country	(n[T], n[V])	Trifarotene	Vehicle	Difference
USA	(407, 395)	-18.2	-15.5	-2.7
Canada	(70, 69)	-18.4	-12.3	-6.1
Germany	(64, 60)	-18	-14	-4
Hungary	(44, 44)	-26.4	-21	-5.4
Puerto Rico	(27, 28)	-24.9	-19	-5.9
Overall	(612, 596)	-19	-15.6	-3.4



Source: Reviewer's analysis
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

Figure 11. Change From Baseline in Facial Noninflammatory Lesion Count at Week 12 by Country, Study 18251

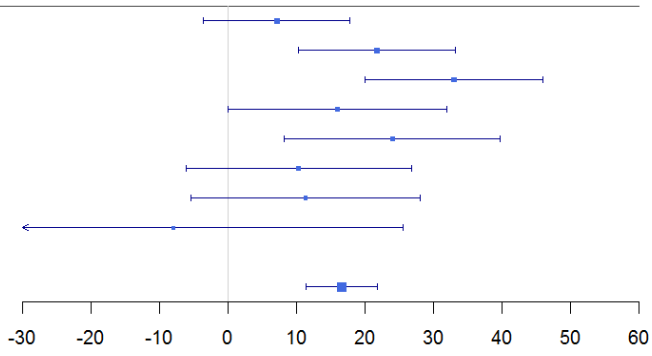
Country	(n[T], n[V])	Trifarotene	Vehicle	Difference
USA	(407, 395)	-23	-17.3	-5.7
Canada	(70, 69)	-25.7	-14.1	-11.6
Germany	(64, 60)	-36.2	-22	-14.2
Hungary	(44, 44)	-33.2	-26.1	-7.1
Puerto Rico	(27, 28)	-36.5	-23	-13.5
Overall	(612, 596)	-26	-18.3	-7.7



Source: Reviewer's analysis.
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

Figure 12. IGA Treatment Effect at Week 12 by Country, Study 18252

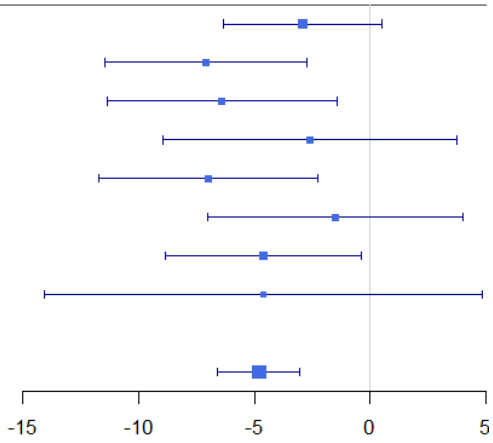
Country	(n[T], n[V])	Trifarotene	Vehicle	Difference
USA	(124, 154)	32.5%	25.4%	7.1%
Russia	(100, 81)	32.8%	11.1%	21.7%
Poland	(92, 96)	53.4%	20.4%	33%
Hungary	(74, 66)	47.5%	31.5%	16%
Ukraine	(71, 74)	58.2%	34.2%	24%
Romania	(64, 65)	41.3%	31%	10.3%
Czech Republic	(63, 60)	41.3%	30%	11.3%
Spain	(14, 14)	25.3%	33.3%	-8%
Overall	(602, 610)	42.3%	25.7%	16.6%



Source: Reviewer's analysis
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.
Abbreviation: IGA = Investigator Global Assessment

Figure 13. Change From Baseline in Facial Inflammatory Lesion Count at Week 12 by Country, Study 18252

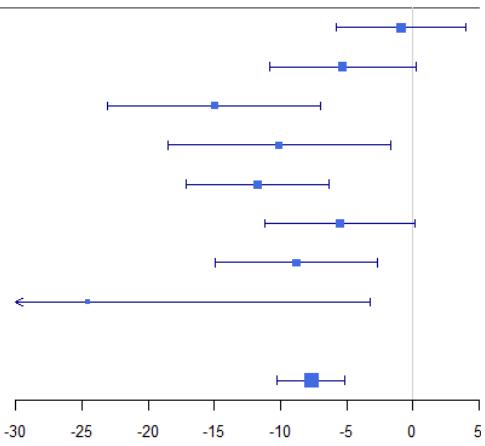
Country	(n[T], n[V])	Trifarotene	Vehicle	Difference
USA	(124, 154)	-19.4	-16.5	-2.9
Russia	(100, 81)	-23.1	-16	-7.1
Poland	(92, 96)	-27	-20.6	-6.4
Hungary	(74, 66)	-26.9	-24.3	-2.6
Ukraine	(71, 74)	-27.4	-20.4	-7
Romania	(64, 65)	-28.7	-27.2	-1.5
Czech Republic	(63, 60)	-20.4	-15.8	-4.6
Spain	(14, 14)	-20.2	-15.6	-4.6
Overall	(602, 610)	-24.2	-19.4	-4.8



Source: Reviewer's analysis
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

Figure 14. Change From Baseline in Facial Noninflammatory Lesion Count at Week 12 by Country, Study 18252

Country	(n[T], n[V])	Trifarotene	Vehicle	Difference
USA	(124, 154)	-25.1	-24.2	-0.9
Russia	(100, 81)	-20.4	-15.1	-5.3
Poland	(92, 96)	-44.5	-29.5	-15
Hungary	(74, 66)	-33.7	-23.6	-10.1
Ukraine	(71, 74)	-31.2	-19.5	-11.7
Romania	(64, 65)	-30.1	-24.6	-5.5
Czech Republic	(63, 60)	-25.2	-16.4	-8.8
Spain	(14, 14)	-42.5	-17.9	-24.6
Overall	(602, 610)	-30	-22.3	-7.7



Source: Reviewer's analysis
Depicts the treatment difference and 95% confidence interval. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of the safety of trifarotene cream, 0.005% for the topical treatment of acne vulgaris focused on pooled data from two phase 3 trials—Trials 18251 and 18252—henceforth called Safety Pool 1. Both phase 3 trials were multicenter, randomized, double-blind, vehicle-controlled trials of identical design (see Section 8.1.1). The two pivotal phase 3 trials enrolled

2,420 subjects ages 9 years and older with moderate acne, 1,220 received trifarotene and 1,200 received vehicle. Subjects applied trifarotene cream, 0.005% to the face and trunk once a day for 12 weeks. Subjects in the trials had a score of 3 on the IGA scale with at least 20 inflammatory and 25 noninflammatory lesions on the face and on the trunk for subjects >11 years old, they had a PGA of 3 with at least 20 inflammatory and between 20 and 100 noninflammatory lesions at baseline.

Additional safety data were provided from a long-term trial, Trial 18250, which consisted of 455 subjects who were treated once a day with trifarotene cream, 0.005% for 52 weeks.

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.

8.2.2. Review of the Safety Database

Overall Exposure

There were 2,420 subjects who were randomized and received topical administration of trifarotene cream, 0.005% (1,220 subjects) or vehicle cream (1,200 subjects) once daily for 12 weeks in Safety Pool 1. The safety population differs from the ITT population because subjects for the safety population were analyzed for the actual treatment received as opposed to the ITT population which was analyzed according to randomized treatment. According to the safety reports, seven subjects in Trial 18251 and three subjects in Trial 18252 received trial treatment other than the treatment to which they were randomly assigned. In Trial 18251, five subjects who were randomized to vehicle received trifarotene cream, 0.005% at or after baseline and two subjects who were randomized to trifarotene cream, 0.005% received vehicle at or after baseline. All of these subjects were included in the trifarotene cream, 0.005% arm for the safety analysis. In Trial 18252, two subjects who were randomized to trifarotene cream, 0.005% received vehicle at or after baseline and one subject who was randomized to vehicle received trifarotene cream, 0.005% at or after baseline. These three subjects were analyzed in the trifarotene cream, 0.005% arm in the safety analysis.

Subjects treated with trifarotene cream, 0.005% had mean treatment compliance of 96.3% and 96.0% for the face and trunk, respectively. Subjects treated with vehicle cream had mean treatment compliance of 98.5% and 98.4% for the face and trunk, respectively (see Table 36).

Table 36. Summary of Treatment Compliance, Safety Pool 1

	Trifarotene, 0.005% Cream N=1,220		Vehicle Cream N=1,200	
	Face	Trunk	Face	Trunk
Treatment compliance (%), n	1,220	1,208	1,200	1,191
Mean (SD)	96.3 (8.86)	96.0 (9.37)	98.5 (3.93)	98.4 (4.14)
Median	100.0	100.0	100.0	100.0
Min, max	19, 200	0, 200	50, 117	50, 117

Source: NDA 211527: Module 2, ISS Table 16, p. 102; ISS Table 1.1.1

There were 455 subjects who were enrolled in the long-term safety trial, Trial 18250. Of those, 453 received the treatment. The mean treatment compliance for trifarotene cream, 0.005% was approximately 95% for both the face and trunk (see Table 37).

Table 37. Summary of Treatment Compliance, Long-Term Safety

	Trifarotene, 0.005% Cream N=453	
	Face	Trunk
Treatment Compliance (%), n	453	446
Mean (SD)	95.3 (9.30)	95.3 (10.66)
Median	98.9	99.2
Min, Max	27, 102	36, 147

Sources: NDA 211527: Module 2, ISS, Table 17; RD.06.SRE. 18250, Table 14

Adequacy of the Safety Database

The safety data base for trifarotene cream, 0.005% was adequate and consisted of the two phase 3 pivotal trial populations which totaled 2,420 subjects and a long-term safety trial in which 453 subjects were treated for 52 weeks (see Table 38 and Table 39 for subject disposition).

Table 38. Summary of Subject Disposition, All Subjects, Safety Pool 1

	Trifarotene Cream, 0.005%	Vehicle Cream	Total
Subjects in safety population	1,220	1,200	2,420
Completed subjects, n (%)	1,103 (90.4)	1,103 (91.9)	2,206 (91.2)
Subjects discontinued from study, n (%)	117 (9.6)	97 (8.1)	214 (8.8)
Primary reason for discontinuation, n (%)			
Lack of efficacy	1 (0.1)	2 (0.2)	3 (0.1)
Adverse event(s)	23 (1.9)	2 (0.2)	25 (1.0)
Withdrawal by subject	58 (4.8)	52 (4.3)	110 (4.5)
Protocol violation(s)	7 (0.6)	2 (0.2)	9 (0.4)
Lost to follow-up	22 (1.8)	34 (2.8)	56 (2.3)
Pregnancy	1 (0.1)	3 (0.3)	4 (0.2)
Other	5 (0.4)	2 (0.2)	7 (0.3)

Sources: NDA 211527: Module 2, ISS, Table 18, p. 104; ISS Table 1.3.1

Table 39. Summary of Subject Disposition, All Subjects, Long-Term Safety

	Trifarotene Cream, 0.005%
Subjects in safety population	455
Subjects treated	453
Completed subjects, n (%)	348 (76.5)
Subjects discontinued from study, n (%)	207 (23.5)
Primary reason for discontinuation, n (%)	
Lack of efficacy	4 (0.9)
Adverse event(s)	16 (3.5)
Withdrawal by subject	53 (11.6)
Protocol violation(s)	4 (0.9)
Lost to follow-up	17 (3.7)
Pregnancy	1 (0.2)
Other	12 (2.6)

Sources: NDA 211527: Module 2, ISS, Table 19, p. 105; RD.06.SRE.18250, Table 14.1.1.1

8.2.3. 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 of trifarotene cream, 0.005%. There were no significant deficiencies discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

For both phase 3 trials—Trials 18251 and 18252—and the long-term safety trial, Trial 18250, 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 trifarotene, 0.005% cream 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 trifarotene cream, 0.005%, 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 capture the incidence of the AEs more effectively .

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 an 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, although pregnancy was not considered an AE, the Applicant categorized abortion (voluntary, spontaneous, or therapeutic), in-utero death, or congenital anomaly as an SAE. Pregnancies and 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: Awareness of signs or symptom, but easily tolerated
- Moderate: Discomfort, enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or perform usual activity

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

Routine Clinical Tests

In Trials 18251 and 18252 (Safety Pool 1), investigators and site staff conducted safety monitoring during clinic visits at baseline, Week 1, 2, 4, 8, and 12/early termination (ET). These evaluations will consist of assessment of local tolerability and adverse events at each visit, vital signs and physical examination at screening, baseline, and at Week 12 ET/unscheduled visits, and laboratory tests at screening and Week 12/ET.

The protocols included clinical laboratory testing at screening and Week 12. The assessments included hematology, serum chemistry and urinalysis. Urine pregnancy testing was performed at the screening, baseline, Week 4, m 8, and 12 final/ET visits or earlier in case of premature study termination.

Local safety assessments included an evaluation of signs (scaling, erythema, and dryness) and symptoms (burning/stinging) at the application site (see Section 8.2.5.2 for scales). These local safety assessments will not be recorded as AEs unless the subject permanently discontinues the treatment at his/her request or at the Investigator's request or the subject requires concomitant treatment, including OTC products or any other medications (other than moisturizer).

8.2.4. Safety Results

Deaths

There were no deaths for the duration of the trials.

Serious Adverse Events

There were six (0.5%) subjects in the trifarotene cream, 0.005% group who presented a total of seven serious TEAEs and six (0.5%) subjects in the vehicle cream group who presented a total of seven serious TEAEs. Of the seven serious TEAEs reported with trifarotene cream, 0.005%, two were mild, one was moderate, and four were severe. Of the seven serious TEAEs reported with vehicle cream, four were moderate, and three were severe.

None of the serious TEAEs were considered to be related to study drug. Except for the serious TEAEs of ligament sprain and facial bones fracture, all these events resolved during the trials. Table 40 delineates the serious adverse events that occurred in Safety Pool 1.

Table 40. Summary of Serious TEAEs by System Organ Class and Preferred Term, Safety Population, Safety Pool 1

System Organ Class/Preferred Term	Trifarotene, Cream, 0.005% N=1,220	Vehicle Cream N=1,200
Number of serious TEAEs	7	7
Subjects with any serious TEAE, n (%)	6 (0.5)	6 (0.5)
Injury, poisoning, and procedural complications	3 (0.2)	0
Facial bones fracture	1 (0.1)	0
Ligament sprain	1 (0.1)	0
Procedural dizziness	1 (0.1)	0
Infections and infestations	2 (0.2)	3 (0.3)
Cellulitis	1 (0.1)	0
Infectious mononucleosis	1 (0.1)	0
Appendicitis	0	1 (0.1)
Atypical pneumonia	0	1 (0.1)
Sinusitis	0	1 (0.1)
Psychiatric disorders	1 (0.1)	1 (0.1)
Suicide attempt	1 (0.1)	1 (0.1)
Major depression	1 (0.1)	0
Congenital, familial, and genetic disorders	0	1 (0.1)
Hereditary angioedema	0	1 (0.1)
Renal and urinary disorders	0	1 (0.1)
Urinary tract infection	0	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	0	1 (0.1)
Asthma	0	1 (0.1)

Source: NDA 211527, Module 2: ISS, Table 29, p. 129
Abbreviation: TEAE = treatment-emergent adverse event

Overall, 12 serious TEAEs were reported by 10 (2.2%) subjects (see Table 41). None of the serious TEAEs were considered related to the study drug. Two of the serious TEAEs were of mild severity: umbilical hernia and supraumbilical hernia (Subject (b) (6); resolved during the study).

Five of the serious TEAEs were of moderate intensity: Crohn's disease (Subject (b) (6); still ongoing at the end of the study), complex regional pain syndrome (Subject (b) (6); resolved during the study), appendicitis (Subject (b) (6); resolved during the study), liver function test abnormal (Subject (b) (6); resolved during the study), and tonsillar hypertrophy (Subject (b) (6) resolved during the study).

Severe serious TEAEs were nasal septum deviation (Subject (b) (6); resolved during the study), pyelonephritis acute (Subject (b) (6); resolved during the study), postprocedural hemorrhage following adenotomy (Subject (b) (6); resolved during the study), abortion spontaneous (Subject (b) (6)), and complex partial seizures (Subject (b) (6); resolved during the study).

Table 41. Summary of Serious TEAEs by System Organ Class and Preferred Term, by Quarter and Overall Safety Population, Study 18250

	Trifarotene Cream, 0.005% N=453				
System Organ Class/Preferred Term	Q1 M=453	Q2 M=384	Q3 M=368	Q4 M=351	Overall N=453
Number of subjects with TEAEs	5	0	5	2	12
Subjects with any serious TEAE, n (%)	4 (0.9)	0	4 (1.1)	2 (0.6)	10 (2.2)
Gastrointestinal disorders	1 (0.2)	0	1 (0.3)	0	2 (0.4)
Crohn's disease	0	0	1 (0.3)	0	1 (0.2)
Umbilical hernia	1 (0.2)	0	0	0	1 (0.2)
Infections and infestations	1 (0.2)	0	1 (0.3)	0	2 (0.4)
Appendicitis	0	0	1 (0.3)	0	1 (0.2)
Pyelonephritis acute	1 (0.2)	0	0	0	1 (0.2)
Nervous system disorders	1 (0.2)	0	0	1 (0.3)	2 (0.4)
Complex partial seizures	1 (0.2)	0	0	0	1 (0.2)
Complex regional pain syndrome	0	0	0	1 (0.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	1 (0.2)	0	1 (0.3)	0	2 (0.4)
Nasal septum deviation	1 (0.2)	0	0	0	1 (0.2)
Tonsillar hypertrophy	0	0	1 (0.3)	0	1 (0.2)
Injury, poisoning, and procedural complications	0	0	1 (0.3)	0	1 (0.2)
Postprocedural haemorrhage	0	0	1 (0.3)	0	1 (0.2)
Investigations	0	0	1 (0.3)	0	1 (0.2)
Liver function test abnormal[a]	0	0	1 (0.3)	0	1 (0.2)
Pregnancy, puerperium, and perinatal conditions	0	0	0	1 (0.3)	1 (0.2)
Abortion spontaneous	0	0	0	1 (0.3)	1 (0.2)

Sources: NDA 211527: Module 2: ISS, Table 30, p. 130; RD.06.SRE. 18250, Table 26.
Abbreviations: TEAE = treatment-emergent adverse event; M = number of subjects at risk (a subject was considered at risk if their date of last study drug application was during or after the summarized period).

Dropouts and/or Discontinuations Due to Adverse Effects

Only a small percentage of subjects discontinued from Safety Pool 1 because of an adverse event, 24 of 1,220 (2.0%) in the trifarotene arm and 2 of 1,200 (0.2%) in the vehicle cream arm. Table 42 delineates the adverse events that resulted in discontinuations. The cutaneous adverse events were related to trifarotene cream, 0.005% and all resolved during the trial with the exception of two events: acne which was reported as worsening and skin irritation, which was reported as hand eczema. The latter patient was lost to follow-up.

The remaining six TEAEs in the trifarotene cream, 0.005% group that led to study discontinuation included bronchitis, drug hypersensitivity (reported term: rash related to antibiotic), muscle rupture, tibia fracture, major depression, and suicide attempt. None of these events were assessed as related to the study drug. All these events resolved during the study except for two events: drug hypersensitivity (outcome unknown as subject was lost to follow-up) and bronchitis (outcome unknown [e.g., subject lost to follow-up]). In the vehicle arm, the events of sinusitis and bronchitis were assessed as not related to trial drug and both events resolved during the trial.

Table 42. Summary of TEAEs Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Safety Pool 1

System Organ Class/Preferred Term	Trifarotene Cream, 0.005% N=1,220	Vehicle Cream N=1,200
Subjects with any TEAE leading to discontinuation, n (%)	24 (2.0)	2 (0.2)
General disorders and administration site conditions	15 (1.2)	0
Application site irritation	13 (1.1)	0
Application site erosion	1 (0.1)	0
Application site pain	1 (0.1)	0
Skin and subcutaneous tissue disorders	5 (0.3)	0
Acne	2 (0.2)	0
Skin irritation	2 (0.2)	0
Dermatitis allergic	1 (0.1)	0
Infections and infestations	1 (0.1)	2 (0.2)
Bronchitis	1 (0.1)	1 (0.1)
Sinusitis	0	1 (0.1)
Injury, poisoning, and procedural complications	1(0.1)	0
Muscle rupture	1 (0.1)	0
Tibia fracture	1(0.1)	0
Psychiatric disorders	1 (0.1)	0
Major depression	1 (0.1)	0
Suicide attempt	1 (0.1)	0

Source: NDA 211527, ISS; Table 2.13.1; p. 607
Abbreviation: TEAE = treatment-emergent adverse event

In the long-term safety trial, 18250, 16 (3.5%) subjects discontinued from the study due to an AE: 13 (2.9%) subjects during the first quarter of the study, two (0.5%) subjects during the second quarter, and one (0.3%) subject during the third quarter.

All of the 16 TEAEs that led to study drug discontinuation were of cutaneous nature, except for one event of polycystic ovaries. Of the cutaneous TEAEs that led to study drug discontinuation, 13 were related to the study drug and were considered as adverse events of special interest (AESIs). None of the remaining three TEAEs that led to study drug discontinuation (i.e., one event of polycystic ovaries and two events of acne [worsening of acne]) were considered related to the study drug.

These percentage of discontinuations that were related to the trial drug, trifarotene cream, 0.005% was very small (0.2%) in Safety Pool 1 because of skin irritation and 13 (2.9%) cutaneous events in the long-term safety trial. This does not rise to a level of safety concern for the use of the drug product.

Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events

Most common TEAEs (i.e., those reported in at least 1% of subjects) were reported by 206 (16.9%) subjects in the trifarotene cream, 0.005% group (total of 297 TEAEs) and in 116 (9.7%)

subjects in the vehicle cream group (total of 140 TEAEs). A higher proportion of subjects who received trifarotene, 0.005% cream compared with vehicle cream experienced TEAEs in the system organ class (SOC) of general disorders and administration site conditions mainly due to application site irritation (84 [6.9%] subjects in trifarotene cream, 0.005% versus 4 [0.3%] subjects in vehicle cream), and in the Injury, poisoning, and procedural complications SOC mainly due to sunburn (33 [2.7%] subjects in trifarotene cream, 0.005% versus 6 [0.5%] subjects in vehicle cream).

Among those TEAEs in the Infections and Infestations SOC, the most commonly occurring PT was nasopharyngitis, with a similar proportion of subjects in each treatment group (trifarotene, cream, 0.005%, 50 [4.1%] subjects; vehicle cream, 56 [4.7%] subjects). The proportion of subjects who had headache, under the Nervous system disorders SOC, was the same between trifarotene cream, 0.005% and vehicle cream; 16 (1.3%) subjects in each treatment group.

Treatment-emergent adverse events which were reported in at least 1% of subjects in the trifarotene cream, 0.005% group (at the PT level) were, by decreasing frequency: application site irritation, nasopharyngitis, sunburn, application site pruritus, upper respiratory tract infection, and headache. Treatment-emergent adverse events which were reported in at least 1% of subjects in the vehicle cream group (at the PT level) were, by decreasing frequency: nasopharyngitis, influenza, upper respiratory tract infection, and headache. Table 43 gives the overall summary of the TEAEs in Safety Pool 1.

Table 43. Overall Summary of TEAEs With Incidence ≥1%, Safety Population, Safety Pool 1

System Organ Class/Preferred Term	Trifarotene Cream, 0.005% N=1,220	Vehicle Cream N=1,200
Number of TEAEs with incidence ≥1%	297	140
Subjects with any TEAE with incidence ≥1%, n (%)	206 (16.9)	116 (9.7)
General disorders and administration site conditions	107 (8.8)	14 (1.2)
Application site irritation	84 (6.9)	4 (0.3)
Application site pruritus	29 (2.4)	10 (0.8)
Infections and infestations	79 (6.5)	89 (7.4)
Nasopharyngitis	50 (4.1)	56 (4.7)
Upper respiratory tract infection	19 (1.6)	16 (1.3)
Influenza	11 (0.9)	18 (1.5)
Injury, poisoning, and procedural complications	33 (2.7)	6 (0.5)
Sunburn	33 (2.7)	6 (0.5)
Nervous system disorders	16 (1.3)	16 (1.3)
Headache	16 (1.3)	16 (1.3)

Source: NDA 211527: Module 2: ISS Table 2.4.1. See also Table 24, p. 119
Abbreviation: TEAE = treatment-emergent adverse event

TEAEs in the long-term safety trial, 18250, did not differ significantly from the two short-term phase 3 pivotal trials, Safety Pool 1. The most frequently reported TEAEs were coded in the SOCs infections and infestations; general disorders and administration site conditions; injury,

poisoning, and procedural complications; skin and subcutaneous tissue disorders; and respiratory, thoracic, and mediastinal disorders. Overall, the majority of subjects, 154 (34%) reported TEAEs during the first quarter of the trial. The most frequently reported TEAE was nasopharyngitis (in a total of 48 [10.6%] subjects) followed by the cutaneous TEAE of sunburn (in 27 [6.0%] subjects), application site pruritus (in 23 [5/1%] subjects), and application site irritation (in 22 [4.9%] subjects). It is notable, that subjects with cutaneous TEAEs significantly decreased over time (see Table 44).

Table 44. Overall Summary of TEAEs With Incidence ≥1% by Quarter and Overall, Safety Population, Trial 18250

	Trifarotene Cream, 0.005% N=453				
System Organ Class/Preferred Term	**Q1 M=453**	**Q2 M=384**	**Q3 M=368**	**Q4 M=351**	**Overall N=453**
Number of TEAEs	249	91	85	43	468
Subject with any TEAE, n (%)	154 (34.0)	68 (17.7)	62 (16.8)	36 (10.3)	218 (48.1)
Infections and infestations	61 (13.5)	41 (10.7)	30 (8.2)	18 (5.1)	116 (25.6)
Nasopharyngitis	23 (5.1)	21 (5.5)	11 (3.0)	8 (2.3)	48 (10.6)
Upper respiratory tract infection	8 (1.8)	5 (1.3)	1 (0.3)	0	13 (2.9)
Influenza	2 (0.4)	3 (0.8)	2 (0.5)	2 (0.6)	9 (2.0)
Infectious mononucleosis	1 (0.2)	2 (0.5)	1 (0.3)	1 (0.3)	5 (1.1)
Tonsillitis	3 (0.7)	0	2 (0.5)	0	5 (1.1)
General disorders and administration site conditions	47 (10.4)	7 (1.8)	8 (2.2)	2 (0.6)	57 (12.6)
Application site pruritus	20 (4.4)	2 (0.5)	4 (1.1)	2 (0.6)	23 (5.1)
Application site irritation	20 (4.4)	1 (0.3)	1 (0.3)	0	22 (4.9)
Injury, poisoning, and procedural complications	32 (7.1)	8 (2.1)	10 (2.7)	6 (1.7)	50 (11.0)
Sunburn	22 (4.9)	2 (0.5)	3 (0.8)	2 (0.6)	27 (6.0)
Ligament sprain	1 (0.2)	3 (0.8)	1 (0.3)	1 (0.3)	6 (1.3)
Skin and subcutaneous tissue disorders	16 (3.5)	4 (1.0)	4 (1.1)	2 (0.6)	25 (5.5)
Acne[a]	4 (0.9)	0	1 (0.3)	0	5 (1.1)
Respiratory, thoracic, and mediastinal disorders	14 (3.1)	2 (0.5)	4 (1.1)	3 (0.9)	23 (5.1)
Oropharyngeal pain	6 (1.3)	2 (0.5)	1 (0.3)	0	9 (2.0)
Nervous system disorders	6 (1.3)	3 (0.8)	0	2 (0.6)	10 (2.2)
Headache	4 (0.9)	1 (0.3)	0	1 (0.3)	6 (1.3)
Gastrointestinal disorders	12 (2.6)	3 (0.8)	4 (1.1)	0	19 (4.2)
Diarrhea	4 (0.9)	0	1 (0.3)	0	5 (1.1)

Sources: NDA 211527: ISS, Table 25, p. 120; RD.06.SRE.18250, Table 23
[a] Preferred term acne refers to worsening of acne. In addition to events coded as acne, I PT of application site acne (= acne nodule on left shoulder) was reported by 1 (0.2%) subject
Abbreviations: TEAE = treatment-emergent adverse event; M = number of subjects at risk (a subject was considered at risk if their date of last study drug application was during or after the summarized period)

TEAEs by Severity

A summary of TEAEs by SOC, PT, and maximum severity is presented for Safety Pool 1 in Table 45. Most of the TEAEs reported in both treatment groups were mild or moderate in intensity. Overall, the proportion of subjects with moderate TEAEs was higher in the trifarotene cream, 0.005% group mainly due to the SOC of General disorders and administration site conditions;

and in this SOC, to the PT of application site irritation. Of the 572 TEAEs in 331 (27.1%) subjects in the trifarotene cream, 0.005% group, 383 were mild and experienced by 199 (16.3%) subjects, and 173 were moderate and experienced by 120 (9.8%) subjects. There were 16 TEAEs that were severe and were experienced by 12 (1.0%) subjects.

Of the 334 TEAEs in 240 (20.0%) subjects in the vehicle cream group, 244 were mild and experienced by 170 (14.2%) subjects, and 82 were moderate and experienced by 62 (5.2%) subjects. There were 8 TEAEs that were severe and were experienced by 8 (0.7%) subjects.

Table 45. Summary of TEAEs by Severity, Safety Pool 1

System Organ Class/Preferred Term	Trifarotene, 0.005% Cream N=1,220	Vehicle N=1,200
Number of TEAEs	572	334
Mild	383	244
Moderate	173	82
Severe	16	8
Subjects with any TEAE, n (%)	331 (27.1)	240 (20.0)
Mild	199 (16.3)	170 (14.2)
Moderate	120 (9.8)	62 (5.2)
Severe	12 (1.0)	8 (0.7)

Source: NDA 211527: Module 2, ISS, p. 127, Table 2.11.1 PRG: \ISS/Statistics\ROUND2\Output\Prog\iss_ae205.sas
Abbreviation: TEAE = treatment-emergent adverse event

In the long-term safety trial, the majority of the TEAEs reported during the trial were of mild and moderate intensity: 286 TEAEs of mild intensity reported in 111 subjects (24.5%) and 170 TEAEs of moderate intensity reported in 98 (21.6%) subjects (see Table 46). A total of nine severe TEAEs were reported in nine (2.0%) subjects, of which three events in three subjects were considered related to the study drug by the Investigator (i.e., application site irritation, application site pruritus, and application site erythema).

Table 46. Summary of TEAEs by Severity, Long-Term Safety Trial, 18250

	Trifarotene Cream, 0.005% N=453				
System Organ Class/Preferred Term	Q1 M=453	Q2 M=384	Q3 M=368	Q4 M=351	Overall N=453
Number of TEAEs	247	90	85	43	465
Mild	159	48	52	27	286
Moderate	83	41	31	15	170
Severe	5	1	2	1	9
Subjects with any TEAE, n (%)	154 (34.0)	68 (17.7)	62 (16.8)	36 (10.3)	218 (48.1)
Mild	88 (19.4)	36 (9.4)	35 (9.5)	21 (6.0)	111 (24.5)
Moderate	61 (13.5)	31 (8.1)	25 (6.8)	14 (4.0)	98 (21.6)
Severe	5 (1.1)	1 (0.3)	2 (0.5)	1 (0.3)	9 (2.0)

Source: NDA 211527: Module 5, Clinical Study Report RD.06.SRE.18250, Table 14.3.6, p. 404
Abbreviations: TEAE = treatment-emergent adverse event; M = number of subjects at risk (a subject was considered at risk if their date of last study drug application was during or after the summarized period)

Adverse Reactions

This section discusses the TEAEs related to study drug, henceforth called adverse reactions. It is not surprising that the adverse reactions are cutaneous, as trifarotene is a topical retinoid and cutaneous reactions to topical retinoids are well documented. The Applicant's analysis of adverse reactions and this reviewer's analysis of adverse reactions differ slightly, which will be discussed.

Table 47 delineates the Applicant's analysis of TEAEs related to the trial drug (adverse reactions), trifarotene cream, 0.005% in Safety Pool 1. In this analysis, the adverse events deemed related to trifarotene, a topical retinoid, relates to cutaneous reactions, application site irritation, application site pruritus, and sunburn. These types of reactions are well documented with topical retinoids.

Table 47. Summary of TEAEs Related to Trifarotene, 0.005% Cream (Adverse Reactions) With Incidence ≥1%, Safety Pool 1, Studies 18251 and 18252

	Safety Pool 1	
System Organ Class/Preferred Term	**Trifarotene Cream, 0.005% N=1,220**	**Vehicle Cream N=1,200**
Number of TEAEs related to study drug	222	21
Subjects with any TEAE related to study drug, n (%)	144 (11.8)	18 (1.5)
General disorders and administration site conditions	112 (9.2)	11 (0.9)
Application site irritation	79 (6.5)	2 (0.2)
Application site pruritus	28 (2.3)	9 (0.8)
Injury, poisoning, and procedural complications	21 (1.7)	0
Sunburn	15 (1.2)	0

Source: NDA 211527, Module 2: ISS, adapted from Table 26, p. 122
Abbreviation: TEAE = treatment-emergent adverse event

In Safety Pool 1, there are some differences in these cutaneous TEAEs between the overall TEAE incidence and the same 3 TEAEs related to study drug. The biggest discrepancy is that of the TEAE sunburn. The Applicant did not include 20 subjects, 18 on study drug and 2 on vehicle who had sunburn in the TEAEs as subjects who had an adverse reaction. The Applicant also did not include five subjects who had application site irritation and one subject who had application site pruritus as having an adverse reaction.

During this review, only one subject was found to be on trifarotene cream, 0.005% out of the 18 subjects who had a sunburn in a place that the trial drug, trifarotene cream, 0.005% was not used, of the subjects listed as "not related." That subject, in Trial 18251, had sunburn on the upper and lower extremities. Drug product was applied in these trials to the face and trunk (chest and upper back and shoulders). There were some that did not have the anatomical location listed, so they are included as related, also. And yet others were considered as "not related" but had their study drug interrupted.

Thus, the change in the number of subjects who experienced an adverse reaction per the review is delineated in Table 48 for both trial drug and vehicle. There were six subjects who had a TEAE of sunburn. For two of the subjects, the anatomical location was listed, the face. Although no anatomical location was listed for the other four, they should be included in the adverse reaction table. This changes the incidence of subjects with an adverse reaction of sunburn to 32 (2.6%) versus 6 (0.5%) for trifarotene cream, 0.005% and vehicle, respectively.

Table 48. Details of Subjects With Sunburn Designated Not Related to Study Drug, Safety Pool 1

Trial/Drug/ Subject No.	Anatomic Location	Relationship to Study Drug	Drug Application Status	Recovery	Serious AE
Trial 18251[a]					
Trifarotene Cream, 0.005%					
(b) (6)	Not listed	No*	Interrupted	Yes	No
	Not listed	No*	Interrupted	Yes	No
	Nose	No*	Reduced	Yes	No
	Face	No*	No change	Yes	No
	Face	No*	Interrupted	Yes	No
	Upper and lower extremities	No	No change	Not recovered	Yes
	Trunk	No*	Interrupted	Yes	No
	Face	No*	Interrupted	Yes	No
	Forehead and chest	No*	Interrupted	Yes	No
	Truncal area	No*	No change	Yes	No
	Not listed	No*	Interrupted	Yes	No
	Not listed	No*	No change	Yes	No
	Face	No*	Interrupted	Yes	No
	Cheeks, shoulder, upper chest	No*	Interrupted	Yes	No
Vehicle					
(b) (6)	Face	No	Interrupted	Yes	No
	Not listed	No	Interrupted	Yes	No
	Face	No	Interrupted	Yes	No
Trial 18252[b]					
Trifarotene Cream, 0.005%					
(b) (6)	Not listed	No*	No change	Yes	No
	Face and trunk	No*	No change	Yes	No
	Face	No*	Interrupted	Yes	No
	Not listed	No*	No change	Yes	No
Vehicle					
(b) (6)	Not listed	No	No change	Yes	No
	Not listed	No	No change	Yes	No
	Not listed	No	No change	Yes	No

[a] Source: NDA 211527: Module 5.3.5.1—Trial 18251—Protocol Deviations: Listing 16.2.9.2, pp. 2456–2626
[b] Source: NDA 211527: Module 5.3.5.1—Trial 18252—Protocol Deviations: Listing 16.2.9.3, pp. 1837–1922
* These subjects should be considered to have had an adverse reaction.
Abbreviation: AE = adverse event

The Applicant did not include five subjects from the overall TEAEs as having a TEAE related to study drug in the trifarotene cream, 0.005% arm for application site irritation. In review of the data, there was only one subject who had an "irritation" not at the site of application. That was

on the neck area. The Applicant did not include two subjects in the vehicle arm as having a TEAE related to study drug, but both of these subjects had irritation at sites of application, the face and cheek. Therefore, they should be included in the adverse reactions (see Table 49). In addition, there were eight subjects who had "skin irritation" as an adverse reaction, but were listed under the category "Skin and subcutaneous tissue disorders" (see Table 56 in Section 8.2.5.1). Those eight subjects should also be added to those that had an adverse reaction categorized as irritation to the trial product.

Table 49. Details of Subjects With Application Site Irritation Designated Not Related to Study Drug, Safety Pool 1

Trial/Drug/ Subject No.	Anatomic Location	Relationship to Study Drug	Drug Application Status	Recovery	Serious AE
Trial 18251[a]					
Trifarotene Cream, 0.005%					
(b) (6)	Left chest	No*	Interrupted	Yes	No
	Not listed	No*	Withdrawn	Yes	No
	Neck	No*	No change	Yes	No
	Upper chest	No*	No change	Yes	No
	Not listed	No*	No change	Yes	No
Vehicle					
(b) (6)	Cheek	No*	No change	Yes	No
	Face	No*	No change	Yes	No
Trial 18252[b]					
Trifarotene Cream, 0.005%					
(b) (6)	Not listed	No*	No change	Yes	No
	Right ant. shoulder	No*	No change	Yes	No
Vehicle					
(b) (6)	Not listed	No*	No change	No	No

[a] Source: NDA 211527: Module 5.3.5.1—Trial 18251—Protocol Deviations: Listing 16.2.9.2, pp. 2456–2626
[b] Source: NDA 211527: Module 5.3.5.1—Trial 18252—Protocol Deviations: Listing 16.2.9.3, pp. 1837–1922
* These subjects should be considered to have had an adverse reaction.
Abbreviations: AE = adverse event; ant. = anterior

The Applicant did not include two subjects as having application site pruritus related to study drug, one each in the trifarotene cream, 0.005% arm and vehicle arm (see Table 50).

Table 50. Details of Subjects With Application Site Pruritus Designated Not Related to Study Drug, Safety Pool 1

Subject No.	Anatomic Location	Relationship to Study Drug	Drug Application Status	Recovery	Serious AE
Trial 18251[a]					
Trifarotene Cream, 0.005%					
(b) (6)	Trunk	No*	Interrupted	Yes	No
Vehicle					
(b) (6) 3	Jowl	No*	No change	Yes	No
Trial 18252[b]					
Trifarotene Cream, 0.005%					
(b) (6)	Not listed	No	No change	Yes	No

[a] Source: NDA 211527: Module 5.3.5.1—Trial 18251—Protocol Deviations: Listing 16.2.9.2, pp. 2456–2626
[b] Source: NDA 211527: Module 5.3.5.1—Trial 18252—Protocol Deviations: Listing 16.2.9.3, pp. 1837–1922
* These subjects should be considered to have had an adverse reaction.
Abbreviation: AE = adverse event

Table 51 is the revised table with the TEAEs related to study drug (adverse reactions) that should be in product labeling (Section 6). These cutaneous TEAEs have been well documented in the use of topical retinoids.

Table 51. Revised Summary of TEAEs Related to Trifarotene Cream, 0.005% With Incidence ≥1%, Safety Pool 1

	Safety Pool 1 (Studies 18251 and 18252)	
System Organ Class/Preferred	**Trifarotene Cream, 0.005% N=1,220**	**Vehicle Cream N=1,200**
Number of TEAEs related to study drug	2,521	28
Subjects with any TEAE related to study drug, n (%)	174 (14.2)1	27 (2.3)
General disorders and administration site conditions	134 (10.9)	18 (1.5)
Application site irritation[1]	91 (7.5)	4 (0.3)
Application site pruritus	29 (2.4)	10 (0.8)
Injury, poisoning, and procedural complications	38 (3.1)	6 (0.5)
Sunburn	32 (2.6)	6 (0.5)

Source: Reviewer's analysis
[1] Includes eight subjects who had skin irritation listed under system organ class—skin and subcutaneous tissue disorders.
Abbreviation: TEAE = treatment-emergent adverse event

Table 52 delineates the summary of Adverse Reactions in the long-term safety trial, Trial 18250, by quarter and overall.

Table 52. Summary of TEAEs Related to Study Drug (Adverse Reactions) System Organ Class and Preferred Term, by Quarter and Overall, Safety Population, Study 18250

	Trifarotene Cream, 0.005% N=453				
System Organ Class/Preferred Term	**Q1 M=453**	**Q2 M=384**	**Q3 M=368**	**Q4 M=351**	**Overall N=453**
Number of TEAEs related to the study drug	80	10	11	2	103
Subjects with any TEAE related to the study drug, n (%)	46 (10.2)	8 (2.1)	9 (2.4)	2 (0.6)	57 (12.6)
General disorders and administration site conditions	40 (8.8)	6 (1.6)	6 (1.6)	2 (0.6)	47 (10.4)
Application site pruritus	19 (4.2)	2 (0.5)	3 (0.8)	2 (0.6)	21 (4.6)
Application site irritation	17 (3.8)	1 (0.3)	1 (0.3)	0	19 (4.2)
Application site dryness	1 (0.2)	2 (0.5)	0	0	3 (0.7)
Application site erythema	3 (0.7)	1 (0.3)	0	0	3 (0.7)
Application site pain	2 (0.4)	0	1 (0.3)	0	2 (0.4)
Application site eczema	0	0	1 (0.3)	0	1 (0.2)
Injury, poisoning, and procedural complications	6 (1.3)	1 (0.3)	2 (0.5)	0	9 (2.0)
Sunburn	5 (1.1)	1 (0.3)	2 (0.5)	0	8 (1.8)
Drug administered at inappropriate site	1 (0.2)	0	0	0	1 (0.2)
Skin and subcutaneous tissue disorders	5 (1.1)	1 (0.3)	0	0	6 (1.3)
Acne	3 (0.7)	0	0	0	3 (0.7)
Rash	1 (0.2)	0	0	0	1 (0.2)
Skin burning sensation	1 (0.2)	0	0	0	1 (0.2)
Skin irritation	0	1 (0.3)	0	0	1 (0.2)

System Organ Class/Preferred Term	Trifarotene Cream, 0.005% N=453 Q1 M=453	Q2 M=384	Q3 M=368	Q4 M=351	Overall N=453
Blood and lymphatic system disorders	1 (0.2)	0	0	0	1 (0.2)
Lymphadenopathy	1 (0.2)	0	0	0	1 (0.2)
Infections and infestations	0	0	1 (0.3)	0	1 (0.2)
Skin candida	0	0	1 (0.3)	0	1 (0.2)

Sources: NDA 211527: Module 2: ISS, Table 28, p. 126; RD.06.SRE.18250, Table 25
Abbreviation: TEAE = treatment-emergent adverse event; M = number of subjects at risk (a subject was considered at risk if their date of last study drug application was during or after the summarized period)

Again, there is a difference in analysis between the Applicant's analysis and this reviewer's analysis where 17 subjects in the long-term safety had the TEAE of "sunburn," yet were not included in the adverse reactions' tabulation. Table 53 delineates the subjects who had a sunburn which was delineated as not related to study drug. In this reviewer's opinion, unless an anatomical location is listed that was outside of application of trial drug, the subjects of these "sunburn" events should be included under adverse reactions (TEAEs related to study drug), as this is a known possible event that can occur with topical retinoids.

Table 53. Details of Subjects With Sunburn Designated Not Related to Study Drug, Long-Term Safety

Subject No.	Anatomic Location	Relationship to Study Drug	Drug Application Status	Recovery
(b) (6)	Face	No*	Interrupted	Yes
	Not listed	No*	No change	Yes
	Not listed	No*	No change	Yes
	Not listed	No*	Interrupted	Yes
	Not listed	No*	No change	Yes
	Not listed	No*	Interrupted	Yes
	Should and face	No*	Interrupted	Yes
	Not listed	No*	Interrupted	Yes
	Not listed	No*	Dose decreased	Yes
	Not listed	No*	No change	Unknown
	Face and trunk	No*	Interrupted	Yes
	Not listed	No*	Interrupted	Yes
	Not listed	No*	Interrupted	Yes
	Not listed	No*	No change	Yes
	Not listed	No*	No change	Yes
	Not listed	No*	No change	Yes
	Face, chest & back	No*	No change	Yes
	Face	No*	Interrupted	Yes

Source: NDA 211527: Module 5.3.5.1—Trial 18250—Protocol Deviations: Listing 16.2.7.2, pp. 1–140
* These subjects should be considered to have had an adverse reaction.

Thus, there were 17 additional subjects who experienced "sunburn" and Table 54 shows the modified table of TEAEs related to study drug in the long-term trial.

Table 54. Revised Summary of TEAEs Related to Study Drug (Adverse Reactions) System Organ Class and Preferred Term, by Quarter and Overall, Safety Population, Study 18250

	Trifarotene, 0.005% Cream N=453				
System Organ Class/Preferred Term	Q1[a] M=453	Q2[a] M=384	Q3[a] M=368	Q4[a] M=351	Overall[b] N=453
Number of TEAEs related to the study drug	80	10	11	2	120
Subjects with any TEAE related to the study drug, n (%)	46 (10.2)	8 (2.1)	9 (2.4)	2 (0.6)	74 (16.3)
General disorders and administration site conditions	40 (8.8)	6 (1.6)	6 (1.6)	2 (0.6)	47 (10.4)
Application site pruritus	19 (4.2)	2 (0.5)	3 (0.8)	2 (0.6)	21 (4.6)
Application site irritation	17 (3.8)	1 (0.3)	1 (0.3)	0	19 (4.2)
Application site dryness	1 (0.2)	2 (0.5)	0	0	3 (0.7)
Application site erythema	3 (0.7)	1 (0.3)	0	0	3 (0.7)
Application site pain	2 (0.4)	0	1 (0.3)	0	2 (0.4)
Application site eczema	0	0	1 (0.3)	0	1 (0.2)
Injury, poisoning, and procedural complications	6 (1.3)	1 (0.3)	2 (0.5)	0	26 (5.7)
Sunburn	5 (1.1)	1 (0.3)	2 (0.5)	0	25 (5.5)
Drug administered at inappropriate site	1 (0.2)	0	0	0	1 (0.2)
Skin and subcutaneous tissue disorders	5 (1.1)	1 (0.3)	0	0	6 (1.3)
Acne	3 (0.7)	0	0	0	3 (0.7)
Rash[a]	1 (0.2)	0	0	0	1 (0.2)
Skin burning sensation	1 (0.2)	0	0	0	1 (0.2)
Skin irritation	0	1 (0.3)	0	0	1 (0.2)
Blood and lymphatic system disorders	1 (0.2)	0	0	0	1 (0.2)
Lymphadenopathy[b]	1 (0.2)	0	0	0	1 (0.2)
Infections and infestations	0	0	1 (0.3)	0	1 (0.2)
Skin candida	0	0	1 (0.3)	0	1 (0.2)

Source: Reviewer's analysis
[a] Not able to break the additional events to overall by quarter
[b] Addition to overall in the sunburn category and corresponding general categories
Abbreviation: TEAE = treatment-emergent adverse event; M = number of subjects at risk (a subject was considered at risk if their date of last study drug application was during or after the summarized period)

Laboratory Findings

In Safety Pool 1, hematology, chemistry, and urine parameters were monitored throughout the trials. Overall, hematology parameters remained stable throughout the study, and there were no remarkable shifts from baseline to the last postbaseline visit for all hematology parameters. No clinically meaningful changes in mean hematology values from baseline to Week 12 were observed in trifarotene cream, 0.005% or vehicle cream groups.

Blood chemistry parameters remained stable throughout the study, and there were no remarkable shifts from baseline to the last postbaseline visit for all blood chemistry parameters. No clinically meaningful changes in mean blood chemistry values from baseline to Week 12 were observed in trifarotene cream, 0.005% or vehicle cream groups. Overall, urinary parameters remained stable throughout the trials, except for four subjects. In Study 18251, clinically significant results that occurred during study participation included out-of-range urinary results for leukocytes at Week 12 in Subjects (b) (6) and (b) (6) as well as an out-of-range urinary result for proteins at Week 12 in Subject (b) (6) These findings were recorded as TEAEs but were considered not related to study treatment. In Study 18252,

clinically significant results that occurred during study participation included an out-of-range urinary result for leukocytes at Week 12 in Subject (b) (6) (reported as a TEAE of mild leukocyturia that was assessed as not related to study drug). This event resolved.

In the long-term safety trial, Trial 18250, overall, >80% of subjects (294 of 334 subjects, 88%) with urinalysis were negative for all of the urinalysis parameters tested. The remaining subjects were positive for blood, leukocytes, or proteins, associated with urinary tract infection or menstruation; and these findings were considered clinically nonsignificant.

Vital Signs

For Safety Pool 1, vital signs remained stable throughout the study for subjects in both treatment groups. No clinically meaningful changes in vital signs were observed from baseline to Week 12. The mean systolic BP was 116.2 and 116.0 at baseline for the trifarotene 50 µg/g cream and vehicle arms, respectively. The mean systolic BP at Week 12 was 116.7 and 116.3 for the trifarotene cream, 0.005% and vehicle arms, respectively. There was not much difference between the minimum and maximum systolic blood pressure for both arms: minimum was 88 and 90 and maximum was 148 and 170 for the trifarotene cream, 0.005% and vehicle arms, respectively at baseline with only a 0.7% and 0.25% change at Week 12 for the cream, 0.005% and vehicle arms, respectively.

The same can be said for the minimum and maximum of the diastolic blood pressure: minimum was 48 and 50 and maximum was 97 and 99 for the trifarotene cream, 0.005% and vehicle arms, respectively at baseline with only a 0.7% and 0.4% change at Week 12 for the trifarotene cream, 0.005% and vehicle arms, respectively. The mean diastolic BP was 72.0 and 72.3 at baseline for the trifarotene cream, 0.005% and vehicle arms, respectively. The mean diastolic BP was 72.3 and 72 at Week 12 for the trifarotene cream, 0.005% and vehicle arms, respectively.

There were no clinically significant differences in pulse rate between the trifarotene cream, 0.005% arm and the vehicle arm. The mean pulse rate at baseline was 73.3 and 73.5 at baseline for the trifarotene cream, 0.005% and vehicle arms, respectively. The mean pulse rate at Week 12 was 73.8 and 73.2 for the trifarotene cream, 0.005% and vehicle arms, respectively. The minimum and maximum pulse rate at baseline was 44 and 114 and 45 and 109 for the trifarotene cream, 0.005% and vehicle arms, respectively. The minimum and maximum pulse rate at Week 12 was 42 and 124 and 49 and 115 for the trifarotene cream, 0.005% and vehicle arms, respectively.

In the long-term safety trial, the values of systolic BP, diastolic BP, and pulse rate at baseline, Week 12, Week 26, and Week 52 visits were not clinically meaningful and mean values of all vital signs parameters remained stable over time. The mean SBP hovered around 115 (±1.3 mm

Hg) and the mean diastolic blood pressure hovered around 70 (±0.5 mm Hg). The mean pulse rate was 72.9 and baseline and maximum change throughout the trial was ±0.8 mm Hg).

QT

The Thorough QT (TQT) team reviewed the TQT study performed by the Applicant. The review was done on August 9, 2014. From the review:

This was a randomized, two periods, partially-blinded, placebo-controlled, positive controlled, four-way crossover study, 173 healthy subjects received CD5789, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 55.

Table 55. Point Estimates and 90% CIs Corresponding to Largest Upper Bound for CD5789 and Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
CD5789	4	1.0	(-1.7, 3.8)
Moxifloxacin	3	12.7	(10, 15.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9 ms.
Abbreviations: QTcF = Fridericia's corrected QT-interval; CI = confidence interval

The TQT team concluded the following:

- No significant QTc prolongation effect of CD5789 was detected in this TQT study in Period 2. The largest upper bound of the two-sided 90% CI for the mean difference between CD5789 and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.
- No clinically relevant effects were seen on PR or QRS.[5]
- It should be noted that Period 1 assessed the optimal treatment duration to be use in Period 2. The reader is referred to the complete review in DARRTs under IND 111091.

Immunogenicity

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

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Cutaneous Adverse Reactions

As with other topical retinoids, local tolerability in regard to cutaneous adverse events are adverse events of special interest. Application site irritation, pruritus, erythema, dryness, and scaling, among others can occur. These parameters were, thus, evaluated at each visit during the pivotal trials, Safety Pool 1, and during the long-term safety trial, Trial 18250, which had a duration of 52 weeks.

[5] TQT team Review by Ng, Moh Jee. In DARRTs dated 8/9/14.

As expected and delineated in Section 8.2.4, cutaneous adverse reactions led the adverse reaction profile. Table 56 delineates the cutaneous adverse events that were related to trial drug (adverse reactions).

Table 56. Summary of Cutaneous Adverse Reactions, Safety Pool 1

	Safety Pool 1 (Trials 18251 and 18252)		LTS Trial Week 12
System Organ Class/Preferred Term	Trifarotene Cream, 0.005% N=1,220	Vehicle Cream N=1,200	Trifarotene Cream, 0.005% N=453
Number of TEAEs related to study drug	222	21	75
Subjects with any TEAE related to study drug, n (%)	144 (11.8)	18 (1.5)	45 (9.9)
General disorders and administration site conditions	112 (9.2)	11 (0.9)	37 (8.2)
Application site irritation	79 (6.5)	2 (0.2)	15 (3.3)
Application site pruritus	28 (2.3)	9 (0.8)	19 (4.2)
Application site pain	8 (0.7)	0	2 (0.4)
Application site dryness	4 (0.3)	0	1 (0.2)
Application site discoloration	2 (0.2)	0	0
Application site erosion	2 (0.2)	0	0
Application site rash	2 (0.2)	0	0
Application site swelling	2 (0.2)	0	0
Application site erythema	1 (0.1)	0	2 (0.4)
Application site urticaria	1 (0.1)	0	0
Application site vesicles	1 (0.1)	0	0
Injury, poisoning, and procedural complications	21 (1.7)	0	6 (1.3)
Sunburn	15 (1.2)	0	5 (1.1)
Drug administered at inappropriate site	3 (0.2)	0	1 (0.2)
Incorrect dosage administered	2 (0.2)	0	0
Accidental overdose	1 (0.1)	0	0
Skin and subcutaneous tissue disorders	19 (1.6)	2 (0.2)	5 (1.1)
Skin irritation	8 (0.7)	0	0
Acne	3 (0.2)	1 (0.1)	3 (0.7)
Dermatitis allergic	3 (0.2)	0	0
Erythema	2 (0.2)	0	0
Eczema	1 (0.1)	0	0
Seborrheic dermatitis	1 (0.1)	0	0
Skin burning sensation	1 (0.1)	0	1 (0.2)
Skin fissures	1 (0.1)	0	0
Skin hyperpigmentation	1(0.1)	0	0
Mechanical urticaria	0	(0.1)	0
Rash	0	0	1 (0.2)
Infections and infestations	2 (0.2)	1 (0.1)	0
Herpes simplex	1 (0.1)	0	0
Tinea versicolor	1 (0.1)	0	0
Oral herpes	0	1 (0.1)	0
Eye disorders	1 (0.1)	0	0
Eyelid exfoliation	1 (0.1)	0	0
Eyelid edema	1 (0.1)	0	0
Gastrointestinal disorders	1 (0.1)	0	0
Cheilitis	1 (0.1)	0	0

Source: NDA 211527: Module 2: Section 2.7.4, ISS: adapted from Table 27, pp. 123–124
Abbreviations: TEAE = treatment-emergent adverse event; LTS = long-term safety

8.2.5.2. Local Tolerability: Erythema, Scaling, Dryness, Stinging/Burning

The adverse events of local tolerability, which included erythema, scaling, dryness, and stinging/burning were assessed and recorded for both the face and the trunk separately from other TEAEs in order to better characterize the events. These events, which are known signs and symptoms of retinoid use, were not considered an adverse reaction unless it led to discontinuation from the trials. Erythema, scaling, and dryness were actively assessed by the Investigator and stinging/burning was assessed after discussion with the subject according to the following scales:

- Erythema: abnormal redness of the skin.

None	0	No erythema
Mild	1	Slight pinkness present
Moderate	2	Definite redness, easily recognized
Severe	3	Intense redness

- Scaling: abnormal shedding of the stratum corneum.

None	0	No scaling
Mild	1	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	2	Obvious but not profuse shedding
Severe	3	Heavy scale production

- Dryness: brittle and/or tight sensation.

None	0	No dryness
Mild	1	Slight but definite roughness
Moderate	2	Moderate roughness
Severe	3	Marked roughness

- Stinging/Burning: prickling pain sensation after dosing.

None	0	No stinging/burning
Mild	1	Slight warm, tingling/stinging sensation; not really bothersome
Moderate	2	Definite warm, tingling/stinging sensation that is somewhat bothersome
Severe	3	Hot, tingling/stinging sensation that has caused definite discomfort

Table 57 shows that these signs/symptoms of local tolerability worsened on the face from baseline primarily in the trifarotene cream, 0.005% arm in Safety Pool 1. The majority of subjects who had erythema, scaling, dryness, and stinging/burning were in the mild/moderate group in terms of severity being 59%, 64.6%, 68.7%, and 56.2%, respectively. These events decreased over time, for at the final visit, the proportion of subjects with erythema, scaling, dryness, and stinging/burning were 28.4%, 29.1%, 31.9%, and 18%, respectively.

Table 57. Summary of Local Tolerability Parameters on the Face, Safety Pool 1

Facial Parameter	Trifarotene Cream, 0.005% N=1,220	Vehicle Cream N=1,200
Erythema		
Final, n	1,214	1,194
Mild (1)	257 (21.2)	103 (8.6)
Moderate (2)	88 (7.2)	22 (1.8)
Severe (3)	13 (1.1)	1 (0.1)
Worst postbaseline, n	1,214	1,194
Mild (1)	371 (30.6)	251 (21.0)
Moderate (2)	345 (28.4)	81 (6.8)
Severe (3)	75 (6.2)	10 (0.8)
Scaling		
Final, n	1,214	1,194
Mild (1)	263 (21.7)	107 (9.0)
Moderate (2)	90 (7.4)	18 (1.5)
Severe (3)	7 (0.6)	2 (0.2)
Worst postbaseline, n	1,214	1,194
Mild (1)	455 (37.5)	283 (23.7)
Moderate (2)	329 (27.1)	71 (5.9)
Severe (3)	59 (4.9)	4 (0.3)
Dryness		
Final, n	1,214	1,194
Mild (1)	300 (24.7)	153 (12.8)
Moderate (2)	88 (7.2)	18 (1.5)
Severe (3)	10 (0.8)	2 (0.2)
Worst postbaseline, n	1,214	1,194
Mild (1)	473 (39.0)	357 (29.9)
Moderate (2)	360 (29.7)	81 (6.8)
Severe (3)	58 (4.8)	9 (0.8)
Stinging/burning		
Final, n	1,214	1,194
Mild (1)	167 (13.8)	50 (4.2)
Moderate (2)	51 (4.2)	12 (1.0)
Severe (3)	13 (1.1)	1 (0.1)
Worst postbaseline, n	1,214	1,194
Mild (1)	432 (35.6)	190 (15.9)
Moderate (2)	250 (20.6)	45 (3.8)
Severe (3)	72 (5.9)	6 (0.5)

Source: NDA 211527: Module 2: ISS, Table 31, p. 147

Trifarotene cream, 0.005% was better tolerated, as expected, on the trunk than on the face for Safety Pool 1. Table 58 delineates the proportion of subjects for mild, moderate, and severe reactions to the drug product. The majority of subjects who had erythema, scaling, dryness, and stinging/burning were in the mild/moderate group in terms of severity being 45.4%, 43.4%, 49.0%, and 37.0%, respectively. These events decreased over time, for at the final visit, the proportion of subjects with erythema, scaling, dryness, and stinging/burning were 19.8%, 17.8%, 21.4%, and 13.5%, respectively.

Table 58. Summary of Local Tolerability Parameters From Baseline on the Trunk, Safety Pool 1

Truncal Parameter	Trifarotene Cream, 0.005% N=1,208	Vehicle Cream N=1,191
Erythema		
Final, n	1,202	1,185
Mild (1)	165 (13.7)	57 (4.8)
Moderate (2)	73 (6.1)	15 (1.3)
Severe (3)	13 (1.1)	0
Worst postbaseline, n	1,202	1,185
Mild (1)	318 (26.5)	150 (12.7)
Moderate (2)	227 (18.9)	52 (4.4)
Severe (3)	63 (5.2)	5 (0.4)
Scaling		
Final, n	1,202	1,185
Mild (1)	168 (14.0)	47 (4.0)
Moderate (2)	46 (3.8)	4 (0.3)
Severe (3)	4 (0.3)	0
Worst postbaseline, n	1,202	1,185
Mild (1)	357 (29.7)	157 (13.2)
Moderate (2)	165 (13.7)	31 (2.6)
Severe (3)	20 (1.7)	1 (0.1)
Dryness		
Final, n	1,202	1,185
Mild (1)	207 (17.2)	73 (6.2)
Moderate (2)	51 (4.2)	7 (0.6)
Severe (3)	3 (0.2)	0
Worst postbaseline, n	1,202	1,185
Mild (1)	396 (32.9)	211 (17.8)
Moderate (2)	193 (16.1)	46 (3.9)
Severe (3)	22 (1.8)	1 (0.1)
Stinging/burning		
Final, n	1,202	1,185
Mild (1)	116 (9.7)	37 (3.1)
Moderate (2)	46 (3.8)	2 (0.2)
Severe (3)	13 (1.1)	1 (0.1)
Worst postbaseline, n	1,202	1,185
Mild (1)	314 (26.1)	109 (9.2)
Moderate (2)	131 (10.9)	26 (2.2)
Severe (3)	52 (4.3)	6 (0.5)

Source: NDA 211527: Module 2: ISS, Table 33, p. 154

Table 59 incorporates the local tolerability signs and symptoms reactions postbaseline visit that were of a worse severity than at baseline for both the face and trunk for Safety Pool 1 and should be included in labeling.

Table 59. Application Site Tolerability Reactions at Any Postbaseline Visit, Safety Pool 1

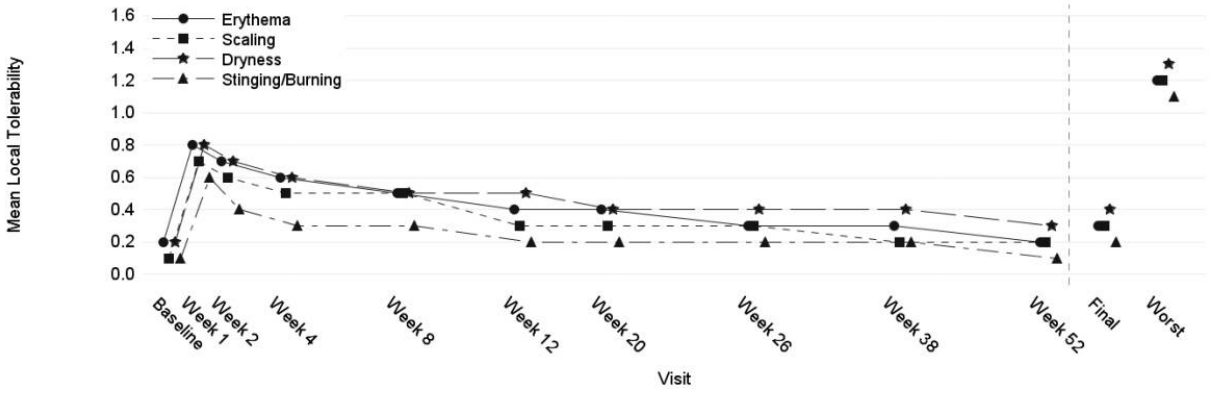
	Trifarotene Cream, 0.005% N=1,214	Vehicle Cream N=1,194
Face	**Mild/Moderate/Severe**	**Mild/Moderate/Severe**
Erythema	65%	29%
Scaling	69%	30%
Dryness	73%	37%
Stinging/burning	62%	20%
	N=1,202	**N=1,185**
Trunk	**Mild/Moderate/Severe**	**Mild/Moderate/Severe**
Erythema	51%	17%
Scaling	45%	16%
Dryness	51%	22%
Stinging/burning	41%	12%

Source: NDA 211527: Module 2: ISS, adapted from Table 31, p. 147 and Table 33, p. 154

Long-term safety from Trial 18250 for the face and trunk had similar results to Safety Pool 1 in terms of local tolerability. Most events of erythema, scaling, dryness, and stinging/burning were mild to moderate. Only a small proportion of subjects had severe events on the face (2.2 for erythema and scaling, 5.8% for dryness, and 7.1% for stinging/burning. The same can be said for the trunk, in terms of severity with only 5.4% subjects for erythema, 2.5% for scaling, 2.7% for dryness, and 4.8% for stinging/burning being rated as severe.

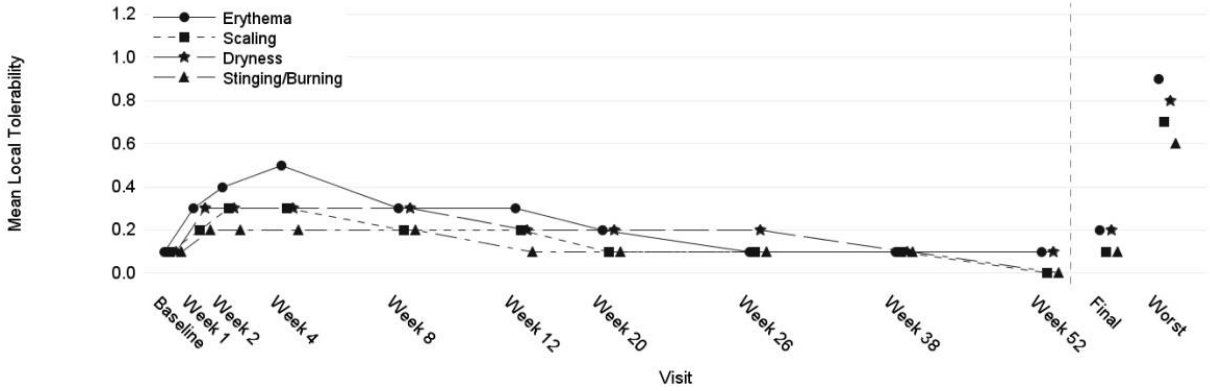
Both Safety Pool 1 and the long-term trial had the same results in terms of onset of the adverse events, peak, and subsequent decrease in severity of these adverse events. Maximum severity of these adverse events occurred during the first 4 weeks of application, with the peak being after 1 week of application for the face and Week 2 for the trunk. Figure 15 and Figure 16 from the long-term safety trial illustrates this point for both the face and the trunk, respectively and is reflective of these events for Safety Pool 1, also.

Figure 15. Mean Local Tolerability Scores on the Face by Visit, Safety Population, Trial 18250



Source: NDA 211527: Module 5, ISS, Figure 8, p. 152, RD.06.SRE.18250, Figure 12

Figure 16. Mean Local Tolerability Scores on the Trunk by Visit, Safety Population, Trial 18250



Source: NDA 211527: Module 5, ISS, Figure 13, p. 159, RD.06.SRE.18250, Figure 13

8.2.6. Safety Analyses by Demographic Subgroups

The incidence of TEAEs was generally consistent across the subgroups and with the results in Safety Pool 1. In general, the proportions of subjects who reported at least one TEAE were higher in the trifarotene, 0.005% g cream group than in the vehicle cream group for most subgroups. Similarly, the proportions of subjects who reported any TEAE related to study drug were higher in the trifarotene, 0.005% cream group compared with the vehicle cream group for each subgroup.

In each demographic subgroup, a higher proportion of subjects who received trifarotene cream, 0.005% compared with vehicle cream experienced TEAEs in the General disorders and administration site conditions SOC mainly due to application site irritation. When summaries of TEAEs were compared between subgroups (e.g., males versus females) in each treatment group, no notable differences in frequencies were observed. Interpretation of the data was limited due to the small sample size in some of the subgroups (e.g., 9 to 11 years and black or African American subgroups). Table 60 delineates the adverse reactions in ≥1% of subjects for the subgroups ages 9 to 11 years, ages 12 to 17 years, and age ≥18 years old.

Table 60. Adverse Reactions ≥1% by Age Category, Safety Pool 1

	Safety Pool 1 (Studies 18251 and 18252)	
System Organ Class/Preferred	**Trifarotene Cream, 0.005% N=1,220**	**Vehicle Cream N=1,200**
9 to 11 Years, n	19	15
Number of TEAEs related to study drug	5	0
Subjects with any TEAE related to study drug, n (%)	4 (21.1)	0
General disorders and administration site conditions	2 (10.5)	0
Application site irritation	2 (10.5)	0
Injury, poisoning, and procedural complications	1 (5.3)	0
Sunburn	1 (5.3)	0

	Safety Pool 1 (Studies 18251 and 18252)	
System Organ Class/Preferred	**Trifarotene Cream, 0.005% N=1,220**	**Vehicle Cream N=1,200**
12 to 17 Years, n	575	553
Number of TEAEs related to study drug	131	13
Subjects with any TEAE related to study drug, n (%)	87 (15.0)	10 (8.1)
General disorders and administration site conditions	60 (10.3)	4 (0.7)
Application site irritation	42 (7.2)	1 (0.2)
Application site pruritus	14 (2.4)	3 (0.5)
Injury, poisoning, and procedural complications	21 (3.6)	0
Sunburn	18 (3.1)	0
Skin and subcutaneous tissue disorders	10 (1.7)	2 (0.4)
Skin irritation	6 (1.0)	0
>=18 Years, n	626	632
Number of TEAEs related to study drug	103	8
Subjects with any TEAE related to study drug, n (%)	70 (11)	8 (1.3)
General disorders and administration site conditions	50 (8.2)	7 (1.1)
Application site irritation	35 (5.5)	1 (0.2)
Application site pruritus	14 (2.2)	6 (0.9)
Injury, poisoning, and procedural complications	16 (2.5)	0
Sunburn	13 (2.0)	2 (0.3)

Source: NDA 211527: ISS, p. 166; adapted from Table 2.9.1.1, pp. 511–517 and from Table 2.2.1.1, pp. 371, 376, and 386
Abbreviation: TEAE = treatment-emergent adverse event

Table 61 describes the adverse reactions for the gender subgroup that occurred ≥1%.

Table 61. Adverse Reactions ≥1% by Gender, Safety Pool 1

	Safety Pool 1 (Studies 18251 and 18252)	
System Organ Class/Preferred Term	**Trifarotene Cream, 0.005% N=1,220**	**Vehicle Cream N=1,200**
Female, n	665	659
Number of TEAEs related to study drug	146	10
Subjects with any TEAE related to study drug, n (%)	96 (14.2)	10 (1.5)
General disorders and administration site conditions	65 (9.6)	8 (1.2)
Application site irritation	45 (6.7)	1 (0.2)
Application site pruritus	16 (2.4)	7 (1.1)
Injury, poisoning, and procedural complications	20 (3.0)	0
Sunburn	14 (2.1)	0
Male, n	555	541
Number of TEAEs related to study drug	93	11
Subjects with any TEAE related to study drug, n (%)	65 (11.6)	8 (1.5)
General disorders and administration site conditions	47 (8.4)	3 (0.6)
Application site irritation	34 (6.0)	1 (0.2)
Application site pruritus	12 (2.1)	2 (0.4)
Injury, poisoning, and procedural complications	18 (3.2)	0
Sunburn	18 (3.2)	0

Source: NDA 211527: ISS, p. 166; adapted from Table 2.9.1.3, pp. 523–528 and from Table 2.2.1.3, pp. 418, 421, and 431
Abbreviation: TEAE = treatment-emergent adverse event

Table 62 delineates the adverse reactions according to subgroup by race.

Table 62. Adverse Reactions ≥1% by Race, Safety Pool 1

	Safety Pool 1 (Studies 18251 and 18252)	
System Organ Class/Preferred Term	**Trifarotene Cream, 0.005% N=1,220**	**Vehicle Cream N=1,200**
White, n	**1,078**	**1,033**
Number of TEAEs related to study drug	205	20
Subjects with any TEAE related to study drug, n (%)	141 (13)	17 (1.6)
General disorders and administration site conditions	95 (8.7)	10 (1.0)
Application site irritation	67 (6.1)	2 (0.2)
Application site pruritus	26 (2.4)	8 (0.8)
Injury, poisoning, and procedural complications	37 (3.4)	0
Sunburn	32 (2.9)	0
Black or African-American, n	**74**	**91**
Number of TEAEs related to study drug	17	1
Subjects with any TEAE related to study drug, n (%)	9 (12.2)	1 (1.1)
General disorders and administration site conditions	7 (9.5)	1 (1.1)
Application site irritation	5 (6.8)	0
Application site pain	2 (2.7)	0
Application site dryness	1 (1.4)	0
Skin and subcutaneous tissue disorders	3 (4.1)	0
Dermatitis allergic	1 (1.4)	0
Erythema	1 (1.4)	0
Skin burning sensation	1 (1.4)	0
Skin hyperpigmentation	1 (1.4)	0
Skin irritation	1 (1.4)	0
Asian, n	**25**	**38**
Number of TEAEs related to study drug	6	0
Subjects with any TEAE related to study drug, n (%)	5 (20.0)	0
General disorders and administration site conditions	4 (16.0)	0
Application site irritation	3 (12.0)	0
Application site pruritus	1 (4.0)	0
Skin and subcutaneous tissue disorders	1 (4.0)	0
Acne	1 (4.0)	0
Other, n	**43**	**38**
Number of TEAEs related to study drug	11	0
Subjects with any TEAE related to study drug, n (%)	6 (14.0)	0
General disorders and administration site conditions	6 (14.0)	0
Application site irritation	4 (9.3)	0
Application site discoloration	2 (4.7)	0
Application site dryness	1 (2.3)	0
Application site rash	1 (2.3)	0
Skin and subcutaneous tissue disorders	1 (2.3)	0
Skin irritation	1 (2.3)	0

Source: NDA 211527: ISS, p. 166; adapted from Table 2.9.1.4 pp. 528–534 and from Table 2.2.1.4, p. 440
Abbreviation: TEAE = treatment-emergent adverse event

Subjects were also evaluated according to the subgroup of skin phototype type according to Fitzpatrick. Table 63 describes the adverse reactions for this subgroup. Both the subgroup of race and skin type show that Caucasians who are skin phototype I-III accounted for the majority of sunburn reactions as compared to the same group in the vehicle arm.

Table 63. Adverse Reactions ≥1% by Skin Phototype, Safety Pool 1

	Safety Pool 1 (Studies 18251 and 18252)	
System Organ Class/Preferred Term	**Trifarotene Cream, 0.005% N=1,220**	**Vehicle Cream N=1,200**
Phototype I-III, n	1,009	972
Number of TEAEs related to study drug	188	18
Subjects with any TEAE related to study drug, n (%)	130 (13.0)	15 (1.5)
General disorders and administration site conditions	85 (8.3)	8 (0.8)
Application site irritation	57 (5.6)	1 (0.1)
Application site pruritus	23 (2.2)	7 (0.7)
Injury, poisoning, and procedural complications	36 (3.5)	0
Sunburn	31 (3.0)	0
Phototype IV-VI, n	211	228
Number of TEAEs related to study drug	50	3
Subjects with any TEAE related to study drug, n (%)	30 (14.2)	3 (1.3)
General disorders and administration site conditions	27 (12.8)	3 (1.3)
Application site irritation	22 (10.4)	1 (0.4)
Application site pruritus	5 (2.4)	0

Source: NDA 211527: ISS, p. 167; adapted from Table 2.9.1.5 pp. 533–537 and from Table 2.2.1.5, p. 460
Abbreviation: TEAE = treatment-emergent adverse event

8.2.7. Specific Safety Studies/Clinical Trials

To support the dermal safety of the to-be-marketed formulation, four trials were conducted that evaluated phototoxicity (Study 40208), cumulative irritation potential (Study 40209), photosensitization potential (Study 40189), and sensitization potential (Study 40190). No potential for sensitization, phototoxicity, and photosensitization was observed in these trials. A dose-dependent cumulative irritancy potential was observed in Study 40209. These results were corroborated in the phase 3 trials, as only irritation at the application site was an adverse reaction observed in ≥1% of the trial population compared to vehicle.

Trial 40208: Evaluation of Phototoxic Potential of Trifarotene Cream, 0.005%

This was a phase 1, single-center, randomized, vehicle- and negative-controlled, evaluator-blinded study using intra-individual comparison to assess the potential of trifarotene cream at 50 µg/g and 100 µg/g to induce phototoxic (photo-irritation) reaction in 18- to 65-year-old healthy subjects.

Study drugs, including trifarotene cream and vehicle cream, were applied by trained personnel under occlusive conditions using two patches (50 µL/patch application) symmetrically distributed on the left and right sides of the middle back for approximately 24 hours. White petrolatum was used as negative control. Based on the minimal erythema dose (MED) obtained (prior to study drug application), application sites were irradiated (ultraviolet [UV] irradiation) immediately after patch removal.

The following safety assessments were performed:

- TEAEs at each visit. AESIs were defined as: phototoxic reaction evaluation score of 2, suspected sensitization (i.e., allergic dermatitis), treatment-related TEAEs that led to study discontinuation, or treatment-related noncutaneous TEAEs.
- Skin reaction assessment using a six-point skin reaction assessment scale at least 30 minutes, and approximately 24 and 48 hours after patch site irradiation:
  - 0 No response
  - 0.5 Questionable or faint, indistinct erythema
  - 1 Well-defined erythema
  - 2 Erythema with slight to moderate edema
  - 3 Vesicles (small blisters) or papules (small, circumscribed elevations)
  - 4 Bullous (large blister), spreading, or other severe reaction
- Phototoxic reaction evaluation using a three-point scale (with 0 = negative; 1 = equivocal; 2 = positive) at Days 3 and 4/ET visits (i.e., approximately 24 and 48 hours after patch site irradiation).

Safety results

A total of 35 subjects were randomized. A total of 20 (57.1%) subjects were female, while 15 (42.9%) subjects were male. The mean age was 37.3 years (ranged from 22 to 63 years). All subjects received the study drugs, and all of them completed the study. Skin reaction scores were overall comparable for all tested products, untreated areas, and for irradiated and nonirradiated sides. All scores were <2. No phototoxic reaction occurred during the study.

There was only one TEAE reported during the study (PT: ligament sprain); the event was considered as not related to the study drug or procedure. No serious TEAEs, TEAEs that led to discontinuation, or AESIs were reported during the study.

Trial 40209: Evaluation of the Cutaneous Cumulative Irritancy Potential of Trifarotene Cream, 0.005%

This was a phase 1, single-center, randomized, vehicle-, negative- and positive-controlled, evaluator-blinded study using intra-individual comparison to determine the cutaneous cumulative irritancy potential of trifarotene cream at 50 µg/g and 100 µg/g following repeated application on the skin of 18- to 65-year-old healthy subjects. White petrolatum was used as

negative control, and 0.25% sodium lauryl sulfate (SLS) aqueous solution was used as a positive control.

Study drugs (20 µL/application) were applied by trained personnel on defined application sites on the subject's back under semi-occlusive conditions once daily, 6 days/week for 3 consecutive weeks (for a total of 18 applications).

The following safety assessments were performed:

- TEAEs at each visit. AESIs were defined as: suspected sensitization (i.e., allergic dermatitis), treatment-related TEAEs that led to study discontinuation, and treatment-related noncutaneous TEAEs.
- Skin reaction assessments using a 6-point skin reaction assessment scale (see second bullet under Trial 40208) at Days 2 to 6, 8 to 13, 15 to 20, and 22/ET visits, at least 30 minutes after patch removal.

Safety results

A total of 35 subjects were randomized. A total of 22 (62.9%) subjects were female, while 13 (37.1%) subjects were male. The mean age was 38.5 years (ranged from 20 to 65 years). All of the subjects received the study drugs, and 33 completed the study (two subjects discontinued due to nonstudy-related reasons).

Overall, eight (22.9%) subjects reported 11 TEAEs. A total of five cutaneous TEAEs were reported, and among them, four were related to trifarotene cream (i.e., two events of eczema and two events of skin irritation, one of each reported with trifarotene 50 µg/g cream and trifarotene 100 µg/g cream). Three AESIs were reported by two subjects as follows: one subject reported a moderate eczema-like reaction on both the trifarotene 50 µg/g cream and trifarotene 100 µg/g cream treated areas; one subject reported a moderate skin irritation on the trifarotene 100 µg/g cream treated area. These two subjects were challenged with the study drugs at least 2 weeks after the last applications, and the results were negative.

Both concentrations of trifarotene cream (i.e., 50 µg/g and 100 µg/g) induced cumulative irritant reaction under semi-occlusive conditions. A slight dose-dependent cumulative irritancy profile was observed. No serious TEAEs or TEAEs that led to discontinuation were reported during the study.

Trial 40189: Evaluation of the Photosensitization of Trifarotene Cream, 0.005% and Corresponding Vehicle Following Repeated Applications

This was a phase 1, single-center, randomized, vehicle- and negative-controlled, evaluator-blinded study using intra-individual comparison to determine the photosensitization potential of trifarotene cream at various concentrations (i.e., 25 and 100 µg/g) and corresponding vehicle cream in 18-to 65-year-old healthy subjects. White petrolatum was used as negative control.

An initial MED determination phase was followed by an induction phase, during which study drugs (20 µL of each study drug) were applied by trained personnel under a semi-occlusive patch to a designated skin site on one side of the subject's midback, twice per week for 3 consecutive weeks (for a total of six applications). During the first week of the induction phase, the designated skin sites were to be irradiated with UVA/UVB radiation 1.5 times the subject's MED; in the second and third weeks, skin sites were to be irradiated 2 times the subject's MED. A skin reaction assessment (based on a 6-point scale; see second bullet under Trial 40208) of the application sites was performed on Days 2, 4, 5, 8, 9, 11, 12, 15, 16, 18, and 19, at least 30 minutes after patch removal, prior to irradiation and study drug application. On Day 22, another skin reaction assessment was performed, and from this day subjects did not receive any application or irradiation for 2 weeks (rest phase).

After the rest phase, on Day 36, an additional application of each study drug was performed (challenge phase), as described above; two untreated sites (one per side) were added. On Day 37, skin reaction assessment of all skin sites was to be performed at least 30 minutes after patch removal (i.e., prior to irradiation). Then, the skin sites in the challenge phase located on the left upper back were irradiated with UVA/UVB 0.75 times the subject's MED, followed by 10 J/cm^2 of UVA radiation. A skin reaction assessment of all sites was performed immediately after irradiation and 48 hours after irradiation. The second set of skin sites on the opposing side of the upper back served as the nonirradiated control. At Day 39, a photosensitization reaction evaluation (0 = negative, 1 = equivocal, 2 = positive) was performed by comparing each study drug's irradiated site with its corresponding nonirradiated site. Subjects with equivocal photosensitization reaction evaluation scores underwent a rechallenge phase.

Apart from the skin reaction assessment and photosensitization reaction evaluation described above, safety assessments included:

- TEAEs at each visit. AESIs were defined as: positive photosensitization reaction (score of 2), treatment-related TEAEs that led to discontinuation, or non–cutaneous treatment-related TEAEs. Of note, an equivocal grade reaction (score of 1) was not reported as a TEAE unless confirmed as positive (score of 2) during challenge or rechallenge. This applied also to any pre-existing sensitization, which would have been detected during the induction phase.
- Vital signs and PE at screening and Day 39/ET visits.

Safety results

A total of 55 subjects were randomized. Overall, the proportion of males and females was similar (28 [50.9%] and 27 [49.1%], respectively), and the mean age was 37.9 years (ranged from 19 to 63 years).

A total of 29 TEAEs were reported by 23 (41.8%) subjects. None of the TEAEs were related to the study drug, and three events were cutaneous in nature (PTs: pruritus and skin irritation)

and occurred outside of the treated areas. No serious TEAEs, severe TEAEs, TEAEs that led to discontinuation, or AESIs were reported during the study.

During the induction phase, none of the skin reaction scores exceeded 2 (i.e., erythema with slight to moderate edema). The same number of subjects had scores of 2 with vehicle cream, white petrolatum, and on the untreated areas (i.e., 12 [21.8%] subjects). Greater irritation was observed with the highest concentration of trifarotene cream (i.e., 100 µg/g). Indeed, scores of 2 were observed more frequently with trifarotene 100 µg/g cream (in 52 [94.5%] subjects) than with trifarotene 25 µg/g cream (in 37 [67.3%] subjects). In addition, the mean skin reaction score increased up to Day 12 and then improved gradually with both concentrations of trifarotene cream, however, the mean values on Day 12 were greater for trifarotene 100 µg/g cream than for trifarotene 25 µg/g cream (1.6 versus 1.3). For the vehicle (white petrolatum) and the untreated zone groups, the mean skin reaction scores were always lower or equal to 1 and decreased slowly over time to very low scores at Day 22. The evolution of mean skin reaction scores was very similar for these three treatments.

Overall, results of the challenge phase showed that there was no potential risk for photosensitization to trifarotene cream on any of the tested areas. In addition, there was no need for a rechallenge phase. No safety concerns were raised from the assessment of vital signs or PE.

Trial 40190: Evaluation of the Sensitization Potential Of Trifarotene Cream and Corresponding Vehicle (Human Repeated Insult Patch Test)

This was a phase 1, single-center, randomized, vehicle- and negative-controlled, evaluator-blinded study using intra-individual comparison to determine the sensitization potential of two concentrations of trifarotene cream (25 and 100 µg/g) and corresponding vehicle cream after repeated applications in 18- to 65-year-old healthy subjects. White petrolatum was used as negative control.

During the induction phase, study drugs (approximately 20 µL of each drug) were applied by trained personnel under semi-occlusive conditions to the same designated skin site on the midback three times a week for 3 consecutive weeks (for a total of 9 applications). A skin reaction assessment (based on a six-point scale; see second bullet under Trial 40208) was performed on the designated skin sites on Days 3, 5, 8, 10, 12, 15, 17, 19, and 22, at least 30 minutes after patch removal. The induction phase was followed by a 2-week rest phase (from Day 22 to Day 35) during which subjects did not receive any application. On Day 36, subjects were exposed to the same study drugs (approximately 20 µL of each drug under semi-occlusive conditions) on naïve sites (on the upper back) for 48 hours (challenge phase).

A skin reaction assessment of these designated skin sites was performed at least 30 minutes and approximately 48 hours after patch removal. In addition, a sensitization reaction evaluation

(0 = negative, 1 = equivocal, 2 = positive) of the designated skin sites was performed approximately 48 hours after patch removal. Subjects with equivocal sensitization reaction were to undergo a rechallenge phase.

Apart from skin reaction assessment and sensitization reaction evaluation, safety assessments included:

- TEAEs at each visit following screening. AESIs were defined as: positive sensitization reaction (i.e., allergic dermatitis; sensitization reaction evaluation score of 2), treatment-related TEAEs that led to discontinuation, or noncutaneous treatment-related TEAEs. Of note, an equivocal grade reaction (sensitization reaction evaluation score of 1) was not to be reported as a TEAE unless confirmed as positive (score of 2) during rechallenge. This applied also to any pre-existing sensitization, which would have been detected during the induction phase.
- Vital signs and PE at screening and Day 40/ET visits.

Safety results

A total of 240 subjects were randomized; of whom, 237 completed the study and 3 discontinued. A total of 171 (71.3%) subjects were female, while 69 (28.8%) subjects were male, and the mean age was 42.6 years (ranged from 19 to 65 years). The subjects who completed the study received 200 µL of each study drug.

Overall, 129 (53.8%) subjects reported 205 TEAEs. A total of 12 treatment-related TEAEs were reported by six subjects, all of them where cutaneous in nature, and none led to discontinuation:

- Five events in four (1.7%) subjects on the site treated with trifarotene 100 µg/g cream (PTs: pruritus and skin sensitization)
- Four events in two (0.8%) subjects on the site treated with trifarotene 25 µg/g cream (PTs: pruritus, skin sensitization, and allergic dermatitis)
- Three events in two (0.8%) subjects on the site treated with vehicle cream (PTs: pruritus, skin sensitization, and urticaria).

Of note, all events of skin sensitization, allergic dermatitis, and urticaria mentioned above were reported by one subject and were assessed as allergy to propylene glycol after patch test investigation.

A total of two pregnancies were reported: one resulted in miscarriage (which was recorded as serious TEAE; PT of spontaneous abortion) and the other reached full term without any safety issues; both subjects discontinued the study. Another subject discontinued the study due to a TEAE of vesicular rash (not related to the study drug). No severe TEAEs were reported during the study.

During the induction phase, there was a dose-dependent skin irritation at the treated sites. Higher mean skin reaction scores with more subjects who had worst scores of ≥2 were observed with trifarotene 100 µg/g cream compared with trifarotene 25 µg/g cream. With both concentrations of trifarotene cream, mean skin reaction scores increased up to Day 15 and then remained stable until Day 22. The time course of the skin reactions observed with trifarotene cream at both concentrations was similar to those of other topical retinoids. For vehicle cream and white petrolatum, mean scores were always around 0.

During the challenge phase, one subject reported a positive sensitization reaction on the sites treated with trifarotene cream (at both concentrations) and an equivocal reaction on the site treated with vehicle cream. When rechallenged with the individual ingredients of the cream, the subject reacted to the propylene glycol ingredient. The positive skin sensitization was reported as an AESI. Two other subjects presented with equivocal reactions to trifarotene cream, but after another reading, only one subject remained equivocal on the 100 µg/g treated area.

Results showed a potential for sensitization to propylene glycol, but no potential risk for sensitization to the active ingredient (i.e., trifarotene) at the two concentrations tested in this study. No safety concerns were raised from the assessment of vital signs or physical examination.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Human Reproduction and Pregnancy

Although the use of a highly effective contraception method was required per protocol in all clinical studies conducted by the Applicant, 12 pregnancies were reported since the beginning of the development program which resulted in:

- Five miscarriages: Four in subjects who had been exposed to trifarotene (alone or in combination with other topical treatments, including corticosteroids) and one in a subject exposed to vehicle
- Four normal deliveries: three healthy babies (one in a subject exposed to trifarotene and two in subjects exposed to vehicle) and one baby with temporary respiratory distress at birth in a subject exposed to trifarotene:
  - One elective abortion in a subject exposed to vehicle, and
  - Two pregnancies with an unknown outcome as subjects were lost to follow-up (both subjects had been exposed to trifarotene cream, 0.005%).

All miscarriages were considered as not related to the study drug considering the limited systemic absorption of the product, the risk factors of the study subject (e.g., concomitant genital infection and/or previous gynecological history), and/or the concomitant contraceptive treatment.

In particular, there were four pregnancies in Safety Pool 1. Three of the subjects had been randomly assigned to vehicle cream. Subject (b) (6) had 25 applications of vehicle cream on the face and trunk before being discontinued from the trial. She gave birth to a healthy baby boy after a normal delivery at 41 weeks. Subject (b) (6) had a total of 28 applications of vehicle cream to the face and trunk. She underwent an elective abortion. Subject (b) (6) had a total of 62 applications to the face and 64 applications to the trunk before being discontinued from the trial. She gave birth to a healthy baby boy at 40 weeks and 6 days.

One subject each had been randomly assigned to the trifarotene cream, 0.005% and vehicle arms, respectively arm. Subject (b) (6) had received 79 applications of trifarotene cream, 0.005% to both the face and trunk before being discontinued from the trial. Unfortunately, despite several attempts by the Investigator, the subject could not be reached and was considered lost to follow-up. Thus, from the data presented in the application, it is too limited regarding the teratogenicity potential for the trifarotene cream, 0.005% to make a definitive statement. Trifarotene cream, 0.005% should only be used during pregnancy if the benefits outweigh the risk.

Pediatrics and Assessment of Effects on Growth

In the phase 3 trials and the PK maximal use trial (MUsT) (Study 18237) the Applicant established the safety and efficacy of trifarotene cream, 0.005% for use in the target pediatric population age 9 to less than 18 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)(A)(i) of the Pediatric Research Equity Act).

The Pediatric Review Committee agreed with the Applicant’s plan for a request of a patient waiver for pediatric patients less than 9 years old (May 31, 2017) and a letter of agreement was sent to the Applicant for the final iPSP on June 13, 2017. 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. Retinoids are not known to have any effect on growth. Thus, no evaluation of this endpoint was assessed.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

In the development program, no subjects reported an overdose of trifarotene, 0.005% cream. There were no TEAE that occurred under maximal use conditions (two clinical pharmacology MUsTs evaluated QD topical application of 50 µg/g and 100 µg/g trifarotene cream for 29 days in adult subjects and in pediatric subjects with acne vulgaris) that were unexpected. As there is no available information regarding overdose, Section 10 OVERDOSE will be omitted in labeling for trifarotene cream, 0.005%.

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.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

This is a new molecular entity and as such there is no postmarket experience.

Expectations on Safety in the Postmarket Setting

As this product is a topical retinoid, an entity where the safety profile has been well characterized; and given that this topical retinoid did not behave remarkably different from other topical retinoids, there is an expectation that the safety of the drug product in the postmarket setting will be the same as delineated in the review of the safety population of this NDA application.

8.2.10. Integrated Assessment of Safety

The safety profile for trifarotene, 0.005% cream was adequately characterized during the drug development program. The primary safety database consisted of 1,220 subjects from phase 3 Trials RD.03.SRE.18251 and RD.03.SRE.18252 (Safety Pool 1). 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 one postbaseline evaluation. Long-term safety up to 52 weeks of treatment came from Trial RD.03.SRE.18250.

Review of the safety data, including the long-term safety data, did not reveal any contraindications to treatment with trifarotene, 0.005% cream to be included in product labeling (Section 4 CONTRAINDICATIONS). 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,

dryness, stinging/burning) at a postbaseline visit was greater in the trifarotene cream, 0.005% group than the vehicle group. In addition, all the adverse events which occurred in ≥1% of subjects treated with trifarotene cream, 0.005% and greater than vehicle related to the application site (irritation, pruritus, and sunburn).

Treatment with trifarotene cream, 0.005% was not associated with an increased risk of mortality or serious adverse events. There were no deaths in the development program for trifarotene cream, 0.005% and there were no serious adverse events assessed as related to either study product. In the pooled safety analysis set (Safety Pool 1), serious adverse events occurred in 0.5% subjects in the trifarotene, 0.005% cream group and 0.5% subjects in the vehicle group. Among subjects in the trifarotene, 0.005% cream group, the serious adverse events included facial bones fracture, ligament sprain, procedural dizziness, cellulitis, infectious mononucleosis, suicide attempt, and major depression (one subject each). Among subjects in the vehicle group, serious adverse events included appendicitis, atypical pneumonia, sinusitis, suicide attempt, hereditary angioedema, urinary tract infection, and asthma (one subject each).

There were 12 pregnancies throughout the development program, 8 on trifarotene cream, 0.005% and 4 on vehicle. Among the eight subjects on trifarotene cream, 0.005%, there were four miscarriages, one normal delivery, one baby with temporary respiratory distress, and two subjects who were lost to follow-up. Among the subjects on vehicle, there was one miscarriage, two healthy babies, and one elective abortion. The Applicant considered any congenital anomaly/birth defect, and any abortion (voluntary, spontaneous, or therapeutic) a serious adverse event. The data collected in the overall program is insufficient to ascertain the teratogenicity of trifarotene cream, 0.005%. However, with low systemic exposure, patients should be advised to use this topical retinoid only if the benefits outweigh the risks. Catherine Roca, M.D., the reviewer from the Division of Pediatric and Maternal Health (DPMH), concluded that the available data from the submission or a review of the literature do not indicate a clear risk for use during pregnancy or lactation, or that there is a clear risk of infertility (review in DARRTs dated June 13, 2019). DRISK also completed a review, in DARRTs dated August 26, 2019, in which they also do not recommend any risk mitigation strategy and that any risk could be adequately conveyed in labeling. Thus, 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. It also includes a precaution for lactating mothers.

The currently available safety data from two 12-week phase 3 trials demonstrate that trifarotene cream, 0.005% appears safe for the treatment of acne vulgaris in patients 9 years of age and older. The safety profile of long-term use of trifarotene cream, 0.005% (52 weeks) appears to be the same as short-term use. Postmarketing risk management will include professional labeling and routine pharmacovigilance. As there were no major safety issues with the use of trifarotene cream, 0.005% and the safety profile is consistent with other topical retinoids, the review team recommends no other risk management tools and assessments (risk evaluation and mitigation strategy or clinical postmarketing studies).

8.3. Statistical Issues

The center by treatment interaction was statistically significant at the 0.1 level for IGA success endpoint at Week 12 in Study 18251 and all of the co-primary endpoints in Study 18252. Based on depictions of efficacy by site for the co-primary endpoints in Figure 27 through Figure 32, it does not appear that any single site or a few sites drove the overall efficacy results. There was a large number of sites in each study, and there was a small number of subjects per treatment arm in most sites.

To investigate this issue further, efficacy by country for the co-primary endpoints was examined in Figure 9 through Figure 14. There were larger observed treatment effects across the co-primary endpoints in subjects from Hungary in Study 18251 compared to the other countries in the study. A similarly large treatment effect was observed in subjects from Poland, Russia, Ukraine, and Hungary in Study 18252 compared to the other countries in the studies. For subjects in the US, the treatment effect for IGA success and change from baseline in inflammatory lesion count was consistent across both trials. For the change from baseline in noninflammatory lesion count, the treatment effect was larger in Study 18251 than Study 18252, though the number of subjects from the US was much larger in Study 18251.

8.4. Conclusions and Recommendations

The Applicant conducted two-identically designed, multicenter, randomized, double-blind, vehicle-controlled trials (Trials 18251 and 18252) to establish the efficacy of trifarotene cream, 0.005% in the treatment of acne vulgaris. The trials enrolled subjects 9 years of age and older with moderate facial acne and moderate truncal acne (truncal acne was optional for subjects 9 to 11 years old). The co-primary endpoints were IGA success rate, defined as the percentage of subjects who achieve an IGA score of 1 (almost clear) or 0 (clear) and at least a two-grade improvement from baseline at Week 12, absolute change in facial inflammatory lesion count from baseline to Week 12, and absolute change in facial noninflammatory lesion count from baseline to Week 12. The co-secondary endpoints mirrored the co-primary endpoints but were evaluated for truncal acne. In both trials, trifarotene cream, 0.005% was statistically superior to vehicle for the co-primary and co-secondary endpoints.

The Applicant conducted a comprehensive assessment of the safety of trifarotene cream, 0.005% 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. None of the safety issues identified in the review of the NDA would preclude market approval. Neither does it necessitate any safety mitigation strategies.

Submitted efficacy and safety data support approval of this NDA for trifarotene cream, 0.005% for the topical treatment of acne vulgaris in the population age 9 years and older.

9. Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application because there were no major safety issues and the adverse event profile was expected to be similar to other topical retinoids.

10. Pediatrics

In the phase 3 and phase 1 trials, the Applicant established the safety and efficacy of trifarotene cream, 0.005% 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 Pediatric Review Committee agreed with the Division that the assessments were adequate (June 13, 2017). 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.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed PI and carton/container labels for AKLIEF (trifarotene) Cream, 0.005%. The review team provided recommendations regarding PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, proposed patient package insert (PPI) and carton/container. These comments are reflected in final labeling. Refer to the OPDP review by Laurie Buonaccorsi, Regulatory Review Officer dated May 31, 2019. In addition, Madhuri R. Patel, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA) provided comments regarding the proposed carton and container labels (review in DARRTs dated August 19, 2019). Recommendations from Catherine Roca, M.D. from the Maternal Health Division of Pediatric and Maternal Health have been incorporated into labeling (see review in DARRTs dated June 13, 2019).

Table 64 provides the location of the labeling discussion for each section.

Table 64. Location of Labeling Discussion for Significant High-Level Labeling Changes

Summary of Significant High level Labeling Changes	
Section	**Location of Reviewer Comments on Proposed Labeling**
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	Section 8.1
4 CONTRAINDICATIONS	Section N/A
5 WARNINGS AND PRECAUTIONS	Section 8.2.2
6 ADVERSE REACTIONS	Sections 8.2.1, 8.2.2
7 DRUG INTERACTIONS	Section 6.3
8 USE IN SPECIFIC POPULATIONS	Sections 8.2.4; 5.5.4
12 CLINICAL PHARMACOLOGY	Section 6.3
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of product labeling (Sections 1, 2, 5, 6)
13 NONCLINICAL TOXICOLOGY	Sections 5.5.2; 5.5.3; 5.5.4; 18.3.2

11.2. Patient Labeling

The Applicant submitted a PPI for AKLIEF (trifarotene) Cream, 0.005%. The Division of Medical Policy Programs and OPDP reviewed and provided comments regarding the PPI. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Sharon Mills in DARRTs (June 24, 2019) for the complete review. In summary, in the collaborative review of the PPI, the Division did the following:

- Simplified wording and clarified concepts where possible
- Ensured that the PPI is consistent with the Prescribing Information (PI)
- Removed unnecessary or redundant information

- Ensured that the PPI is free of promotional language or suggested revisions to
- Ensured that it is free of promotional language
- Ensured that the PPI meets the criteria as specified in FDA's guidance, *Useful Written Consumer Medication Information* (July 2006)

12. Risk Evaluation and Mitigation Strategies

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

13. Postmarketing Requirements and Commitment

None.

14. Division Director (DHOT) Comments

N/A

15. Division Director (OCP) Comments

16. Division Director (Clinical) Comments

See Section 17.

17. Office Director, Acting, Comments

Galderma Research and Development, LLC submitted NDA 211527 for AKLIEF (trifarotene) Cream 0.005%, a new molecular entity (NME), in support of an indication for the treatment of acne vulgaris in patients age 9 and older. Trifarotene, the active ingredient in AKLIEF, is a retinoid that acts as a retinoic acid receptor agonist. Currently approved therapies for the treatment of acne vulgaris include the topical retinoids tretinoin and tazarotene, topical and oral antibiotics, and systemic hormonal therapies.

To support a claim for the treatment of acne vulgaris, the applicant conducted two identically designed, multicenter, randomized, double-blind, vehicle-controlled trials comparing trifarotene cream 0.005% versus vehicle applied once daily in the evening for 12 weeks for the treatment of moderate facial and truncal acne vulgaris. Eligible subjects were age 11 years and older with moderate acne vulgaris of the face and trunk or age 9 to ≤ 11 years with moderate facial acne. Both trials assessed the changes from baseline to Week 12 on the face of trifarotene cream 0.005% as compared to vehicle on the absolute change in the mean inflammatory and noninflammatory lesion counts and the percentage of subjects who achieved an Investigator Global Assessment (IGA) score of clear or almost clear and at least two-grade improvement from baseline. Trifarotene cream 0.005% was statistically superior to vehicle on all endpoints.

Review of the safety data identified safety issues consistent with the use of topical retinoids and supports the potential for skin irritation, pruritis, and sunburn; Section 5.1 of the package insert includes relevant warnings. Local tolerability signs and symptoms of erythema, scaling, dryness, and stinging/burning occurred in more than 50% of subjects on the face, and slightly fewer than 50% on the trunk. The majority of these reactions were mild to moderate in severity, with a few being severe.

The available safety and efficacy data supports the approval of AKLIEF (trifarotene) Cream 0.005% for the topical treatment of acne vulgaris in patients 9 years of age and older. I concur with the review team's recommendation for approval.

18. Appendices

18.1. References

Bhate, K and HC Williams, 2013, Epidemiology of acne vulgaris, Br J Dermatol, 168(3):474-485.

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Shatkin, JA and HS Brown, 1991, Pharmacokinetics of the dermal route of exposure to volatile organic chemicals in water: a computer simulation model, Environ Res, 56(1):90-108.

Thiboutot, D and A Zaenglein, 2018, Pathogenesis, clinical manifestations, and diagnosis of acne vulgaris, UpToDate, accessed August 21, 2019, https://www.uptodate.com/contents/pathogenesis-clinical-manifestations-and-diagnosis-of-acne-vulgaris.

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Zaenglein, AL, AL Pathy, BJ Schlosser, A Alikhan, HE Baldwin, DS Berson, WP Bowe, EM Graber, JC Harper, S Kang, JE Keri, JJ Leyden, RV Reynolds, NB Silverberg, LF Stein Gold, MM Tollefson, JS Weiss, NC Dolan, AA Sagan, M Stern, KM Boyer, and R Bhushan, 2016, Guidelines of care for the management of acne vulgaris, J Am Acad Dermatol, 74(5):945-973 e933.

18.2. Financial Disclosure

The Applicant certified on FDA Form 3454 that the Applicant has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). Furthermore, none of the investigators was the recipient of significant payments of the sorts defined in 21 CFR 54.2(f). Most of the 12 investigators who did have financial disclosures, according to the Applicant had a calculated risk of bias of less than 1%, with three investigators having a risk approaching 2.5%. These latter three had a total of 60 patients between them.

Table 65. Covered Clinical Studies 18251 and 18252

Was a list of clinical investigators provided:	Yes X☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 221		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none named		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Trial 18251 had 10 investigators with significant payment of other sorts above the disclosable value of $25,000. Trial 18252 had two such investigators.		
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: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X☐	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)

18.3. Nonclinical Pharmacology/Toxicology

18.3.1. Nonclinical Labeling

Sections 8.1, 8.3, 11, 12.1, 12.2, 13.1, and 13.2 of the labeling of the product should be modified as indicated below. Other portions of the proposed labeling are acceptable with respect to nonclinical issues. The INDICATIONS AND USAGE section of the draft labeling submitted by the Applicant states that the product is a retinoid. This statement of the pharmacological class is acceptable; trifarotene is a retinoid. The "dose multiples" (nonclinical exposures expressed in terms of the maximum observed clinical exposure) stated in the label are based upon comparison of systemic exposure values ($AUC_{nonclinical}/AUC_{clinical}$). The maximum observed clinical systemic exposure ($AUC_{0\text{-}24h}$) resulting from use of AKLIEF Cream in accordance with the label was determined empirically to be 0.106 ng•h/mL. Trifarotene was evaluated for potential to induce carcinogenesis, and for effects on fertility, embryofetal development, and perinatal development. Systemic exposure data associated with those studies are summarized in Table 66.

Table 66. Summary of Systemic Exposure Values, as Referenced in Label

Study Type	Dose of Interest (either the NOAEL or dose at which toxicity was observed, as described in the label)	Estimated AUC (ng•hr/mL)	Dose Multiple*
Carcinogenesis:			
Topical Mice:	Males and Females:	Males: 8.64	82
	0.001% w/w	Females: 10.5	99
Oral Rats:	Males: 0.75 mg/kg/day	68.4	645
	Females: 0.2 mg/kg/day	174	1,642
Fertility	Males: 0.75 mg/kg/day	186	1,755
	Females: 0.2 mg/kg/day	183	1,726
EFD (Female Rats)	0.1 mg/kg/day	172	1,623
EFD (Female Rabbits)	5 mg/kg/day	84.8	800
Perinatal Development (Female Rats)	0.1 mg/kg/day	63	594

* Dose Multiple refers to the ratio of the AUC at the dose of interest in the nonclinical study to the maximum AUC value observed in patients who used the product per the label in trials (0.106 ng•hr/mL for both genders), i.e., $AUC_{nonclinical}/AUC_{clinical}$.
Abbreviations: AUC = area under the concentration-time curve; EFD = embryo-fetal development; NOAEL = no adverse effect level

As proposed by the Applicant, Section 8.2, "Lactation," includes the following sentence:

(b) (4)

This statement is supported by submitted data (see "Distribution" portion of Section 5.4 of this review for detailed information), and is acceptable.

(b) (4)

18.3.1.1. Recommended Changes to Proposed Product Labeling by Section

Recommended changes from the Applicant's proposed product labeling in regard to Sections 8.1, (b) (4) 11, 12.1, 12.2, 13.1, (b) (4) are indicated below through use of strikeout (deletions) and underline (additions) fonts.

8.1. Pregnancy

Risk Summary

(b) (4)

Available data from clinical trials with AKLIEF Cream used in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are case reports of major birth defects similar to those seen in fetuses exposed to oral retinoids in pregnant women exposed to other topical retinoids, but these case reports do not establish a pattern or association with retinoid-related embryopathy.

In animal reproduction studies, (b) (4) oral doses of trifarotene administered to pregnant rats and rabbits during organogenesis that resulted in systemic exposures more than 800 times the systemic exposure at the maximum recommended human dose (MRHD) of AKLIEF Cream resulted in adverse fetal effects, including fetal deaths and external, visceral, and skeletal malformations (*see Data*). The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

(b) (4)

(b) (4)

Data

Animal Data

Oral administration of trifarotene to pregnant rats during the period of organogenesis~~,~~ at doses (b) (4) that resulted in systemic exposures greater than 1600 (b) (4)-times (b) (4)-those in humans at the MRHD of AKLIEF Cream~~,~~ resulted in adverse fetal effects, including fetal deaths, reduced mean fetal weight, and external, visceral, and skeletal malformations (b) (4)

Oral administration of trifarotene to pregnant rabbits during the period of organogenesis at doses (b) (4) that resulted in systemic exposures at least 800 (b) (4) times (b) (4)-those in humans~~,~~ at the MRHD of AKLIEF Cream resulted in adverse fetal effects, including defects of the tail, limbs, urogenital organs, and vertebral colum (b) (4)

Trifarotene administered orally to female rats from gestation Day 6 to lactation Day 20, at doses (b) (4)-that resulted in systemic exposures (b) (4) up to 594 (b) (4) times those in humans at the MRHD of AKLIEF Cream, had (b) (4) no effect on (b) (4) maternal function or behavior, including gestation, delivery, pup-rearing, lactation and nursing, or survival or development of pups- (b) (4) There were no effects of maternal treatment on behavior, learning, memory, or reproductive function of pups.

(b) (4)

(b) (4)

12.1. Mechanism of Action

(b) (4) Trifarotene is an agonist of retinoic acid receptors (RAR), with particular activity at the gamma subtype of RAR. Stimulation of RAR results in modulation of target genes which are associated with various processes, including cell differentiation and mediation of inflammation. The exact process by which trifarotene

ameliorates acne is unknown.-

(b) (4)

(b) (4)

(b) (4)

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Trifarotene was not carcinogenic when topically applied to mice daily for up to 24 months in the vehicle of the product (AKLIEF Cream) at concentrations of 0.0005% or 0.001% w/w (b) (4)

-The systemic exposures at the highest doses evaluated in mice (b) (4) (b) (4) were approximately (b) (4)2 (males) and 99 (females) times higher than the human exposure at the MRHD of AKLIEF Cream.

Trifarotene was not carcinogenic when administered orally to rats daily for up to 24 months at doses up to 0.75 mg/kg/day in males and 0.2 mg/kg/day in females. (b) (4) The systemic exposures at the highest doses evaluated in rats were approximately 64(b) (4)5 (males) and 164(b) (4)2 (females) times higher than the human exposure at the MRHD of AKLIEF Cream (b) (4)

Trifarotene was negative (b) (4) in an in vitro (b) (4)-bacterial reverse mutation (Ames) assay, an in vitro micronucleus assay in primary human lymphocytes, an in vitro mouse lymphoma assay with L5178Y/TK$^{+/-}$ (b) (4) cells, and an in vivo (b) (4)-micronucleus assay in rats.

(b) (4)

Trifarotene was assessed for effects on fertility or general reproductive function in rats. (b) (4) (b) (4) Males received trifarotene via (b) (4) oral gavage for 4 weeks prior to mating, during mating, and up to scheduled termination (approximately 6 weeks in total), and females were treated via (b) (4) oral gavage for 2 weeks prior to mating through (b) (4) Day 7 of gestation. No adverse effects on fertility or reproductive parameters, including sperm motility and concentration, were observed at the highest doses evaluated, which resulted in systemic exposures approximately 175(b) (4)5 (males) and (b) (4) 1726 (females) times higher than the human exposure at the MRHD of AKLIEF Cream.

(b) (4)

18.3.2. Review of Carcinogenicity Studies Conducted With Trifarotene

Table 67. CD5789 Cream, 104-Week Dermal Carcinogenicity Study in the CD1 Mouse

Study no.	AB02557, study report no. RDS.03.SRE.12847
Study report location	DSN 1
Conducting laboratory and location	(b) (4)
GLP compliance	Yes
Drug, lot #, and % purity	CD5789 cream placebo, lot No. 12.00092 CD5789 0.0005% cream, lot Nos. 12.01774 and 12.02481 CD5789 0.001% cream, lot No. 12.00097 CD5789 0.0025% cream, lot No. 12.00183 CD5789 0.005% cream, lot No. 12.00095
Prior ECAC dose concurrence	Y
Basis for dose selection	MTD

Abbreviations: ECAC = Executive Carcinogenicity Assessment Committee; GLP = good laboratory practice; MTD = maximum tolerated dose

Reviewer Carcinogenicity Conclusion (negative/ positive)

Negative

Executive Carcinogenicity Assessment Committee (ECAC) Carcinogenicity Conclusion (negative/ positive)

Negative

Tumor Findings

No statistically significant differences in tumor incidence were observed in mice of either sex in this study, according to the statistical criteria used by the Executive Carcinogenicity Assessment Committee of CDER.

Table 68. Methods of 104-Week Dermal Carcinogenicity Study in the CD1 Mouse

Method	
Doses	0 (water control), 0 (vehicle control), 0.001% CD5789 cream, and 0.0005% CD5789 cream
Frequency of dosing	Once daily
Number/sex/group	60
Dose volume	2 mL/kg/day
Formulation/vehicle	Topical cream/vehicle of the to-be-marketed product
Route of administration	TOPICAL
Species	MOUSE
Strain	CD1(ICR)
Age	Approx. 5 weeks at initiation of treatment.
Comment on study design and conduct	The study included a "water" control group, which was treated the same as the vehicle control groups, except that water for injection was topically applied. Test articles were applied to a 2x3 cm shaved dorsal area (approx. 10% BSA) and spread with a spatula. No dressing was applied. Once weekly, approx. 6 hours postdosing, the application site was washed with warm water and dried.
Dosing comments (dose adjustments or early termination)	Analysis of batch No. 12.01774 of CD5789 0.0005% cream indicated that the actual concentration of this material was 0.00035% instead of 0.0005%. Group 7 animals were treated with this material from 10/24/2012 to 12/18/2012. Starting 12/18/2012, group 7 animals were treated with CD5789 0.0005% cream batch No. 12.02481, which exhibited a concentration of 0.0005%, for the remainder of the study. This deviation is not considered to have affected the outcome of the study. Initially, the study included treatment groups of 0.001%, 0.0025%, and 0.005% CD5789 cream, but the 0.0025% and 0.005% materials were not tolerated, and, with concurrence of the ECAC, those groups were taken down without processing in Week 22. A new "ultra-low-dose" group, to be treated with 0.0005% CD5789 cream, and a new "concurrent" vehicle control group, were started at that time. Following 76 weeks of treatment, the Applicant reported that survival of males treated with 0.001% had declined to 25/60 animals. The following instructions were communicated to the Applicant, with concurrence of the ECAC:

Method	
Dosing comments (dose adjustments or early termination) *(continued)*	"In the event that survival of a given gender within group 3 should decline to 20 animals, then it is recommended that test-article application ("treatment") of the remaining animals of that gender within group 3 be stopped. In addition, test-article application of the animals of that same gender within the associated control groups (groups 1 and 2) should stop. In the event that survival of a given gender within either group 2 (vehicle control) or group 3 (0.001% CD5789) should then decline to 15 animals, then all remaining animals of that gender within groups 1, 2, and 3 should be sacrificed and subjected to necropsy and processing per the protocol. If the numbers of animals of a given gender within groups 2 and 3 do not decline to 15 animals, then groups 1, 2, and 3 (with respect to a given gender) should continue until the scheduled terminal sacrifice. In the event that survival of a given gender within group 7 should decline to 20 animals, then it is recommended that treatment of the remaining animals of that gender within group 7 be stopped. In addition, test-article application of the animals of that same gender within the associated control group (group 6) should stop. In the event that survival of a given gender within either group 6 (vehicle control) or group 7 (0.0005% CD5789) should then decline to 15 animals, then all remaining animals of that gender within groups 6 and 7 should be sacrificed and subjected to necropsy and processing per the protocol. If the numbers of animals of a given gender within groups 6 and 7 do not decline to 15 animals, then groups 6 and 7 (with respect to a given gender) should continue until the scheduled terminal sacrifice." On Day 607 (Week 87), the number of surviving group 3 males reached 20, and treatment of groups 1, 2, and 3 males was stopped (following 608 administrations). On Day 701 (Week 101), the number of surviving group 3 males reached 15, and terminal sacrifice of groups 1, 2, and 3 males was performed. On Day 669 (Week 96), the number of surviving group 3 females reached 20, and treatment of groups 1, 2, and 3 females was stopped (following 669 administrations). On Day 696 (Week 100), the number of surviving group 3 females reached 15, and terminal sacrifice of groups 1, 2, and 3 females was performed. On Day 703 (Week 101), the number of surviving group 6 females reached 20, and treatment of groups 6 and 7 females was stopped (following 704 administrations). Surviving groups 6 and 7 females, and surviving groups 6 and 7 males, were killed and processed at scheduled sacrifice, Week 104. Groups 6 and 7 males received up to 735 administrations.

The study design is summarized in Table 69.

Table 69. Study Design: CD5789 Cream, 104-Week Dermal Carcinogenicity Study in the CD1 Mouse

Group/Treatment	Theoretical dose volume (mL/kg/day)	Concentration of formulation (%)	Dose level (mg/kg/day)	Number of animals			
				Main study		Satellite study	
				Males	Females	Males	Females
1. Control (water)	2	0	0	60	60	6	6
2. Placebo I	2	0	0	60	60	6	6
3. Low dose	2	0.001	0.02	60	60	15	15
4. Intermediate dose[(a)]	2	0.0025	0.05	60	60	15	15
5. High dose[(a)]	2	0.005	0.1	60	60	15	15
6. Placebo II[(a)]	2	0	0	60	60	6	6
7. Ultra-low dose[(a)]	2	0.0005[(b)]	0.01	60	60	15	15

Treatment of groups 1 to 5 started March 28, 2012, (males) and March 30, 2012 (females). Groups 4 and 5 were sacrificed August 28, 2012, (males) and August 29, 2012, (females) due to intolerance issues and the animals were discarded without processing. Treatment of groups 6 and 7 started October 24, 2012, (males) and October 26, 2012, (females). These changes were made with concurrence of the ECAC.

Dosing Solution Analysis

Adequate. As noted elsewhere, the concentration of the 0.0005% CD5789 cream formulation used for the first 3 weeks was subpotent; analysis demonstrated it contained only 0.00035% CD5789. This was corrected, and subsequently used material was the correct concentration.

Observations and Results

Mortality

Survival was significantly reduced among males at 0.001% (group 3), in comparison to the vehicle control (group 2). No significant differences in rate of survival were observed for males at 0.0005% (group 7), or for females of either groups 3 or 7. However, a trend toward reduced survival of group three females seems apparent, and it is likely that the difference would have achieved statistical significance if treatment of group three females had not been stopped. No difference in survival of vehicle-treated animals in comparison to water-treated animals (group 2 versus group 1) was apparent in either sex. Table 70 presents mortality (numbers of deaths) of each group and sex at various time points, copied from the submission.

Table 70. Mortality at Different Occasions During Treatment Period (n=60/sex/group)

	Males					Females				
Groups	1	2	3	6	7	1	2	3	6	7
Dose (mg/kg/day)	0	0	0.02	0	0.01	0	0	0.02	0	0.01
Cream %	0	0	0.001	0	0.0005	0	0	0.001	0	0.0005
Day 357 / Week 52	3	7	18	2	2	2	3	6	7	5
Day 607[*] : Week 87	15	14	40[*]	18	15	24	23	33	26	28
Day 669[**] / Week 96	22	21	44	27	29	34	35	40[**]	33	36
Day 696[#] / Week 100	27	25	44	29	35	38	37	45[#]	38	38
Day 701[##] / Week 101	28	25	45[##]	29	35	/	/	/	39	39
Day 703[¤] : Week 101	/	/	/	29	36				40[¤]	39
Week 104	/	/	/	31	37	/	/	/	42	43

[*]Group 3 males: as the number of survivors declined to 20 animals, treatment was stopped for group 1, 2 and 3 males and animals were only kept for an observation period.
[**]Group 3 females: as the number of survivors declined to 20 animals, treatment was stopped for group 1, 2 and 3 females and animals were only kept for an observation period.
[#] Group 3 females: as the number of survivors declined to 15 animals, all remaining group 1, 2 and 3 females were sacrificed and subjected to necropsy.
[##] Group 3 males: as the number of survivors declined to 15 animals, all remaining group 1, 2 and 3 males were sacrificed and subjected to necropsy.
[¤] Group 6 females: as the number of survivors declined to 20 animals, treatment was stopped for group 6 and 7 females and animals were only kept for an observation period.

Clinical signs

Erythema, dryness, and scabs were observed at the treatment site in animals treated with 0.0005% or 0.001% CD5789 cream, in comparison to vehicle. The incidence, severity, and shortness of time to onset were dose-dependent. No other treatment-related signs were observed. No signs suggestive of systemic toxicity were observed.

Body weights

No treatment-related effects on mean BW were observed.

Feed consumption

No treatment-related effects on mean food consumption were observed.

Gross pathology

No treatment-related effects on incidence of palpable masses was observed. The incidence of sores/crusts and scaly appearance of skin at the treatment site was much higher in groups treated with CD5789, in comparison to vehicle-treated groups, and was more marked in males than females. The sores/crusts correlated with microscopic observations of scab/ulceration and the scaly appearance correlated with epidermal hyperplasia/hyperkeratosis. These skin findings were associated with enlargement of axillary, mandibular, inguinal lymph nodes, and/or the spleen, which correlated histologically with lymphoid hyperplasia.

Histopathology

- Peer Review Conducted: Yes
- Historical Control Provided for Tumor Incidence: No

Histopathology was performed on a standard list of tissues, plus any gross lesions, from all animals in groups 1 (water control), 2 (vehicle control 1), 3 (0.001% CD5789 cream), 6 (vehicle control 2), and 7 (0.0005% CD5789 cream), including both premature decedents and animals killed at terminal sacrifice.

Neoplastic

No statistically significant differences in tumor incidence were observed in mice of either sex in this study, according to the statistical criteria used by the exec-CAC.

Non-neoplastic

Treatment-related nonneoplastic microscopic findings were noted in the skin, lymph nodes, and spleen:

- Skin. Treatment-related changes of skin in animals treated with CD5789 cream included scab/ulceration and epidermal hyperplasia/hyperkeratosis graded minimal to severe; incidence and severity was dose (concentration) dependent. Males tended to be more affected than females.
- Lymphoid tissues. Scabs/ulcerations of skin were associated with minimal to severe lymphoid hyperplasia in the axillary lymph nodes, which were the draining lymph nodes of the skin site where treatment was applied. Lymphoid hyperplasia of associated structures, including the mandibular and inguinal lymph nodes, and the spleen, and increased cellularity of sternal bone marrow, were observed, and the incidence and severity were greater among animals that received CD5789 than in controls. These effects were likely secondary to limited infection associated with skin lesions.

Toxicokinetics

Toxicokinetic data obtained following 26 weeks of dosing are summarized below. Animals that nominally received 0.01 mg/kg/day or 0.02 mg/kg/day trifarotene were treated with 0.0005% CD5789 cream and 0.001% CD5789 cream, respectively.

Table 71. Toxicokinetic Data Following 26 Weeks of Dosing: CD5789 Cream, 104-Week Dermal Carcinogenicity Study in the CD1 Mouse

Day	Dose (mg/kg/day)	Sex	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	AUC_{0-24h}/Dose
Day 182	0.01	Female	1.00	0.432	2.42	242
		Male	1.00	0.362	2.32	232
	0.02	Female	1.00	1.47	10.5	527
		Male	1.00	1.84	8.64	432

Table 72. CD5789: 104-Week Oral (Gavage) Carcinogenicity Study in the Wistar Rat

Study no.	AB02556, study report no. RDS.03.SRE.12846
Study report location	DSN 1
Conducting laboratory and location	(b) (4)
GLP compliance	Yes
Drug, lot #, and % purity	Trifarotene, Batch N, 97.9% pure
Prior ECAC dose concurrence	Y
Basis for dose selection	MTD

Abbreviations: ECAC = Executive Carcinogenicity Assessment Committee; GLP = good laboratory practice; MTD = maximum tolerated dose

Reviewer Carcinogenicity Conclusion (negative/ positive)

Negative

ECAC Carcinogenicity Conclusion (negative/ positive)

Negative

Tumor Findings

No statistically significant differences in tumor incidence were observed in rats of either sex in this study, according to the statistical criteria used by the executive Carcinogenicity Assessment Committee of CDER.

Table 73. Methods of 104-Week Oral (Gavage) Carcinogenicity Study in the Wistar Rat

Method	
Doses	Males: 0, 0.1, 0.3, 0.75 mg/kg/day Females: 0, 0.05, 0.1, 0.2 mg/kg/day
Frequency of dosing	Once daily
Number/sex/group	60
Dose volume	2 mL/kg/day
Formulation/vehicle	Suspension/0.5% carboxymethyl cellulose and 0.1% Tween 80 in water
Route of administration	ORAL GAVAGE
Species	RAT
Strain	WISTAR HAN
Age	5 weeks at initiation of treatment
Comment on study design and conduct	Adequate
Dosing comments (dose adjustments or early termination)	None
Dosing solution analysis	Adequate

Observations and Results

Mortality

A statistically significant dose response relationship in mortality was not observed in either males or females. Animal disposition is summarized in Table 74.

Table 74. Dose-Response Relationship in Mortality: CD5789, 104-Week Oral (Gavage) Carcinogenicity Study in the Wistar Rat

Number of rats necropsied as scheduled or before the end of the study								
	Males				Females			
Dosage (mg/kg/day):	0	0.1	0.3	0.75	0	0.05	0.1	0.2
Moribund	10	11	10	14	13	16	22	10
Found dead	0	1	0	2	3	1	0	1
Terminally sacrificed	50	48	50	44	44	43	38	49

Clinical signs

Clinical signs that were considered to be directly related to treatment were limited to sores and/or scabs. These lesions were observed in all groups, including controls, but increased in incidence with increasing dose.

Body weights

Mean body weight was reduced in the HD groups of both sexes. BW data from Week 104 are summarized in Table 75.

Table 75. Mean Body Weight, Week 104 (mean±SD, g)

Group (mg/kg/day, males/females)	Males (% of Control)	Females (% of Control)
1 Control (0/0)	636.51±89.92	386.68±69.23
2 Low-dose (0.1/0.05)	632.83±91.25 (99%)	376.41±60.31 (97%)
3 Mid-dose (0.3/0.1)	607.83±78.12 (96%)	368.66±57.99 (95%)
4 High-dose (0.75/0.2)	562.40±79.51** (88%)	337.81±59.12* (87%)

* p<0.01

Graphical representations of mean BW data between Weeks 25 and 105 are presented in the figures below.

Figure 17. Mean Body Weights (g) From Week 25, Males

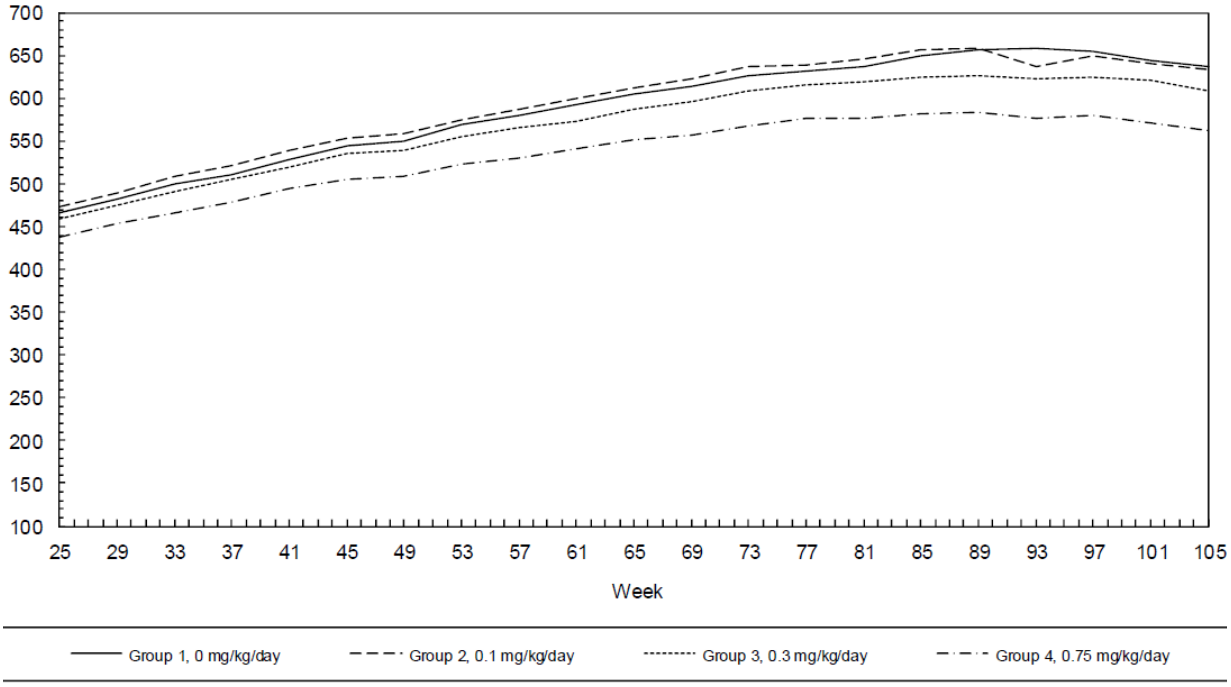
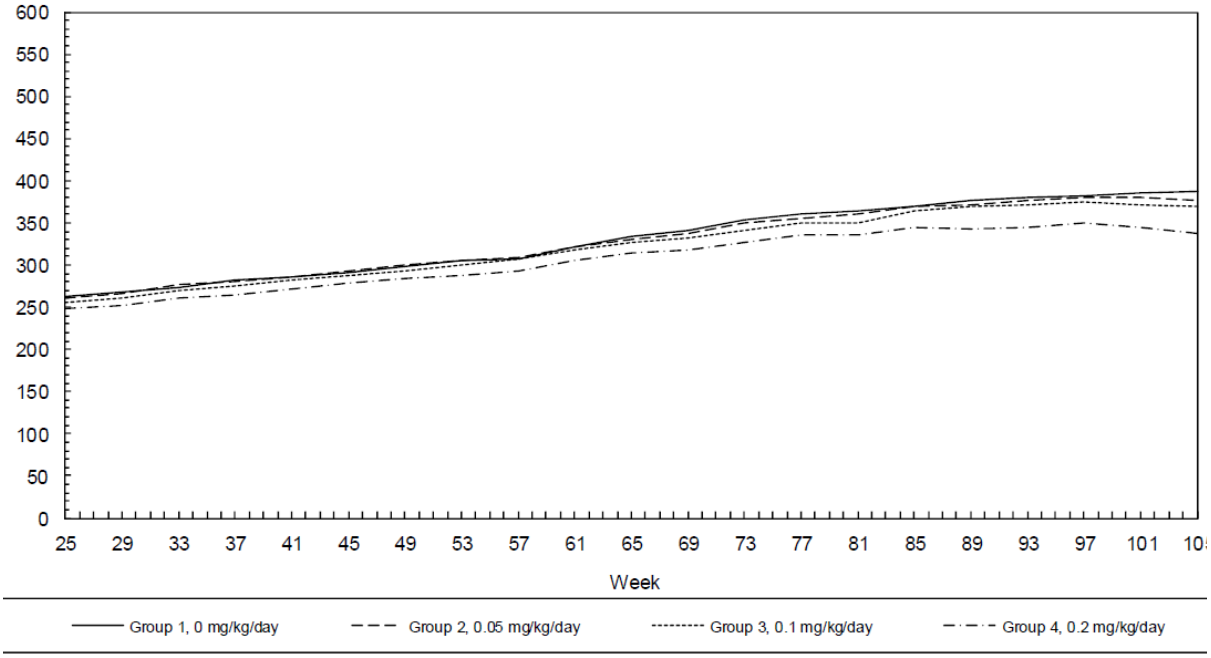


Figure 18. Mean Body Weights (g) From Week 25, Females



Feed consumption

Food consumption tended to decrease slightly with increasing dosage, although the effect was minimal.

Gross pathology

Gross observations that exhibited a positive relationship between dosage and incidence included sores on the skin, thickened wall of the stomach, and dark foci of the liver. The incidences of these observations are summarized in Table 76.

Table 76. Incidence of Noteworthy Abnormalities

	Males				Females			
Dosage (mg/kg/day):	0	0.1	0.3	0.75	0	0.05	0.1	0.2
Skin/subcutis [a]	**19**	**31**	**24**	**27**	**27**	**22**	**32**	**26**
Sore/crust	4	12	11	25	5	8	21	19
Stomach [a]	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Thickened wall	6	6	7	11	2	5	2	2
Liver [a]	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Dark focus	14	19	26	18	13	20	10	32
Dark depressed focus	5	6	6	4	-	1	6	4

[a]: number of animals in which the tissue was examined at necropsy.
-: finding not observed in the group.

Histopathology

- Peer Review Conducted: Yes
- Historical Control Provided for Tumor Incidence: No

Histopathology was performed on a standard list of tissues from control and high-dose animals killed at scheduled sacrifice, plus all main-study premature decedents from all groups. Histopathological examination was performed for all gross lesions sampled at necropsy from animals in all groups.

Neoplastic

No statistically significant differences in tumor incidence were observed in rats of either sex in this study, according to the statistical criteria used by the exec-CAC.

Non-neoplastic

Treatment-related nonneoplastic microscopic findings were noted in the stomach, skin, and femur/stifle joint:

- Stomach. High-dose group animals of both genders exhibited changes in the mucosa of the nonglandular region and the limiting ridge of the stomach, including degeneration of the epithelium and ulceration, graded minimal to moderate. There were no test item-related effects in the stomach in male and female rats given the low and intermediate doses.
- Skin. Skin that exhibited macroscopic lesions was sampled at necropsy. These samples, including skin from the abdomen, head, tail, ears, and foot pads, exhibited “crust/pustule,” “scab/ulceration with inflammation,” and acanthosis/hyperkeratosis graded minimal to marked. The incidence and/or severity of the lesions tended to increase with dosage.

- Femur/stifle joint. Test item-related histological changes were observed in the femur and stifle joint in male and female rats given the high dose, including irregular thickness of the growth plate, degenerative arthropathy, and bone resorption/fibrosis, graded minimal to moderate.

Toxicokinetics

Table 77. Mean CD5789 Toxicokinetic Parameters From Treated Groups After 26 Weeks of Treatment

Sex	Dose (mg/kg/day)	Day 182		
		T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)
Male	0.100	1.00	3.71	17.9
	0.300	1.00	6.38	39.4
	0.750	1.00	15.4	68.4
Female	0.0500	1.00	7.89	58.3
	0.100	1.00	13.2	86.3
	0.200	1.00	20.1	174

Abbreviations: AUC_{0-24h} = area under the 24-hour concentration time-curve; C_{max} = maximum concentration; T_{max} = time to maximum concentration

18.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

18.4.1. Clinical Pharmacology Studies

18.4.1.1. Study RD.06.SRE.18237 (Maximal Use PK study in Pediatrics)

A pharmacokinetic study of trifarotene following dermal application of trifarotene 50 µg/g or 100 µg/g cream under maximal use conditions in subjects 9 to 17 years of age with acne vulgaris.

Objective

To assess the systemic exposure to trifarotene under maximal use conditions in subjects 9 to 17 years of age with acne vulgaris when trifarotene 50 µg/g cream or 100 µg/g cream was applied once daily for 29 days.

Study Population

Thirty-five pediatric subjects aged 9 to 17 years (inclusive) with an IGA of at least 3 on the face (Subjects 9 to 11 years of age) or an IGA of 4 with a minimum of 25 inflammatory lesions and a minimum of 40 noninflammatory lesions on the face (Subjects 12 to 17 years of age).

Dosing Regimen

Once daily (QD) for 4 weeks (total 29 topical applications).

Study Duration

Four-week treatment period followed by a 3-day follow-up period.

Methods

The study enrolled a total of 35 pediatric subjects with moderate to severe acne vulgaris. Subjects were randomized and received one of two treatments, trifarotene 50 µg/g cream or 100 µg/g cream once daily for 29 days. Qualified staff topically applied the product evenly to all zones potentially affected by acne (i.e., the face, shoulders, upper back, and upper chest) except the neck. The amount of daily dosage was extrapolated from the adult dose based on µg/kg of body weight (Up to a maximum of 2 g). Assuming that the 2 g daily dose was applied to a 60-kg adult with a body surface area (BSA) of 1.8 m^2, the Applicant estimated that maximal daily dose to be 1.67 µg/kg and 3.34 µg/kg for pediatric subjects receiving 50 µg/g and 100 µg/g cream formulations respectively. The daily dose was adjusted according to the individual body weight, which ranged from 1.1 g to 2 g. Blood samples were collected for PK assessment as scheduled in Table 78. Plasma trifarotene concentrations were determined using a validated liquid chromatography-coupled tandem mass spectrometry (LC-MS/MS) method, and the limit of quantification (LOQ) was 5 pg/mL.

Table 78. PK Blood Sampling Time Points

PK Sampling Day/Time	Baseline/Day 1 [a]	Day 2	Day 15	Day 16	Day 29/ET [b]	Day 30	Day 31
Before study drug application		Before study drug application (pre-dose)	Before study drug application (pre-dose)	Before study drug application (pre-dose)	Before study drug application (pre-dose)		
After morning study drug application	2, 4, 6, 10, and 12 hours post-dose		2, 4, 6, 8, 10, and 12 hours post-dose		2, 4, 6, 8, 10, and 12 hours post-dose		
After the last study drug application in the Treatment period (morning of Day 29)						24 hours post-dose	48 hours pose-dose

Source: Table 6, Protocol Amendment N 2, 04 Feb 2013, Section 16.1.1
a Baseline/Day 1 is the first day in the Treatment period
b Day 29/Early Termination (ET) is the last day in the Treatment period and final application were given in the morning. In case of ET, a PK sample was to be collected if within 48 hours following the last study drug application.

Source: Table 2 of Study report RD.06.SRE.18237
Abbreviation: PK = pharmacokinetic

Results

Demographics

The mean age was 14.8 years old (range from 10 to 17). There were only two subjects in the 9-to-11-year-olds group due to a difficulty to recruit young subjects; one was 10 years old and the

other was 11 years old. There were 10 (29%) females and 25 males (71%) enrolled in the study. Racial groups were 28 (80.0%) Caucasian (white), 5 (14.3%) African-American, and 2 (5.7%) others.

The total treated BSA was calculated as the actual treated surface area of the upper back and upper chest, including shoulder, and the estimated face surface area (2% of total BSA). The mean ± SD of treated BSA in trifarotene cream 50 µg/g cohort and trifarotene cream 100 µg/g cohort was 6.89±1.8% and 6.86±1.95% of total BSA, respectively.

PK analysis

Mean plasma trifarotene concentrations over time after topical application are shown in Figure 1. The trifarotene concentration profile on Day 1 was not presented due to a high number of samples with concentrations below the LOQ. In estimating the PK parameters, the nonquantifiable plasma concentrations were replaced by the LOQ value (5 pg/mL). All subjects who received the first topical application of trifarotene 50 µg/g cream presented with concentrations below the LOQ, and two (2/17, 12%) subjects who received trifarotene 100 µg/g cream presented peak plasma trifarotene concentration (C_{max}) of 5 pg/mL and 7 pg/mL (Table 79).

On Day 15, plasma concentration of trifarotene in all subjects in trifarotene 50 µg/g cream group remained undetectable. Nine (9/13, 69%) subjects in trifarotene 100 µg/g cream group showed C_{max} ranging between 5 and 52 pg/mL. The mean ± SD C_{max} and the mean ± SD $AUC_{0\text{-}24h}$ of trifarotene 100 µg/g cream group was 18±17 pg/mL and 163±123 pg·h/mL, respectively (Table 79).

On Day 29 (i.e., End of treatment period), four (4/17, 24%) subjects in trifarotene 50 µg/g cream group had quantifiable levels of plasma trifarotene showing C_{max} ranging from 5 to 9 pg/mL and $AUC_{0\text{-}24h}$ ranging from 89 to 106 pg/mL. Eleven (11/16, 69%) subjects in trifarotene 100 µg/g cream group had quantifiable levels and presented a mean ± SD C_{max} of 12±12 pg/mL and a mean ± SD $AUC_{0\text{-}24h}$ of 137±119 pg·h/mL (Table 79). The time of peak plasma concentration (T_{max}) was approximately 4 hours postdose regardless of dose amount. Due to the lack of distinct elimination phase, half-life ($t_{1/2}$) was determined in only two subjects, which was approximately 3 hours.

Table 79. Summary of Trifarotene PK Parameters

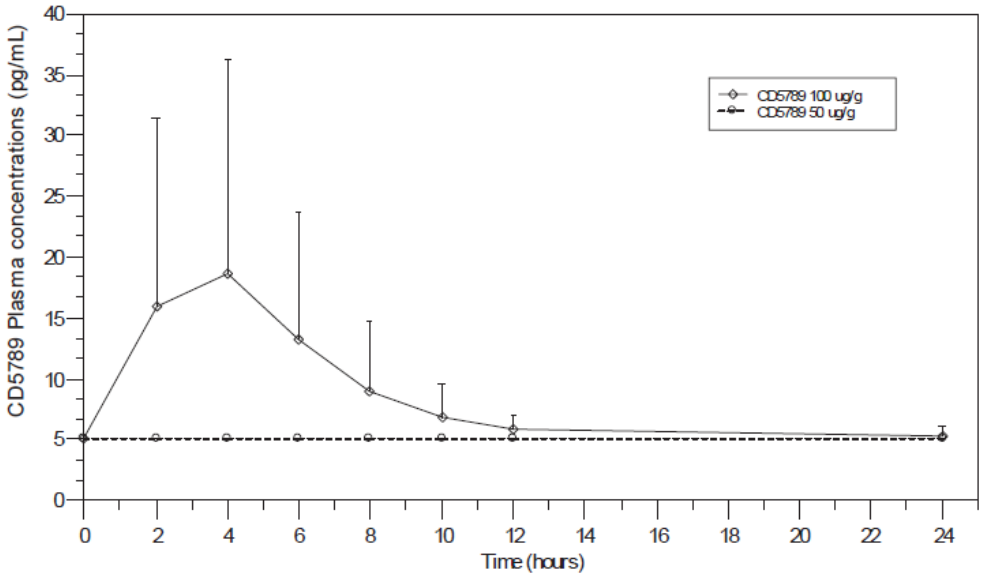
		CD5789 50 µg/g Cream				CD5789 100 µg/g Cream			
		C_{max}	T_{max}	AUC_{0-24h}	AUC_{0-t}	C_{max}	T_{max}	AUC_{0-24h}	AUC_{0-t}
		(pg/mL)	(h)	(pg.h/mL)	(pg.h/mL)	(pg/mL)	(h)	(pg.h/mL)	(pg.h/mL)
Day 1	**Mean ± SD**	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
	N (N quantifiable)	18 (0)	-	18 (0)	18 (0)	17 (2)	2	17 (2)	17 (2)
	Min - Max	-	-	-	-	5 - 7	4 – 4	68 - 83	15 - 31
	CV (%)	-	-	-	-	N.R.	N.R.	N.R.	N.R.
Day 15	**Mean ± SD**	N.R.	N.R.	N.R.	N.R.	18 ± 17	3.6 ± 0.9	163 ± 123	118 ± 134
	N (N quantifiable)	14 (0)	-	14 (0)	14 (0)	13 (9*)	9	13 (9)	13 (9)
	Min - Max	-	-	-	-	5 - 52	2 – 4	68 - 416	15 - 416
	CV (%)	-	-	-	-	95%	24%	75%	114%
Day 29	**Mean ± SD**	N.R.	N.R.	N.R.	N.R.	12 ± 12	3.5 ± 1.3	137 ± 119	90 ± 133
	N (N quantifiable)	17 (3)	17 (3)	17 (3)	17 (3)	16 (11*)	11	16 (11)	16 (11)
	Min - Max	7 - 9	4 - 4	89 - 106	22 - 41	5 - 52	2 – 6	68 - 547	15 - 547
	CV (%)	N.R.	N.R.	N.R.	N.R.	98%	37%	87%	148%

Source: Section 14.2, Table 14.2.1.2
*Seven subjects had quantifiable values at both time points.
N.R.: Not reportable when less than 50% of the data are quantifiable
Note: for descriptive statistics calculations BLQ data (<5 pg/mL) were replaced by the LOQ for C_{max} (i.e. 5pg/mL) and by the lowest AUC value (15 pg.h/mL and 68 pg.h/mL for AUC_{0-t} and AUC_{0-24h}, respectively).

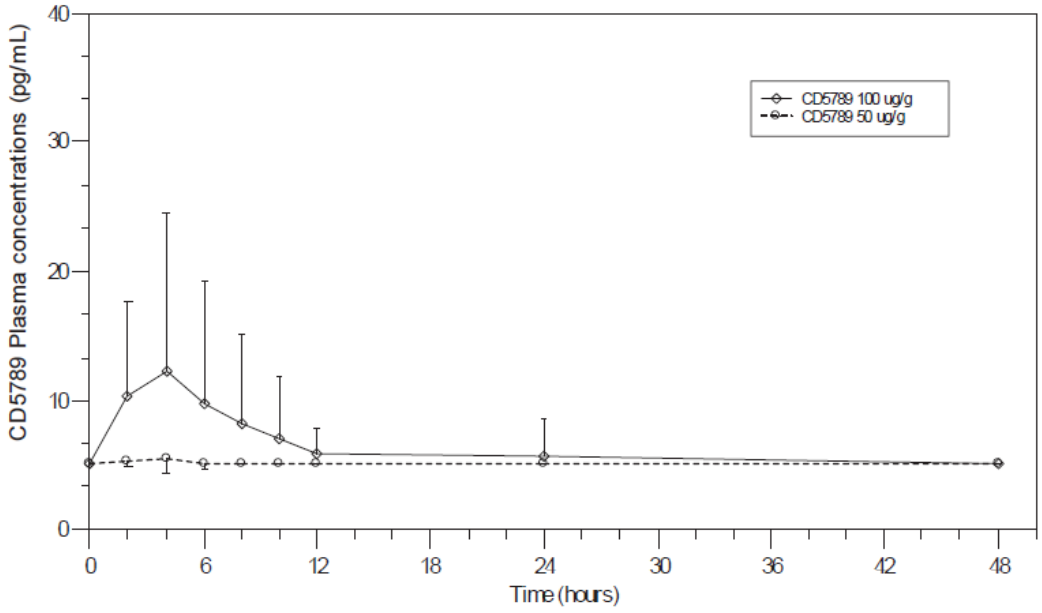
Source: Table 9 of Study report RD.06.SRE.18237
Abbreviations: AUC = area under the concentration-time curve; BLQ = below the limit of quantification; C_{max} = maximum concentration; CV = coefficient of variation; LOQ = limit of quantification; SD = standard deviation; T_{max} = time to maximum concentration

Figure 19. Mean Plasma Trifarotene Concentration-Time Profile on Days 15 and 29, Study RD.06.SRE.18237

(a) day 15 PK profile



(b) day 29 PK profile



Note: non-quantifiable concentrations were replaced by the LOQ (i.e.5 pg/mL). All CD5789 50 µg/g plasma concentrations were below the LOQ at Day 1 and 15 and only few quantifiable CD5789 plasma concentrations at Day 1 for CD5789 100 µg/g Cream, then, plasma profile at Day 1 was not presented.

Source: Figure 2 of Study report RD.06.SRE.18237
Abbreviations: LOQ = limit of quantification; PK = pharmacokinetics

Reviewer's comments: The demographic data of the study indicated that there were only 2 pediatric subjects between age 9 and 11 years old inclusive, and both were in trifarotene 50 µg/g cream group. This low number of subjects in the lowest age range is acceptable because acne vulgaris mostly occurs in subjects who hit puberty and the number of patients in this age range is expected to be low.

The pediatric patients received topical treatment of trifarotene to lesions rather than to the entire face, shoulders, upper chest, and upper back. The treated BSA appears to be underestimated as the Applicant estimated the face as 2% of BSA. The amount of trifarotene cream used ranged from 1.1 to 2 g/day as a maximal usage condition which are generally comparable to the average amount of trifarotene cream used in two phase 3 trials: Mean ± SD of trifarotene cream used in Studies 18251 and 18252 was 1.3±0.74 g/day and 1.8±1.2 g/day. Additionally, there was low systemic exposure of trifarotene following application of the to-be-marketed strength (50 µg/g) and additional safety data following application of the higher strength (100 µg/g) under maximal use conditions that suggests lack of any systemic safety concerns. In totality, the evidence provides support towards accepting this pediatric MUsT for trifarotene cream 50 µg/g in spite of the drug being applied to lesions rather than field treatment on the entire face, shoulders, upper chest, and upper back.

18.4.1.2. Study RD.03.SRE.40182 (Maximal Use PK study in Adults)

Pharmacokinetic study of trifarotene cream 50 and 100 µg/g in subjects with severe acne vulgaris under maximal use conditions.

Objective

To assess the systemic exposure of trifarotene after repeated once daily topical application of trifarotene 50 µg/g or 100 µg/g cream in subjects with the Investigator Global Assessment (IGA) of 4, with at least 30 noninflammatory lesions and at least 40 inflammatory lesions on the face over 4 weeks.

Study Population

Thirty-nine male and female subjects aged 18 to 35 years, with acne vulgaris on the face with a severity grade of 4 on the IGA, with at least 30 noninflammatory lesions and at least 40 inflammatory lesions on the face.

Dosing Regimen

QD for 4 weeks (total 29 topical applications).

Study Duration

Four-week treatment period followed by a 3-day follow-up period.

Methods

This study was a randomized, double-blind, parallel-group PK study of two dosages of trifarotene cream (50 µg/g and 100 µg/g) in adult subjects with acne vulgaris under maximal use conditions. In addition to the inclusion criteria of IGA score of 4 and lesion numbers, subject with body weight between 45 kg and 100 kg and with body mass index between 18 kg/m^2 and 30 kg/m^2 was included in the study. Subjects receive topical application of one dose (2 g) of trifarotene cream (50 µg/g or 100 µg/g) each morning for 29 days of treatment period. The qualified staff topically applied trifarotene cream evenly to all zones potentially affected by acne (i.e., the face, shoulders, upper back, and upper chest) except the neck. Blood samples were collected for PK assessment as shown in Table 80. Plasma trifarotene concentrations were determined using a validated LC-MS/MS method, and the LOQ was 5 pg/mL. In estimating the PK parameters, the nonquantifiable plasma concentrations were to be replaced by the LOQ value.

Table 80. Pharmacokinetic Blood Sampling Time Points, Study RD.03.SRE.40182

PK Sampling Day	Day 1	Day 2	Day 10	Day 15	Day 16	Day 22	Day 29 / Early Termination	Day 30	Day 31	Day 32
Plasma samples time points [a]	2, 4, 6, 8, 10, 12, and 16 hours after the initial dose	24 hours after initial dose (Pre-dose)	Pre-dose	Pre-dose, 2, 4, 6, 8, 10, 12, and 16 hours after the morning dose	24 hours after Day 15 dose (Pre-dose)	Pre-dose	Pre-dose, 2, 4, 6, 8, 10, 12, and 16 hours after the morning dose	24 hours after last dose on Day 29	48 hours after last dose on Day 29	72 hours after last dose on Day 29
Systemic PK parameters	C_{max}, T_{max}, AUC_{0-24h}	C_{trough}	C_{trough}	C_{trough}, C_{max}, T_{max}, AUC_{0-24h}	C_{trough}	C_{trough}	C_{trough}, C_{max}, T_{max}, AUC_{0-24h}, AUC_{0-t}, AUC_{0-inf}, K_{el}, $T_{1/2}$			

PK = Pharmacokinetic; C_{trough} = Residual drug concentration (pre-dose level); C_{max} = Observed peak drug concentration; T_{max} = Time at which C_{max} occurred; AUC_{0-24h} = Area under the concentration-time curve from pre-dose through 24 hours post-dosing; AUC_{0-t} = Area under the concentration-Time curve from T0 up to the sampling time corresponding to the last quantifiable concentration; AUC_{0-inf} = Area under the concentration-time curve from T0 to extrapolated to time infinity; K_{el} = Elimination rate constant value; $T_{1/2}$ = Terminal half-life value; T0 = Pre-dose time.
[a]. Sampling times were determined from time of the application start.

Source: Table 1 of Study report RD.03.SRE.40182

Results

Demographics

The study had a total of 36 subjects with mean age of 21 years old, which includes 30 (76.9%) male and 9 (23.1%) female subjects. All subjects were Caucasians (white) in this study.

PK analysis

On Day 1, all subjects who received trifarotene 50 µg/g cream presented with plasma trifarotene concentration below the LOQ. Two (2/18, 11%) subjects in trifarotene 100 µg/g cream group presented low but quantifiable plasma trifarotene concentrations: The C_{max} of each subject was 6.4 and 6.8 pg/mL.

On Day 15, two (2/19, 11%) and nine (9/18, 50%) subjects in trifarotene 50 µg/g cream and 100 µg/g cream groups, respectively, presented quantifiable plasma trifarotene concentrations. The C_{max} of each subject in trifarotene 50 µg/g cream group was 6.0 and 7.6 pg/mL. The mean ± SD

C_{max} and the mean ± SD $AUC_{0\text{-}24hr}$ in trifarotene 100 µg/g cream group was 9.5±10.4 pg/mL and 113±88.1 pg·hr/mL, respectively (Table 81).

On Day 29 (i.e., end-of-treatment period), seven (7/19, 37%) subjects in trifarotene 50 µg/g cream group presented low close concentrations to LOQ with C_{max} ranging from 5.0 to 9.6 pg/mL and $AUC_{0\text{-}24hr}$ ranging from 75.2 to 103.6 pg·hr/mL. Eleven (11/18, 61%) subjects in trifarotene 100 µg/g cream group presented the mean ± SD C_{max} of 10.8±7.7 pg/mL and the mean ± SD $AUC_{0\text{-}24hr}$ of 118.7±53.0 pg·hr/mL (Table 81).

The time of peak plasma concentration (T_{max}) was approximately 4 hours in both trifarotene 50 µg/g cream and 100 µg/g cream groups (Table 81 and Figure 20). Due to the lack of a distinct terminal phase, half-life ($t_{1/2}$) value was determined in only three subjects receiving trifarotene 100 µg/g cream who had $t_{1/2}$ of 2.4, 9.1, and 3.2 hours. Relatively short $t_{1/2}$ suggest that accumulation of trifarotene is unlikely to occur after longer duration of treatment with trifarotene cream 50 µg/g. However, this could not be confirmed due to lack of sufficient quantifiable data.

Table 81. Summary of Trifarotene PK Parameters of Adult Subjects, Study RD.03.SRE.40182

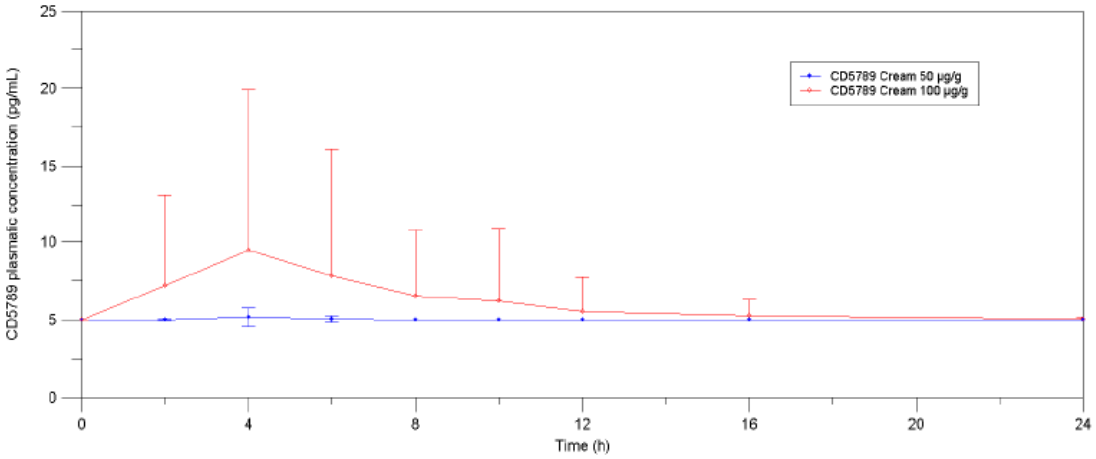
		CD5789 50 µg/g				CD5789 100 µg/g			
		C_{max}	T_{max}	$AUC_{0\text{-}24h}$	$AUC_{0\text{-}t}$	C_{max}	T_{max}	$AUC_{0\text{-}24h}$	$AUC_{0\text{-}t}$
		(pg/mL)	(hr)	(pg.hr/mL)	(pg.hr/mL)	(pg/mL)	(hr)	(pg.hr/mL)	(pg.hr/mL)
Day 1	**Mean±SD**	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
	N (N quantifiable)	19 (0)	19 (0)	19 (0)	19 (0)	18 (2)	18 (2)	18 (2)	18 (2)
	Min-Max	<5.0	N.R.	N.R.	N.R.	<5.0-6.8	4.0-4.0	79.9-82.8	16.4-29.5
	CV (%)	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Day 15	**Mean±SD**	N.R.	N.R.	N.R.	N.R.	9.5±10.4	4.3±1.6	113.0±88.1	60.5±101.7
	Geometric mean	N.R.	N.R.	N.R.	N.R.	7.4	N.R.	99.2	36.4
	N (N quantifiable)	19 (2)	19 (2)	19 (2)	19 (2)	18 (9)	18 (9)	18 (9)	18 (9)
	Min-Max	<5.0-7.6	4.0-6.0	85.7-99.5	23.2-32.0	<5.0-49.0	2.2-8.1	78.7-455.7	21.3-455.7
	CV (%)	N.R.	N.R.	N.R.	N.R.	110	37	78	168
Day 29	**Mean±SD**	N.R.	N.R.	N.R.	N.R.	10.8±7.7	4.4±1.2	118.7±53.0	67.1±60.7
	Geometric mean	N.R.	N.R.	N.R.	N.R.	8.8	N.R.	109.7	47.8
	N (N quantifiable)	19 (7)	19 (7)	19 (7)	19 (7)	18 (11)	18 (11)	18 (11)	18 (11)
	Min-Max	<5.0-9.6	3.9-4.0	75.2-103.6	20.2-41.2	<5.0-31.3	4.0-8.0	78.7-243.9	21.3-208.7
	CV (%)	N.R.	N.R.	N.R.	N.R.	71	28	45	91

AUC = Area under the concentration-time curve; PK = Pharmacokinetic; C_{max} = Observed peak drug concentration; T_{max} = Time at which C_{max} occurred; $AUC_{0\text{-}24h}$ = Area under the concentration-time curve from pre-dose through 24 hours post-dosing; $AUC_{0\text{-}t}$ = Area under the concentration-time curve from T0 up to the sampling time corresponding to the last quantifiable concentration; SD = Standard deviation; N.R. = Not reportable; Min = Minimum; Max = Maximum; CV = Coefficient of variation; LOQ = Limit of quantification; BLQ = Below the limit of quantification.
Note: Data were considered as not reportable when less than 50% of the data were quantifiable.
For descriptive statistics calculations, BLQ data (<5 pg/mL) were replaced by the LOQ for C_{max} (i.e. 5 pg/mL) and by the lowest AUC value (i.e. 21.3 and 78.7 pg.hr/mL for the CD5789 100 µg/g group $AUC_{0\text{-}t}$ and $AUC_{0\text{-}24h}$, respectively).
Data Source: Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, and 14.2.1.5.

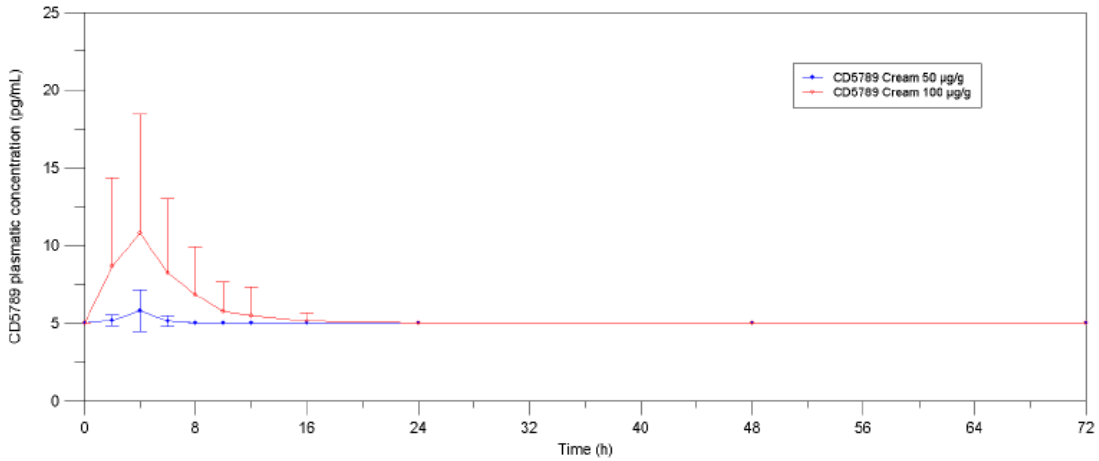
Source: Table 15 of Study report RD.03.SRE.40182

Figure 20. Mean Plasma Trifarotene Concentration-Time Profile on Days 15 and 29, Study RD.03.SRE.40182

a) Day 15–24 h PK profile



b) Day 29–72 h PK profile



Source: Kinetica software

Note: non-quantifiable concentrations were replaced by the LOQ (i.e.5 pg/mL). All CD5789 50 µg/g plasma concentrations were below the LOQ at Day 1 and 15 and only few quantifiable CD5789 plasma concentrations at Day 1 for CD5789 100 µg/g Cream, then, mean plasma profile at Day 1 was not presented.

Source: Figures 1 of Study report RD.03.SRE.40182 Appendix 16.1.12
Abbreviations: LOQ = limit of quantification; PK = pharmacokinetics

18.4.1.3. In Vivo DDI Study (Study 103918)

This phase 1, open-label, two-period, single-sequence drug-drug interaction study evaluated the effects of multiple dose trifarotene cream 100 µg/g on the pharmacokinetics of single-dose levonorgestrel (LNG, 0.15 mg) and ethinyl estradiol (EE, 0.03 mg) tablets in healthy adult female subjects.

Objectives

- To evaluate the effects of multiple-dose trifarotene 100 µg/g topical cream (2 g of topical formulation applied once daily for 14 days) on the pharmacokinetics of a single-dose of LNG (0.15 mg)/EE (0.03 mg) in healthy adult female subjects.
- To assess the safety and tolerability of multiple-dose trifarotene 100 µg/g topical cream (2 g of topical formulation applied once daily for 14 days) in healthy adult female subjects.

Study Population

Twenty-two female subjects aged 19 to 35 years.

Reviewer's comments: A total of 24 healthy female subjects were enrolled and received the treatment, but two subjects were excluded due to major protocol deviations: One subject had a positive pregnancy test at Day 18 visit, and the other subject had plasma LNG concentration (6.48 ng/mL) at predose on Day 18 exceeding the exposure limit (5% of the subject's C_{max} value [10.85 ng/mL]).

The subject with a positive pregnancy test stopped receiving the treatment but remained in the study for systemic exposure assessment of trifarotene cream 100 µg/g treatment prior to the pregnancy test. The PK data of the subject with a positive pregnancy were excluded from the PK analysis of 100 µg/g cohort. The subject was exposed to trifarotene cream for approximately 13 days (b) (6) *and the Applicant stated that the pregnancy was progressing well at the last follow-up on* (b) (6) *The subject with predose plasma LNG concentration of 6.48 ng/mL was excluded.*

Dosing Regimen

QD for 14 days.

Study Duration

Fourteen-day treatment period with trifarotene.

Methods

This study was a phase 1, open-label, two-period, single-sequence DDI study assessing the effects of steady state trifarotene 100 µg/g on the PK of a single-dose of LNG (0.15 mg)/EE (0.03 mg) in healthy female subjects. In this study, trifarotene 100 µg/g cream was the 'perpetrator' product and oral contraceptive was the 'victim' drug. Subjects received a single-dose of oral contraceptive (LNG/EE) tablet on Days 1 and 18. From Day 1 to Day 4, subjects underwent daily

blood sampling to obtain the oral contraceptive 72-hour PK profile. On Day 5, subjects returned to the study site and received QD topical application of trifarotene 100 µg/g cream until Day 18 (i.e., 14 treatments). A total of 2 g/day trifarotene 100 µg/g cream was topically applied to face, shoulders, upper chest, and upper back. On Day 18, subjects received the second single-dose of oral contraceptive (LNG/EE) in addition to trifarotene 100 µg/g cream. From Day 18 to Day 21, subjects underwent blood sampling to obtain the oral contraceptive and trifarotene 72-hour PK profiles.

Results

Levonorgestrel

The mean ± SD C_{max} of LNG was 3.2±1.3 ng/mL, and the mean ± SD AUC_{0-t} was 31.4±25.7 ng·h/mL after the first administration of the oral contraceptive. After 14 topical applications of trifarotene 100 µg/g cream and the second administration of the oral contraceptive on Day 18, mean ± SD C_{max} was 3.0±1.2 ng/mL, and a mean ± SD AUC_{0-t} was 30.8±19.3 ng·h/mL (Table 82).

Ethinyl estradiol

The mean ± SD C_{max} of EE was 0.10±0.02 ng/mL, and the mean ± SD AUC_{0-t} was 0.4±0.1 ng·h/mL after the first administration of the oral contraceptive. After 14 topical applications of trifarotene 100 µg/g cream and the second administration of the oral contraceptive on Day 18, mean ± SD C_{max} was 0.06±0.02 ng/mL, and a mean ± SD AUC_{0-t} was 0.4±0.1 ng·h/mL (Table 82).

Table 82. Inferential PK Parameter Analysis of LNG and EE on Days 1 and 18, Study RD.06.SRE.103918

EE N = 22	Geometric mean[a] (Arithmetic mean ± SD)		Geometric mean ratio	90% CI	
	Day 1	Day 18		Lower limit	Upper limit
C_{max} (ng/mL)	0.063 (0.065 ± 0.017)	0.062 (0.063 ± 0.016)	0.980	0.879	1.094
AUC_{0-t} (ng.h/mL)	0.412 (0.427 ± 0.108)	0.398 (0.418 ± 0.136)	0.968	0.860	1.090

a) Geometric means are based on least square means of Ln-transformed values.

Source: Tables 10 and 11 of Study report RD.06.SRE.103918
Abbreviations: AUC = area under the concentration-time curve; CI = confidence interval; C_{max} = maximum concentration; EE = ethinyl estradiol; LNG = levonorgestrel; SD = standard deviation

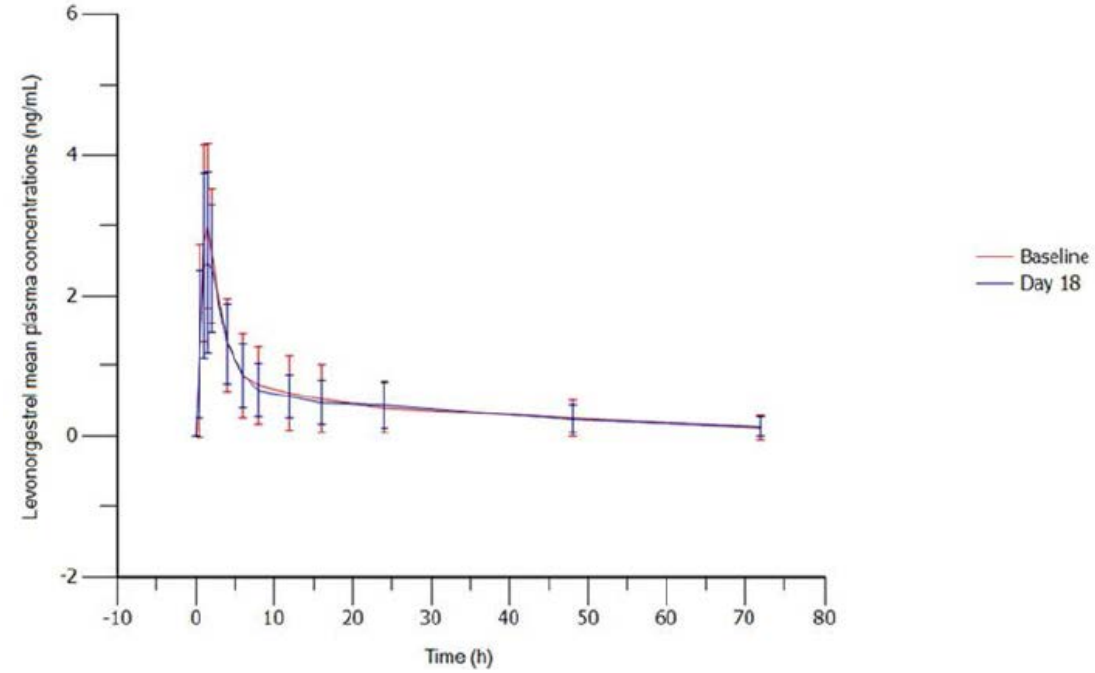
Trifarotene

Six out of 22 subjects with trifarotene 100 µg/g cream treatment presented quantifiable plasma trifarotene concentrations. The C_{max} ranged from 5.1 pg/mL to 10.8 pg/mL and the AUC_{0-t} ranged from 39.4 to 97.5 pg·h/mL.

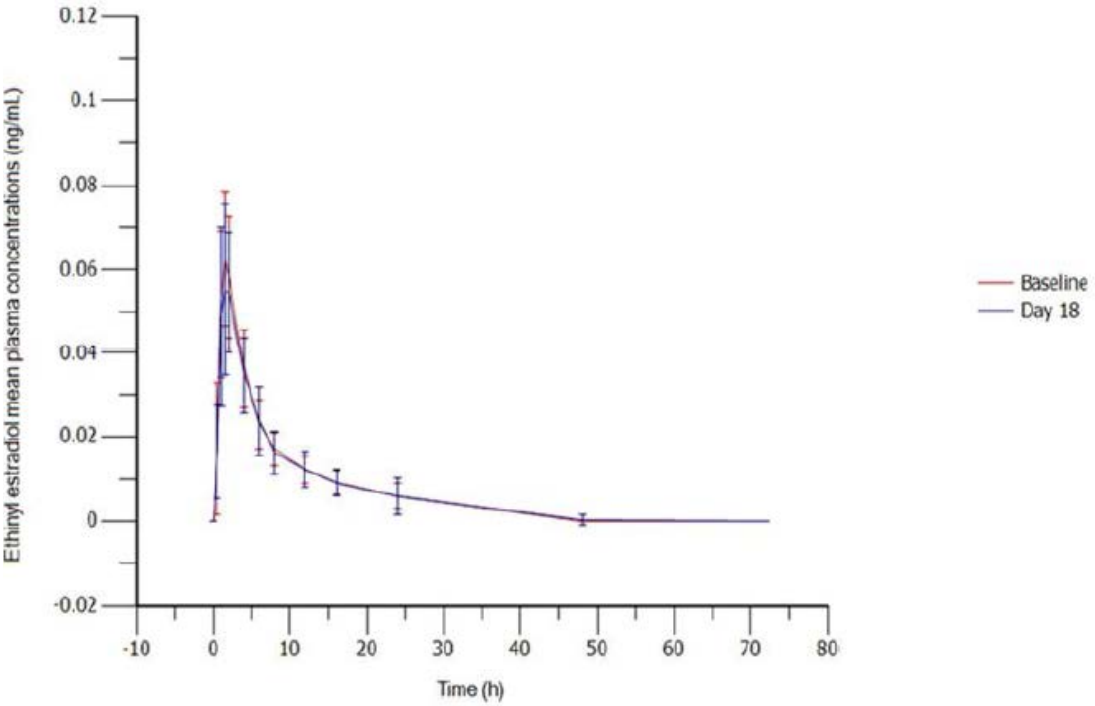
Comparison analyses of C_{max} and AUC_{0-t} of LNG and EE between Day 1 and Day 18 suggest comparable systemic exposure of LNG and EE before and after repeated treatment with trifarotene 100 µg/g cream (Figure 21).

Figure 21. Mean Plasma Concentration Profile of LNG and EE on Days 1 and 18, Study RD.06.SRE.103918

LNG Mean Plasma Concentration Profile



EE Mean Plasma Concentration Profile



Source: Figures 2 and 4 of study report RD.06.SRE.103918
Abbreviations: EE = ethinyl estradiol; LNG = levonorgestrel

Reviewer's comments: The Applicant used a higher strength (100 µg/g) of trifarotene cream compared to the intended to-be-marketed formulation (50 µg/g) purposely to ensure that the plasma trifarotene concentration obtained in healthy subjects was comparable to the plasma trifarotene concentration of the most exposed acne subjects treated with trifarotene 50 µg/g cream under maximal use conditions (AUC_{0-24hr}: 104 pg·h/mL in Study RD.03.SRE.40182). While C_{max} of 10.76 pg/mL and AUC of 97.47 pg·h/mL from this study is comparable to the highest levels of C_{max} and AUC in two maximal usage PK studies following application of trifarotene 50 µg/g dose, the interpretation of study result should be limited as the number of subjects exhibiting quantifiable systemic exposure of trifarotene was low (6 out of 22 subjects). In the opinion of this reviewer, quantifiable trifarotene concentrations in only six subjects do not represent adequate number of subjects to permit any definitive conclusions to be made.

It should be noted that results from in vitro DDI studies suggested lack of DDI with trifarotene 50 µg/g and data from animal toxicity studies suggested the safety margins for teratogenicity and reproductive toxicity to be approximately 100-fold and higher; this reviewer is of the opinion that topical application of trifarotene cream 50 µg/g is not expected to affect the circulating concentrations of oral hormonal contraceptives containing LNG and EE. Furthermore, application to more BSA compared to what was studied under maximal use conditions is unlikely because acne vulgaris is confined to face, shoulders upper chest and upper back. Hence any further increase in the systemic exposure of trifarotene is not expected under clinical use conditions that would impact the conclusion from this clinical DDI study.

18.4.1.4. In Vitro DDI Studies

The Applicant conducted the following in vitro studies to assess trifarotene metabolism and evaluate a potential perpetrator activity (inhibition or induction) on CYP enzymes and transporters.

- Study RDS.03.SRE.31111: Determination of the major human liver enzymes involved in the metabolism of [^{14}C]-CD5789.
- Study RDS.03.SRE.82059: Evaluation of four metabolites of trifarotene in RARα, RARβ, and RARγ transactivation assays.
- Study RDS.03.SPR.31109: In vitro cytochrome P450 inhibition using human liver microsomes.
- Study RDS.03.SRE.31108: In vitro evaluation of the potential to induce CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes.
- Study RDS.03.SRE.102468: In vitro interaction studies of trifarotene with human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 uptake transporters.
- Study RDS.03.SRE.109588: In vitro interaction studies of trifarotene with human BSEP, BCRP, MDR1, and MRP2 efflux (ABC) transporters.

Results

Study 31111 demonstrated that 4 CYP enzymes are mainly responsible for metabolism of trifarotene: CYP2C9 (67%), CYP2C8 (16%), CYP3A4 (17%), and CYP2B6 for a lesser extent. This indicates that CYP2C9 inhibition may cause an increase in trifarotene exposure, so the Applicant

assessed the drug interaction potential using a physiologically-based pharmacokinetic (PBPK) model to support that an increase in trifarotene exposure from CYP2C9 inhibition is not going to have any clinically meaningful effects under the proposed topical treatment regimen. The PBPK model was to estimate the overall increase of trifarotene systemic exposure when used concomitantly with fluconazole, a moderate inhibitor of CYP2C9 and CYP3A4. The Applicant found that the mean ratio of AUC and C_{max} values obtained in the presence of the inhibitor to those obtained in the absence were 1.19 and 1.17, respectively when moderate CYP inhibitor was coadministered. The simulation with a strong CYP inhibitor, a worst-case scenario, predicted that mean C_{max} and AUC could increase by 2.3- and 2.9-fold, respectively. Nonetheless, simulated highest systemic exposure of trifarotene appeared to still be lower than the safety margin of trifarotene cream 50 µg/g under clinical use conditions. For further details, refer to the PBPK review below (Section 18.4.2).

The Applicant reported the identification of five metabolites including one glucuro-conjugate metabolite and found that three of four phase 1 metabolites (i.e., CD06530, CD06700, and CD09986) were pharmacologically active in vitro Study 82059. However, systemic concentrations of the metabolites were below the LOQ in subjects treated with trifarotene cream 50 µg/g.

Study 31109 evaluated the inhibitory activity of trifarotene on CYP enzymes including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The study data showed that trifarotene is a reversible, competitive inhibitor of CYP2C8 (IC_{50}=7.8µM, Ki =3.7µM) and CYP2C9 (IC_{50}=3.9µM, Ki =0.9µM). Study 31108 evaluated the induction activity of trifarotene on CYP1A2, CYP2B6, and CYP3A4 in human hepatocyte cultures. Trifarotene did not increase the CYP activities and mRNA levels at concentrations up to 3µM (equivalent to 1.4 µg/mL).

Studies 102468 and 109588 evaluated the inhibitory activity of trifarotene on the major hepatic and renal uptake/efflux transporters. Trifarotene inhibited the OATP1B1 and OATP1B3 uptake transporters with IC_{50} ranging from 1.65 to 2.14µM. Trifarotene showed no inhibitory activity on the MDR1 efflux transporter and weak inhibition of the BSEP or MRP2 efflux transporters. Trifarotene appears to be an inhibitor of the BCRP efflux transporter with a maximum inhibition of 75% of the BCRP-mediated prazosin transport observed at 17.5µM. Trifarotene IC_{50} of BCRP efflux was 2.78µM which is approximately 140,000-fold higher than the C_{max} of trifarotene (9.6 pg/mL equivalent to 0.00002µM) measured in a maximal usage PK study (Study 40182). Overall, the in vitro DDI studies showed that the potential for trifarotene to inhibit CYP enzymes and transporters was observed at high concentrations, with IC_{50} values of 1.65µM or higher.

Overall, results from in vitro DDI studies indicated that trifarotene is mainly metabolized by 3 CYP enzymes (CYP2C9, CYP2C8, and CYP3A4) and that trifarotene has an inhibitory activity to CYP2C8 and CYP2C9 and 2 transporters (OAP1B1 and OAP1B3) with IC_{50} in µM markedly higher than observed systemic exposure of trifarotene in human under maximal use conditions. Hence the drug interaction potential of trifarotene cream 50 µg/g is low.

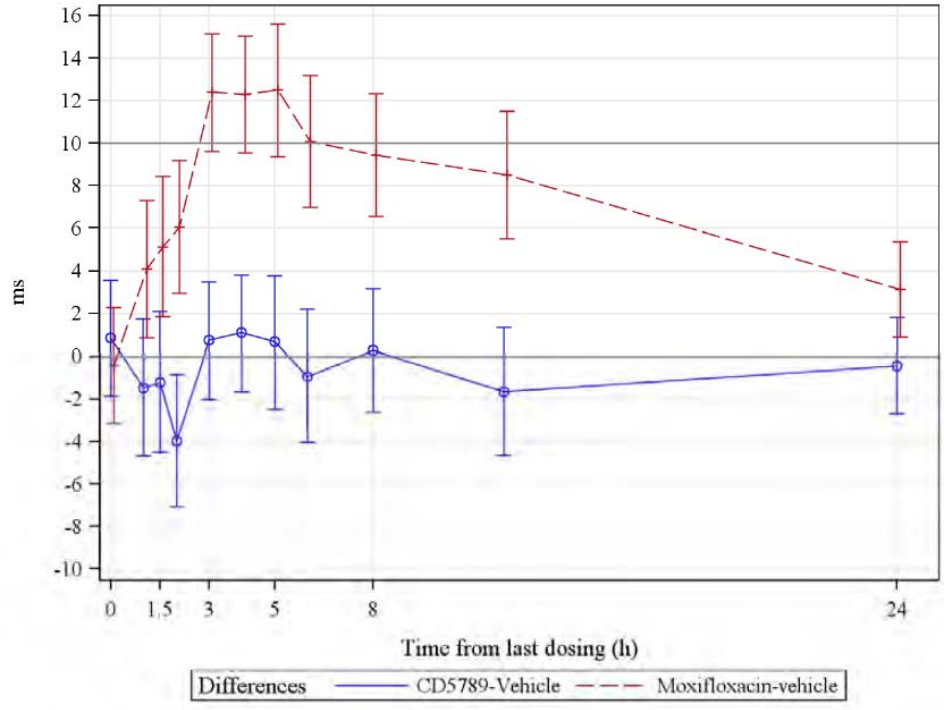
18.4.1.5. Study RD.03.SPR.40196 (Thorough QT-TQT Study)

Study 40196 was a vehicle controlled, parallel group study in a total of 180 healthy adult subjects (age between 19 and 65 years old, inclusive) with moxifloxacin as a positive control. Subjects received repeated topical applications of 12 g of CD5789 gel once daily applied on 6,000 cm^2 of BSA for 15 days. The primary evaluation was to compare the time-matched, baseline (Day -1) - adjusted mean difference between CD5789 and vehicle in the Fridericia's corrected QT-interval (QTcF).

Results

Repeated topical application of CD5789 gel for 15 days resulted in a mean ± SD C_{max} of 33±34 pg/mL (highest C_{max}: 187 pg/mL). The median T_{max} was 4.2 hour. The estimates of QTcF double-delta (baseline – adjusted, placebo – subtracted) over time are shown in Figure 22. The QTc double-delta data suggest that there was no statistical CD5789 – induced QT/QTc prolongation at supratherapeutic dose.

Figure 22. Mean QTcF (ms) Time-Matched Changes Over Time, Study RD.03.SPR.40196



SD = standard deviation; QTcF = Fridericia's corrected QT-interval
Data Source: Figure 6, RD.03.SRE.40196

Source: Figure 5 in Summary of Clinical Pharmacology Studies

Reviewer's comments: The Applicant used a trifarotene gel formulation which is not the final to-be-marketed trifarotene cream formulation. However, systemic exposure of trifarotene following the topical application of the gel formulation was adequately high as a supratherapeutic dose and covered the exposure of the to-be-marketed cream formulation (50 µg/g). Interdisciplinary review team for QT studies reviewed the study results (review dated

August 9, 2014, under IND 111091) and reported that there was no significant QTc prolongation effect of trifarotene in this TQT study.

The interdisciplinary review team for QT studies review summarized that the largest upper bound of the two-sided 90% CI for the mean difference between trifarotene and placebo was below 10 ms, the threshold for regulatory concern according to ICH E14 guidelines. Hence results of this study were considered acceptable and applicable to the to-be-marketed cream formulation due to lack of effect at approximately 3.4-fold higher exposure than the maximal usage studies.

18.4.1.6. Bioanalytical Method Validation

The plasma levels of trifarotene and three metabolites were determined using a validated liquid chromatographic-mass spectrometry (LC-MS/MS) method. The linear concentration range was 5 pg/mL to 1,000 pg/mL trifarotene with performance characteristics as shown in Table 83. The trifarotene standard in human plasma was stable for at least 12 months at -20°C, and this long-term stability duration was adequate to support the storage stability of the PK plasma samples.

Table 83. Precision and Accuracy of Bioanalytical Method

Variable	Range (% of Relative Error)
Inter-assay precision	4.3 to 7.1
Inter-assay accuracy	-1.3 to 2.8
Intra-assay precision	2.6 to 5.3
Intra-assay accuracy	-5.6 to 2.5

Source: Summary of biopharmaceutic studies and associated analytical methods

18.4.2. Physiologically Based Pharmacokinetic Analyses

Executive Summary

The objective of this review is to evaluate the adequacy of the following PBPK analyses reports from the Applicant and their response to our information request (IR).

- RD/14/27190 (dated May 31, 2016): Quantitative prediction of the systemic exposure of CD5789 after topical application of Cream B formulation using prior in vitro and in vivo data: Physiologically Based Pharmacokinetics (PBPK) model development, performance verification and model application for simulation of potential drug-drug interactions.
- GAL/4/A (dated February 26, 2018): Quantitative prediction of the systemic exposure of CD5789 in 9 to 11 years of age pediatric subjects after topical application of Cream B formulation using an existing physiologically-based pharmacokinetic model developed within the Simcyp population-based simulator.
- Responses to FDA's IR submitted on April 16, 2019, and May 3, 2019.

Specifically, the modeling analyses were used for the following purposes:

- Evaluate the drug-drug interaction potential for CD5789 (trifarotene) as a CYP3A4 and CYP2C9 substrate
- Estimate the systemic exposure of CD5789 in 9 to 11 years of age

The Division of Pharmacometrics has reviewed the report, supporting modeling files, and the Applicant's responses to our IR submitted on April 16, 2019, and May 3, 2019, and concluded the following:

- The trifarotene PBPK model was able to describe the observed PK in adults and pediatric population 12 to 17 years of age. The model predicted plasma exposure in pediatric population 9 to 11 years of age was considered exploratory due to the lack of experience in predicting skin absorption and in vivo PK data for model validation.
- The model was adequate to be used as a risk assessment tool to estimate the DDI potential for trifarotene as a CYP substrate. The model predicted that the geometric mean C_{max} and AUC of trifarotene could be increased by 2.3 and 2.9-fold, respectively, when trifarotene was coadministered with a hypothetical CYP2C9 and CYP3A4 strong inhibitor. The simulated highest geometric mean C_{max} was still lower than the safety margin of trifarotene 50 µg/g Cream based on non-clinical studies which ranged from 98- to 1,877-fold.

Background

Trifarotene (also referred to as CD5789) is a potent retinoic acid receptor γ ($RAR_γ$) agonist and was developed in a cream formulation (Cream B) containing 50 µg/g of active substance as a treatment of acne vulgaris in subjects 9 years of age and older.

In human hepatocytes, CYP2C9 accounted for 67% of the total metabolism of trifarotene, CYP2C8 and CYP3A4 accounted for 16% and 17% of the total metabolism of the parent compound, respectively. Trifarotene is a substrate for BCRP. Trifarotene was not actively transported by uptake transporters: MATEs, OAT1/3, OATP1B1/3, and $OCT_{1/2}$. Trifarotene was not actively transported by efflux transporters: MDR1 (P-gp) (0.1, 1, and 10µM), BSEP (0.25 and 2.5µM) and MRP2 (1 and 10µM) efflux transporters at the tested concentration ranges.

The plasma protein binding of trifarotene was measured at various concentrations of CD5789 (5 ng/mL to 1,000 ng/mL) in solution containing human serum albumin and human α-acid glycoprotein. The average of the measured % binding was around 99.9% with highest value of 99.92% at drug concentration of 50 ng/mL and lowest value of 99.88% at 1,000 ng/mL drug concentration.

In vitro, trifarotene showed reversible inhibitory effects toward CYP2C8 (IC_{50}=7.8µM, Ki =3.7µM) and CYP2C9 (IC_{50}=3.9µM, Ki =0.9µM). Trifarotene is likely an inhibitor of the BCRP with a maximum inhibition of 75% of the BCRP-mediated prazosin transport at 17.5µM and a calculated IC_{50} value of 2.78µM. The Ki values were much higher than the observed C_{max} at steady-state in subjects with acne under maximal use conditions (i.e., 0.0000096 µg/mL corresponding to 0.00002µM). Therefore, trifarotene inhibitory effects towards CYP2C8, CYP2C9, and BCRP were unlikely to occur under clinical use conditions.

In vivo studies were conducted to assess trifarotene exposure and used for model validation. In general, trifarotene had low systemic exposure after topical administration of trifarotene cream. The relevant in vivo PK studies used for mode development and validation are summarized in the PBPK Model Validation section.

Methods

Software

Simcyp® (Certara) Version 15 (V15) was used to conduct the initial trifarotene PBPK model in adults and DDI assessment (PBPK report RD/14/27190). The adult model was updated and reverified using Version 17 (V17) in PBPK report GAL/4/A due to an update in the method to predict V_{ss}, and update in fluconazole perpetrator model. "Sim-Pediatric" population file in the V17 was used for PK prediction in pediatric population 9 to 11 years of age.

Overview of modeling strategy

The trifarotene PBPK model was developed in adults. The model was verified by comparing the model prediction to observed PK in adults and pediatric population (12 to 17 years of age). The model was then applied to evaluate the exposure of trifarotene in pediatric population (9 to 11 years of age) following topical administration of trifarotene Cream B, and DDI potential for trifarotene as a victim drug.

PBPK model structures and parameters

Absorption: The MechDermA model consisting of stratum corneum (SC) and viable epidermis (VE) within Simcyp V15 was used to model trifarotene absorption following topical administration. A more complicated skin absorption model, multiphase multilayer MechDermA model, was available in V17, but not used in the trifarotene PBPK model.

Distribution

Trifarotene has high protein binding (>99%). In the PBPK model, unbound plasma protein binding (f_{up}) was set to be 1% to allow a conservative estimation of free drug concentration in the plasma. A full PBPK model was used to describe the volume of distribution of trifarotene. The tissue distribution following intravenous dosing in rats was used to calculate V_{ss} (volume of distribution at steady state) in human as there was a significant difference in the predicted V_{ss} using Method 1 (by Poulin and Theil, 4.37 L/kg) and Method 2 (by Rodgers, 0.54 L/kg). Furthermore, Method 1 provided similar predicted tissue-to-plasma partition coefficients (K_t:p) compared to the values extrapolated from rat for the four highly perfused tissues, heart, lung, liver, and kidney. Therefore, Method 1 was chosen to calculate volume of distribution. In the updated model (PBPK report GAL/4/A), the K_t:p-values for bone and gut were recalculated using tissue distribution experimental data because it was noticed that the Method 1 overestimated partition coefficients for some of the low perfusion tissues such as bone and gut. The V_{ss} was updated to be 3.04 L/kg.

Elimination

The apparent clearance was calculated based on the elimination rate constant (K_e) estimated from the terminal phase of the observed PK profiles at steady state following topical administration of 200 µg dose of Cream B to acne vulgaris patients (Study 40182) using equation 1, where K_e was the average K_e obtained from five subjects, V_{ss} was predicted by the Method 1, and BW was the body weight.

$$CL = K_e\ (h^{-1}) * V_{ss}\ (L/kg) * BW\ (kg) = 0.16*4.2*81 = 54\ L/h \quad \text{(equation 1)}$$

The in vitro f_m (fraction metabolized by a particular pathway) values for CYP3A4, CYP2C8 and CYP2C9 were 16.7%, 16% and 67.3%, respectively. Using the retrograde calculator within the Simcyp, the intrinsic clearances for each pathway were calculated and used during model development and performance verifications. Less than 1% of total clearance was designated to renal and biliary clearance.

Pediatric population

The pediatric population in Simcyp V17 was used to simulate the systemic PK of trifarotene in pediatric population (9 to 17 years of age). The pediatric population integrated physiology and enzyme ontogenies. Specifically, physiology parameters that affect skin absorption include the pH of skin, the thickness of skin layers, and the age-related change in blood flow to skin tissue. Physiology parameters that affect distribution and clearance include hematocrit and serum albumin levels, and the ontogenies of the three enzymes involved in the metabolism of trifarotene.

The trifarotene PBPK model input parameters are summarized in Table 84.

Table 84. Summary of Applicant's Trifarotene PBPK Model Input Parameters

Key Parameters	Values	Source
MW (g/mol)	459.58	In-house data
logP	6.65	Calculated
Compound type	Ampholyte	In-house data
pK_a	3.58 (acid), 6.57 (base)	Calculated
Absorption		
$f_{ni,\ skin\ surface}$	0.0009	Calculated at skin pH of ~5.5 by Simcyp
$Kp_{SC:w,\ unionized}$	1654.63	QSAR Predicted (Vecchia and Bunge 2003)
$Kp_{SC:w,\ ionized}$	1	Assumed
$Kp_{VE:SC}$	4.3	QSAR Predicted (Shatkin and Brown 1991)
$Kp_{B:VE}$	2.857	QSAR Predicted (Shatkin and Brown 1991)
f_{uSC}	0.003	QSAR Predicted (Nitsche et al. 2006)
D_{SC} (cm^2/h)	1.42E-07	QSAR Predicted (Potts and Guy 1992; Vecchia and Bunge 2003)
D_{VE} (cm^2/h)	0.00119	QSAR Predicted (Bunge and Cleek 1995)
Metabolism in skin	Negligible	Assumed, lack of experimental evidence
Formulation	Cream B, or aqueous solution	In-house data
Distribution and elimination		
V_{ss} (L/kg)	3.04	Estimated by Method 1 + rat K_t:p for bone and gut (updated model)
f_m	CYP2C9: 67%, CYP3A4: 17%, CYP2C8: 16%	In vitro hepatocyte study
f_{up}	0.01	guidance cutoff value, higher than measured (0.0002)
CL (L/h)	54	Equation 1
$CL_{biliary}$ (L/h)	<1	estimated from in vitro sandwich-culture human hepatocytes
CL_{hep} (L/h)	45.6	$CL_{int,\ hep}$ =26 µL/h/10^6 hepatocytes and $f_{u,\ Hep}$ =0.013 (QSAR prediction)

Source: Tables 2, 3 in the PBPK report RD/14/27190, and description in the PBPK reports RD/14/27190 and GAL/4/A
Abbreviations: $f_{ni,\ skin\ surface}$ = fraction nonionized at skin surface; $Kp_{SC:w}$ = unionized (formulation vehicle (water) to stratum corneum partition coefficient for unionized molecule); $Kp_{SC:w}$ = ionized (formulation vehicle (water) to stratum corneum partition coefficient for unionized molecule); $Kp_{VE:SC}$ = VE-to-SC partition coefficient; $Kp_{B:VE}$ = blood-to-VE partition coefficient; f_{uSC} = unbound fraction in SC; D_{SC} = diffusion coefficient in SC; D_{VE} = diffusion coefficient in VE; QSAR = Quantitative Structure-Activity Relationship; MW = molecular weight; CL = clearance

Reviewer's comments:

- *In vitro, trifarotene is a BCRP substrate. In preclinical studies, trifarotene was mainly excreted in the feces through biliary clearance. The estimated human biliary clearance from a sandwich-culture human hepatocyte system was less than 1%. In the absence of a human mass balance study, human biliary clearance was difficult to estimate. Nevertheless, the low biliary clearance assigned to the trifarotene PBPK model will provide a conservative estimation of the enzyme-mediated DDI potential.*

- *Trifarotene is a substrate for CYP2C9, CYP2C8, and BCRP. In vitro, trifarotene also showed inhibitory effects towards CYP2C8, CYP2C9, and BCRP. The inhibition is unlikely to occur under clinical use conditions due to the low systemic exposure. Therefore, it is acceptable that the trifarotene inhibitory effects were not introduced into the PBPK model of trifarotene.*

- *The Quantitative Structure-Activity Relationship (QSAR) modeling approach was used to derive several skin absorption parameters. The reviewer noticed that QSAR-derived parameters are empirical parameters. Given the limited regulatory experience in skin absorption modeling, using this approach may only be considered appropriate when there are relevant clinical data available for model validation.*

- *The model assumed that the skin physiology and blood flow to the skin were the same in subjects with acne vulgaris as compared to general healthy population.*

- *The facial skin physiology was assumed for other topical cream application sites, such as face, shoulder, back and chest. According to the Applicant, assuming facial skin physiology for simulations would give a more conservative assessment of systemic exposure as facial skin is believed to give relatively higher absorption.*

PBPK Model Validation

The in vivo PK studies that were used for model validation were summarized in Table 85.

Table 85. Summary of Human PK Data Used for Model Development and Validation

Study No.	Description	N	Formu-lation	Dose	Treated Surface Area (cm^2)	C_{max} (pg/mL)	AUC_{0-24} (pg•hr/mL)	PBPK Report
40182	MUsT in subjects with acne vulgaris	19 (7)	Cream B	2 g of 50 µg/g	1,000	NR (<5.0-9.6)	NR (75.2-103.6)	RD/14/27190 GAL/4/A
		18 (11)	Cream B	2 g of 100 µg/g	1,000	10.8±7.7 (<5.0-31.3)	118.7±53.0 (78.7-243.9)	
18237	MUsT in peds patients 9-17yrs	17 (3)	Cream B	2 g of 50 µg/g	1,220 (mean)	NR (7-9)	NR (89-106)	GAL/4/A
		16 (11)	Cream B	2 g of 100 µg/g	1,184 (mean)	12±12 (5-52)	137±119 (68-547)	
40128	Plasma and dermal PK, multiple formulations, adult HVs	10 (0)	Group F (Cream B)	2 g of 50 µg/g	1,000	<10	NR	RD/14/27190 GAL/4/A

Source: For Study 40182 and Study 18237, Day 29 PK parameters were presented in Table 11 and Table 13 in the summary of clinical pharmacology studies, respectively. For Study 40128, results were in Table 32 of the summary of clinical pharmacology studies
C_{max} and AUC_{0-24} were presented as Mean ± SD (Min-Max);
Abbreviations: MUsT (maximal usage trial); AUC_{0-24} = area under the curve from predosing through 24 hours postdosing; C_{max} = maximum concentration; N = N quantifiable; NR = nonreportable (i.e., when less than 50% of the data were quantifiable); PBPK = physiologically-based pharmacokinetic modeling; PK = pharmacokinetic; SC = stratum corneum; VE = viable epidermis

Reviewer's comments:

- *A mechanistic dermal absorption model was adapted to simulate the exposure of trifarotene following topical administration. The focus of the PBPK analyses was the systemic exposure but not the skin local exposure. Therefore, it is acceptable that the model predictive performance was validated by comparing model prediction to observed systemic exposure.*

- *In the Study 18237, only two subjects were in the 9 to 11 years of age group and both were in the 50 µg/g dose group. Plasma concentrations were mostly blow LOQ (limit of quantification).*

PBPK Model Application

The developed PBPK models were used to simulate the PK of trifarotene in pediatric population 9 to 11 years of age and the DDI potential of trifarotene as a victim drug. The effects of fluconazole (a moderate CYP3A4 and CYP2C9) on trifarotene exposure was assess in V15 and then updated in V17. In response to FDA's IR, the Applicant conducted sensitivity analyses and assessed 'worst-case' scenarios where the exposure of trifarotene can be increased.

Reviewer's comments: In the fluconazole model, the inhibitory effects (K_i) and fraction of unbound drug in the in vitro microsomal incubation (fu_{mic}) values were changed from 7.92uM and 1 in V15 to 20.4uM and 0.89 in V17, respectively. These changes led to less potent effects of fluconazole on a CYP2C9 substrate. Nevertheless, the Applicant conduct sensitivity analyses to assess hypothetical worst-case scenarios.

Results

Evaluation of the trifarotene PBPK model performance in predicting the PK of trifarotene in adults and pediatric populations following topical administration of Cream B

In general, the trifarotene PBPK model could describe the observed PK in adults (Figure 23 and Figure 24) and pediatric subjects 12 to 17 years of age (Figure 25 and Figure 26) following topical administration of 2 g of 100 µg/g Cream B (Studies 40182 and 40128) by visual inspection as shown in Figure 23 and Figure 25.

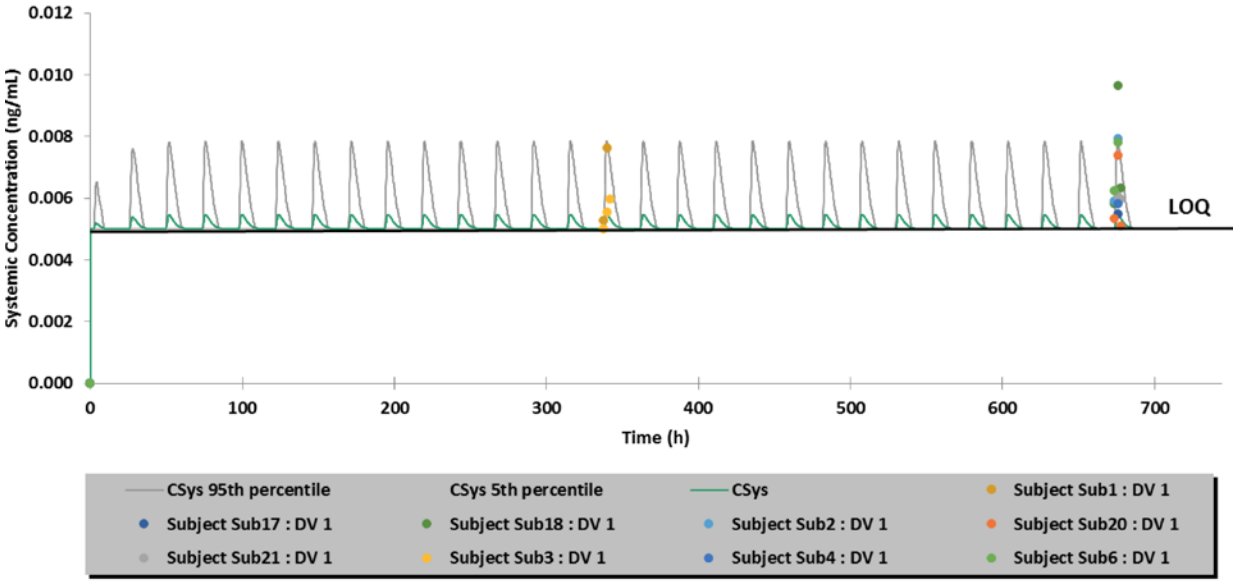
In human PK studies, the plasma concentrations were very low and many of them were close to or below the LOQ. However, in simulations, there is no LOQ. Therefore, the selection of data analysis method, specifically how to treat values below LOQ, may affect the descriptive statistics between model predictions and observed PK. The Applicant analyzed simulated trifarotene C_{max} and T_{max} using three methods: (1) simulated PK data without LOQ applied; (2) simulated PK data with Cp = LOQ when Cp < LOQ; and (3) simulated PK data with Cp removed when Cp < LOQ. These three methods gave the lowest, middle, and highest estimates of PK parameters, respectively.

In human PK study data analysis (e.g., Studies 40182 and 18237), for descriptive statistics calculations, results below the LOQ were replaced by the LOQ for C_{max} and by the lowest AUC value. This method may overestimate the PK parameters. As shown in Table 86, the predicted C_{max} and AUC were within 0.5 to 1.5 of observed PK parameters. A trend of underprediction could be due to the simulated PK data were analyzed without LOQ being applied. In addition, the model predicted SC concentrations were compared to the observed SC concentrations obtained in Study 40128. The model appeared able to capture the observed SC concentration.

Following trifarotene PBPK model validation in adults and pediatric population 12 to 17 years of age, the Applicant applied the model to estimate the systemic exposure of trifarotene in pediatric subjects 9 to 11 years of age. The model estimated 24% and 17% increase in C_{max} and AUC, respectively, comparing the 9 to 11 years age group to the 12 to 17 years age group. In the MUsT in pediatric population (Study 18237), only two subjects were enrolled in the 9 to 11 years age group and were administered 2 g of 50 µg/g. The plasma PK were not quantifiable, and therefore, no PK data were available for model validation in subjects 9 to 11 years of age.

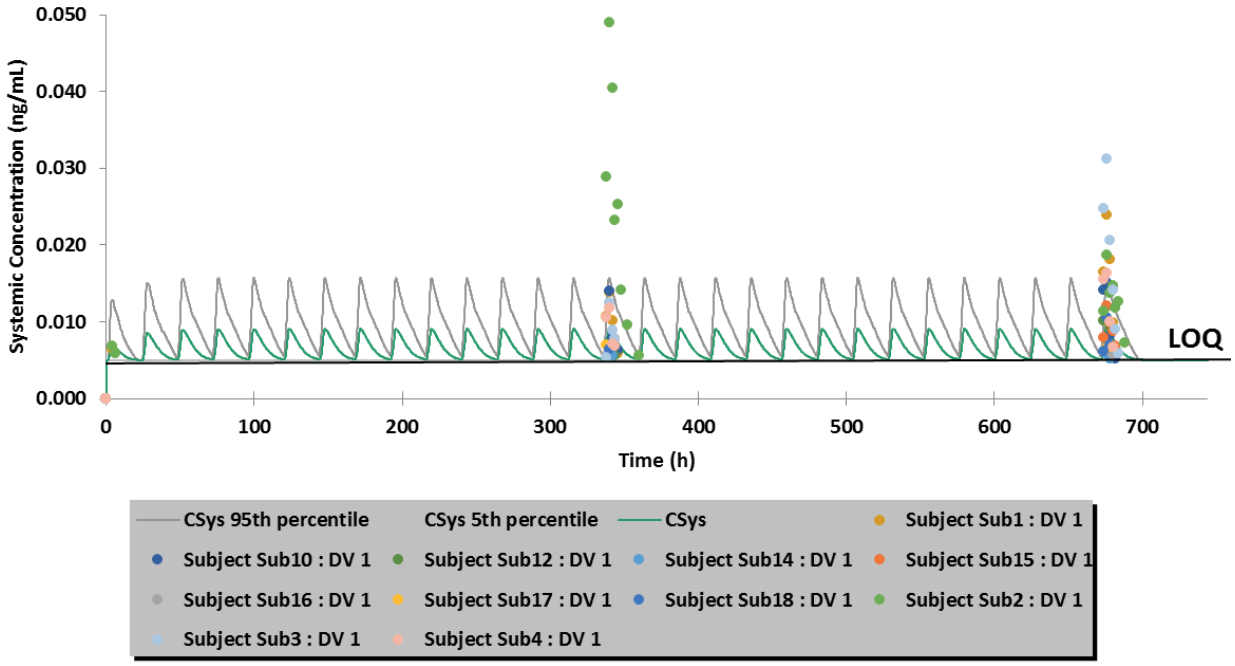
The Applicant's model incorporated the ontogenies of the physiology parameters that may affect trifarotene PK, such as the pH of skin, the thickness of skin layers, and the age-related change in blood flow to skin tissue, the hematocrit and serum albumin levels, and the ontogenies of the three enzymes involved in the metabolism of trifarotene. The changes of these parameters seem reach plateau after 9 years of age except for the blood flow to skin. On the other hand, there are still uncertainties in mechanistic modeling of skin absorption due to the lack of relevant clinical data for model validation. Therefore, due to the lack of experience in predicting skin absorption using a mechanistic model, and in vivo PK data for model validation in 9 to 11 years of age, the model is considered exploratory.

Figure 23. Simulated and Observed Trifarotene Plasma PK Profiles Following Topical Administration of Multiple Doses of Trifarotene Cream B (50 µg/g) in Adults



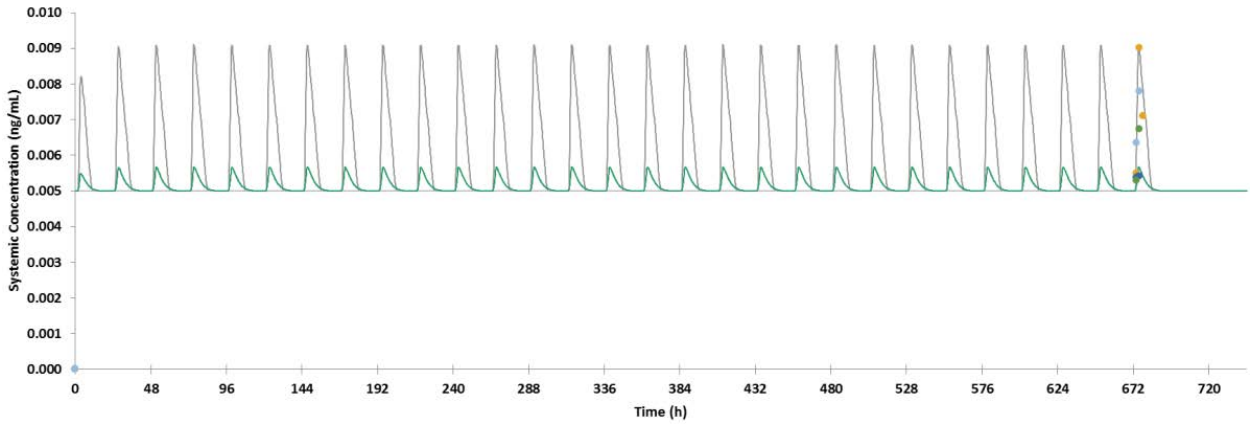
Source: Figure 2A in PBPK report GAL/4/A
Lines: green = mean, dark grey =95th percentile, light grey =5th percentile, dark black = LOQ
Simulated with Cp = LOQ when Cp < LOQ and clinically observed (markers) profiles after once-daily application of 2 g of 50 µg/g of Cream B for 29 days (RD.03.SPR40182)
Abbreviations: LOQ = limit of quantification; PK = pharmacokinetics

Figure 24. Simulated and Observed Trifarotene Plasma PK Profiles Following Topical Administration of Multiple Doses of Trifarotene Cream B (100 µg/g) in Adults



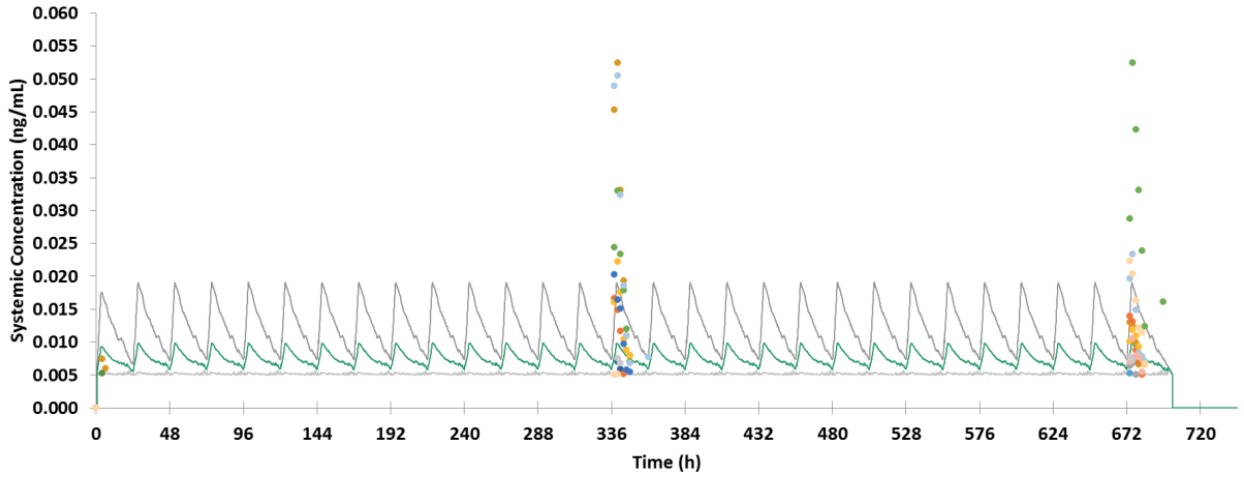
Source: Figure 5A in PBPK report GAL/4/A
Lines: green = mean, dark grey =95th percentile, light grey =5th percentile, dark black = LOQ
Simulated with Cp = LOQ when Cp < LOQ and clinically observed (markers) profiles after once-daily application of 2 g of 100 µg/g of Cream B for 29 days (RD.03.SPR40182)
Abbreviations: LOQ = limit of quantification; PK = pharmacokinetics

Figure 25. Simulated and Observed Trifarotene Plasma PK Profiles Following Topical Administration of Multiple Doses of Trifarotene Cream B (50 µg/g) in Pediatric Subjects 12 to 17 Years of Age



Source: Figure 9 in PBPK report GAL/4/A
Lines: green = mean, dark grey =95th percentile, light grey =5th percentile
Simulated with Cp = LOQ when Cp < LOQ and clinically observed (markers) profiles after once-daily application of 2 g of 50 µg/g of Cream B for 29 days in 12 to 17 years old subjects (RD.06.SPR18237)
Abbreviations: LOQ = limit of quantification; PK = pharmacokinetics

Figure 26. Simulated and Observed Trifarotene Plasma PK Profiles Following Topical Administration of Multiple Doses of Trifarotene Cream B (100 µg/g) in Pediatric Subjects 12 to 17 Years of Age



Source: Figure 6 in PBPK report GAL/4/A
Lines: green = mean, dark grey =95th percentile, light grey =5th percentile
Simulated with Cp = LOQ when Cp < LOQ and clinically observed (markers) profiles after once-daily application of 2 g of 100 µg/g of Cream B for 29 days in 12 to 17 years old subjects (RD.06.SPR18237)
Abbreviations: LOQ = limit of quantification; PK = pharmacokinetics

Table 86. Summary of Predicted and Observed Trifarotene PK Parameters (Geometric Means) Following Topical Administration of 2 g of 100 µg/g Cream B in Adults (Study 40182) and Pediatric Subjects 12 to 17 Years of Age (Study 18237)

Study	Dose	PK Day	N (N Quantifiable)	PK Parameter	Observed	Predicted	Pred./Obs.
40182	2 g of 100 µg/g	15	18 (2)	C_{max} (pg/mL)	7.4	8.4	1.14
				AUC_{0-24} (pg•hr/mL)	99.2	133.4	1.34
40182	2 g of 100 µg/g	29	18 (11)	C_{max} (pg/mL)	8.8	8.4	0.95
				AUC_{0-24} (pg•hr/mL)	109.7	133.4	1.22
18237	2 g of 100 µg/g	15	17 (13)	C_{max} (pg/mL)	12.0	7.9	0.66
				AUC_{0-24} (pg•hr/mL)	129.3	100.2	0.77
18237	2 g of 100 µg/g	29	17 (16)	C_{max} (pg/mL)	9.4	7.9	0.84
				AUC_{0-24} (pg•hr/mL)	112.2	100.2	0.89

Source: Tables 14.2.1.1, and 14.2.1.2 in Clinical Study Report – RD.03.SRE.40182, Table 14.2.1.2 in Clinical Study Report—Clinical Study Report—RD.06.SRE.18237, and reviewer's simulation using the Applicant submitted workspace files
For Study 40182, for descriptive statistics calculations, results below the LOQ (<5 pg/mL) were replaced by the LOQ for C_{max} (i.e., 5 pg/mL) and by the lowest AUC value (i.e., 21.3 and 78.7 pg•hr/mL for the CD5789 100 µg/g group AUC_{0-t} and AUC_{0-24h}, respectively)
For Study 18237, for descriptive statistics calculations results below the LOQ (<5 pg/mL) were replaced by the LOQ for C_{max} (i.e., 5pg/mL) and by the lowest AUC value (15 pg•h/mL and 68 pg•h/mL for AUC_{0-t} and AUC_{0-24h}, respectively)
Simulated PK parameters were calculated without LOQ being applied
Abbreviations: AUC_{0-24} = area under the concentration-time curve from predose through 24 hours postdosing; C_{max} = maximum concentration; LOQ = limit of quantification; PK = pharmacokinetic

Evaluation of the PBPK model to assess the DDI potential of trifarotene as a victim drug

In vitro, trifarotene was mainly metabolized by CYP2C9, CYP3A4, and CYP8. Different in vitro systems provided slightly different f_m values (response to FDA's IR submitted on May 3, 2019).

- In human liver microsomes: $f_m$cyp2c9=71.1%, $f_m$cyp3a4=1.88%, $f_m$cyp2c8 = NA
- In recombinant CYP (rCYP): $f_m$cyp2c9=48.4%, $f_m$cyp3a4=25%, $f_m$cyp2c8=14%
- In human hepatocytes: $f_m$cyp2c9=67.3%, $f_m$cyp3a4=16.7%, $f_m$cyp2c8=16%

There was no human mass balance study or in vivo DDI study to confirm the clearance pathways and the f_m values measured in vitro. As discussed in the 'PBPK model structures and parameters' section, there were inconsistency in biliary clearance estimation between the preclinical animal (rat and dog) systems and the in vitro system. Nevertheless, a less than 1% biliary clearance was assigned to the human trifarotene PBPK model, which maximize the contribution from metabolic enzymes to the overall clearance and therefore is a conservative approach for DDI potential estimation. Due to the uncertainty in f_m assignment, the model is considered as a risk assessment tool for DDI potential estimation.

The Applicant assumed four combinations of f_m values based on the measurements in human liver microsomes, rCYP, and hepatocytes system, and an arbitrary combination with fmcyp2C9 of 90%. For each combination, the Applicant simulated DDI with hypothetical strong inhibitors of CYP2C9 and CYP3A4. Hypothetical-1, and Hypotehtical-2 were hypothetical strong CYP2C9 and CYP3A4 inhibitors obtained by increasing the fluconazole CYP2C9 and CYP3A4 inhibition potential by 10- and 1,000-fold, respectively.

The simulated effects of fluconazole and hypothetical inhibitors on the PK of trifarotene for three different f_m combinations are summarized in Table 87. The $f_m$cyp2C9 measured in rCYP was the lowest and expected to have lower DDI magnitude caused by a CYP2C9 inhibitor, and therefore was not included in the table.

Simulation suggested a "worst-case" scenario where the geometric mean C_{max} and AUC of trifarotene could increase by 2.3 and 2.9-fold, respectively, when trifarotene was coadministered with a hypothetical inhibitor (Hypothetical-2). Nevertheless, the simulated highest geometric mean C_{max} was still lower than the safety margin of trifarotene 50 µg/g Cream based on non-clinical studies, which ranged from 98- to 1,877-fold (Nonclinical Overview and Summary of Clinical Pharmacology Studies).

Table 87. Summary of Simulated Change in Trifarotene C_{max} and AUC_{0-24} at Steady State When 2 g of 100 µg/g Cream B QD Was Coadministered With Fluconazole (400 mg QD) or CYP2C9 Pathway Was Completely Inhibited

Perpetrator	Baseline f_m	System	C_{max}inh (pg/mL)	AUCinh (pg•hr/mL)	C_{max}R	AUCR
Fluconazole 400 mg QD	CYP2C9: 67%, CYP3A4: 17%, CYP2C8: 16%	Hepatocyte	10.0	162.5	1.16	1.19
Hypothetical-1			13.5	238.6	1.58	1.75
Fluconazole 400 mg QD	CYP2C9: 71.1%, CYP3A4: 1.88%, Unassigned: 27%	HLM	9.3	150.4	1.10	1.12
Hypothetical-1			10.8	181.7	1.28	1.36
Hypothetical-1	CYP2C9: 90%, CYP3A4: 1.88%, Unassigned: 8%	Arbitrary	14.9	269.3	1.74	1.98
Hypothetical-2			11.4	389.7	2.34	2.87

Source: Output files submitted on May 3, 2019
C_{max}inh and AUCinh are the C_{max} and AUC when trifarotene was coadministered with fluconazole or the CYP2C9 pathway was completely inhibited, C_{max}R, AUCR PK parameters are expressed in geometric means
Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum concentration; HLM = human liver microsomes, QD = once daily

Conclusions

The Applicant developed a PBPK model to describe trifarotene systemic exposure and for DDI assessment following topical administration of trifarotene cream. The model was able to describe the observed PK in adults and pediatric population 12 to 17 years of age. The PBPK analyses of plasma exposure of trifarotene in pediatric population 9 to 11 years of age was considered exploratory due to the lack of experience in predicting skin absorption using a mechanistic model, and in vivo PK data for model validation.

The model was adequate to be used as a risk assessment tool to estimate the DDI potential for trifarotene as a CYP substrate. The model predicted that the geometric mean C_{max} and AUC of trifarotene could be increased by 2.3 and 2.9-fold, respectively, when trifarotene was coadministered with a hypothetical strong CYP2C9 and CYP3A4 inhibitor. The simulated highest geometric mean C_{max} was still lower than the safety margin of trifarotene 50 µg/g based on non-clinical studies which ranged from 98- to 1,877-fold.

18.5. Additional Clinical Outcome Assessment Analyses

N/A

18.6. Clinical/Biostatistics Appendices

Table 88 presents the baseline disease characteristics of ITTT subjects, i.e., those who had moderate truncal acne at baseline. Table 89 presents the sensitivity analyses for the co-secondary endpoints which were consistent with the primary analysis.

Table 88. Baseline Disease Characteristics of ITTT Subjects Enrolled, Studies 18251 and 18252

	Study 18251		Study 18252	
ITTT Population	**Trifarotene N=600**	**Vehicle N=585**	**Trifarotene N=598**	**Vehicle N=609**
PGA (trunk)				
Moderate (3)	600 (100%)	585 (100%)	598 (100%)	609 (100%)
Inflammatory lesions (trunk)				
Mean (SD)	37 (17)	36 (16)	39 (16)	39 (17)
Median	32	32	35	34
Range	11, 140	4, 115	6, 100	2, 220
Noninflammatory lesions (trunk)				
Mean (SD)	47 (21)	48 (21)	46 (20)	46 (20)
Median	42	43	42	43
Range	16, 125	12, 107	11, 180	8, 260

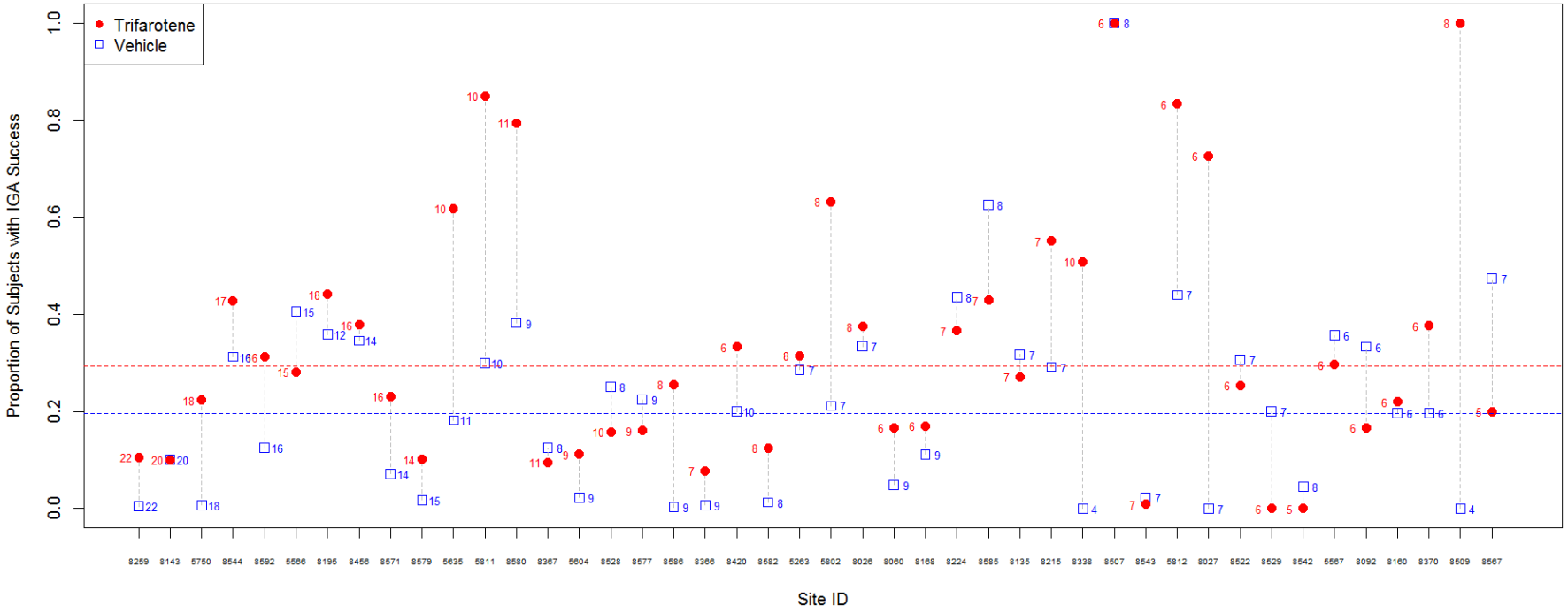
Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: ITTT = intention-to-treat on the trunk; PGA = Physician Global Assessment; SD = standard deviation

Table 89. Sensitivity Analyses of Co-secondary Endpoints (Trunk) at Week 12, Studies 18251 and 18252

	Study 18251			Study 18252		
	Trifarotene N=600	Vehicle N=585	Trt Effect (p-value)	Trifarotene N=598	Vehicle N=609	Trt Effect (p-value)
PGA success (trunk)						
ITT population						
Primary–MI	35.7%	25.0%	10.7% (<0.001)	42.6%	29.9%	12.7% (<0.001)
MI (MNAR)	35.0%	24.9%	10.1% (<0.001)	42.2%	29.9%	12.3% (<0.001)
LOCF	33.5%	23.6%	9.9% (<0.001)	40.1%	24.3%	15.8% (<0.001)
MAF	31.8%	23.3%	8.6% (<0.001)	40.5%	24.5%	16.0% (<0.001)
Per-protocol population	N=495	N=493		N=475	N=542	
MI	35.5%	25.0%	10.6% (<0.001)	44.9%	31.3%	13.6% (<0.001)
Inflammatory lesions, LS mean						
ITT population						
Primary–MI	-21.4	-18.8	-2.5 (<0.001)	-25.5	-19.8	-5.7 (<0.001)
MI (MNAR)	-21.2	-18.8	-2.4 (0.001)	-25.2	-19.7	-5.6 (<0.001)
LOCF	-20.5	-18.0	-2.5 (0.001)	-25.1	-19.3	-5.8 (<0.001)
MAF	-21.1	-18.8	-2.3 (0.001)	-25.1	-19.2	-5.9 (<0.001)
Per-protocol population	N=495	N=493		N=475	N=542	
MI	-22.2	-19.4	-2.8 (<0.001)	-26.3	-20.5	-5.8 (<0.001)
Noninflammatory lesions, LS mean						
Primary–MI (ITT)	-21.9	-17.8	-4.1 (0.001)	-25.9	-20.8	-5.0 (<0.001)
MI (MNAR, ITT)	-21.7	-17.8	-3.9 (0.002)	-25.7	-20.8	-4.9 (<0.001)
LOCF	-21.0	-16.8	-4.2 (0.002)	-25.0	-19.9	-5.1 (<0.001)
MAF	-22.8	-18.7	-4.1 (<0.001)	-25.6	-20.1	-5.5 (<0.001)
Per-protocol population	N=495	N=493		N=475	N=542	
MI	-23.2	-18.8	-4.5 (<0.001)	-26.9	-21.5	-5.4 (<0.001)

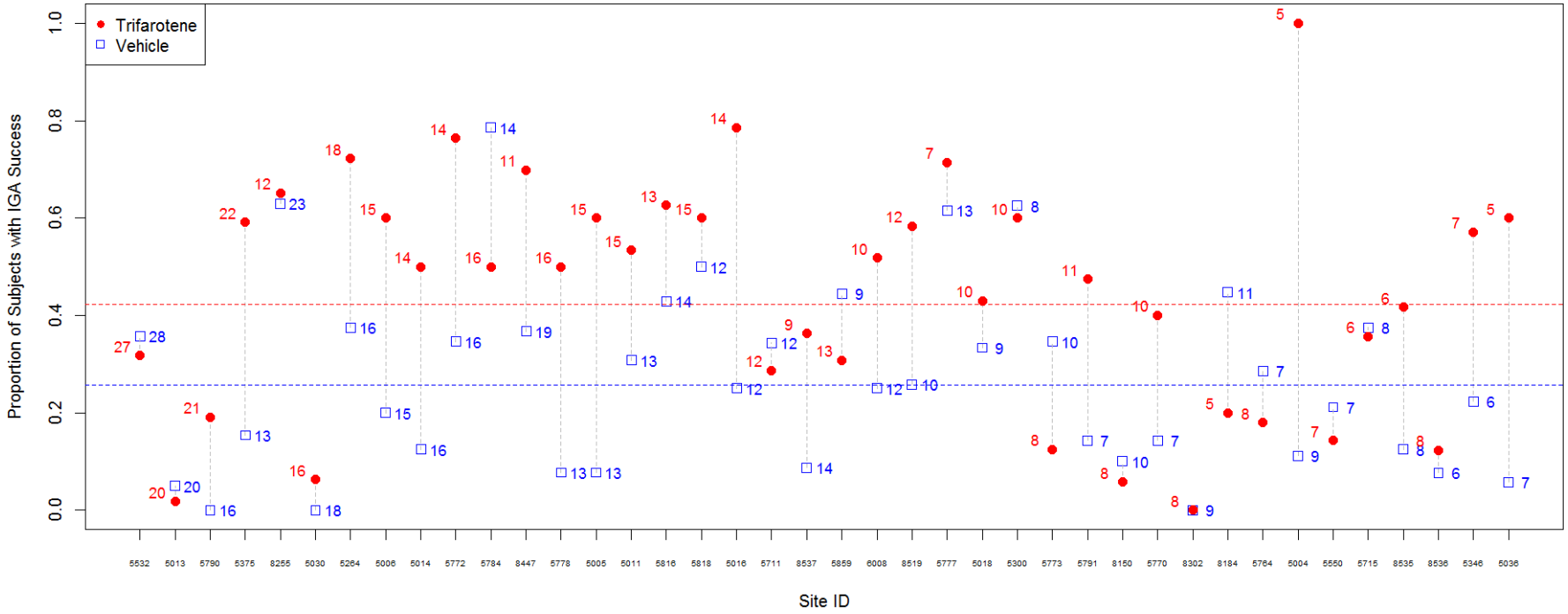
Source: Reviewer's analysis (similar to Applicant's analysis)
LS means presented for lesion counts. Missing data imputed using multiple imputation, and results combined from 50 imputed datasets. P-value for PGA success calculated from Cochran-Mantel-Haenszel test stratified by analysis center. P-value for change in lesion counts calculated from an analysis of covariance model including factors for baseline count, analysis center, and treatment. LOCF results differ from Applicant's, as the clinical study report states that baseline data were not carried forward to impute the missing observations. As the statistical analysis plan does not mention this, reviewer applied LOCF to ITT population.
Abbreviations: LS = least square; ITT = intention-to-treat; IGA = Investigator Global Assessment; MI = multiple imputation; MAF = missing as failure; MNAR = missing not at random; LOCF = last observation carried forward; Trt = treatment

Figure 27. Investigator Global Assessment Efficacy at Week 12 by Center, Study 18251



Source: Reviewer's analysis
Missing data imputed using multiple imputation and results combined from 50 imputed datasets

Figure 28. Investigator Global Assessment Efficacy at Week 12 by Center, Study 18252

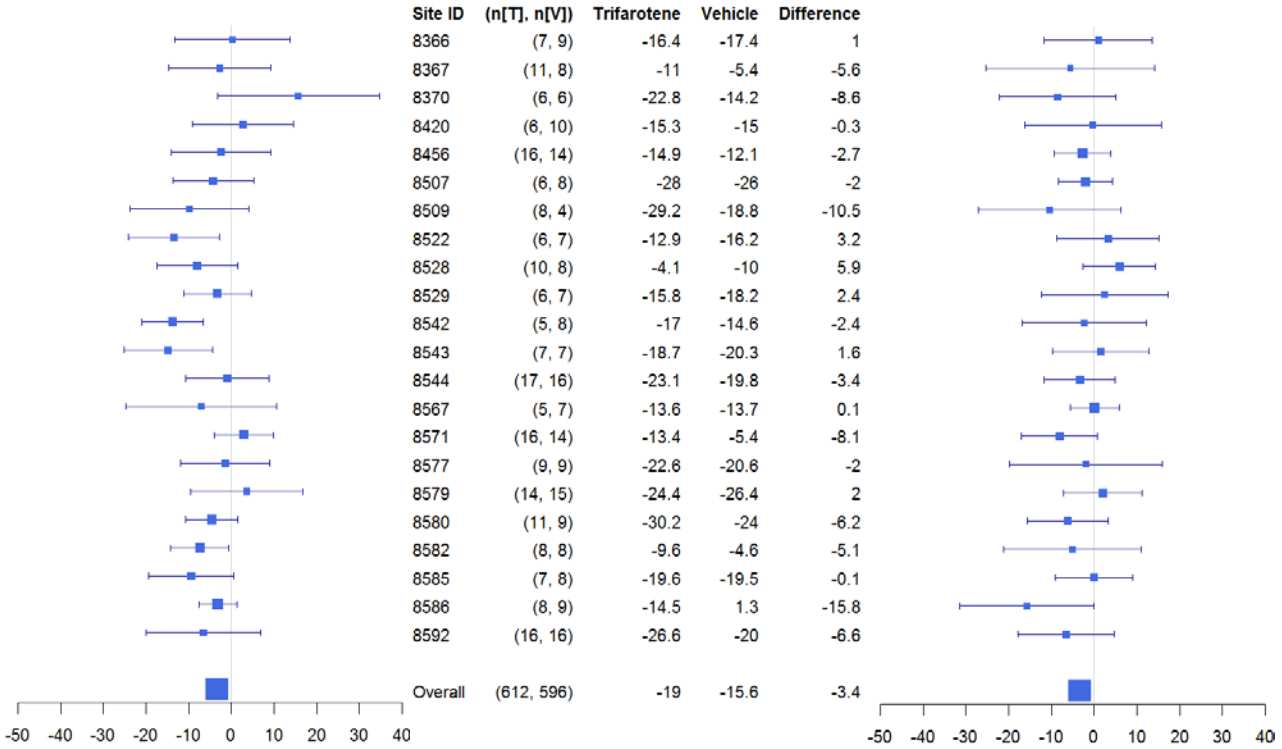


Source: Reviewer's analysis
Missing data imputed using multiple imputation and results combined from 50 imputed datasets

Figure 29. Change From Baseline in Facial Inflammatory Lesion Count at Week 12 by Site, Study 18251

Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
5263	(8, 7)	-22.1	-22.3	0.2
5566	(15, 15)	-20.8	-18.1	-2.7
5567	(6, 6)	-19.5	-35.2	15.7
5604	(9, 9)	-11.7	-14.3	2.7
5635	(10, 11)	-26.3	-23.8	-2.5
5750	(18, 18)	-9.7	-5.4	-4.3
5802	(8, 7)	-21.2	-11.3	-9.9
5811	(10, 10)	-32.2	-18.7	-13.5
5812	(6, 7)	-25.5	-17.5	-8
8026	(8, 7)	-16.8	-13.5	-3.3
8027	(6, 7)	-16.5	-2.7	-13.8
8060	(6, 9)	-30.7	-15.9	-14.8
8092	(6, 6)	-21.5	-20.5	-1
8135	(7, 7)	-21.1	-14	-7.1
8143	(20, 20)	-16.8	-19.6	2.9
8160	(6, 6)	-19.3	-17.8	-1.5
8168	(6, 9)	-15.2	-18.8	3.6
8195	(18, 12)	-27	-22.4	-4.6
8215	(7, 7)	-17.9	-10.4	-7.5
8224	(7, 8)	-24.4	-14.9	-9.5
8259	(22, 22)	-16	-12.8	-3.2
8338	(10, 4)	-17.9	-11.2	-6.6
Overall	(612, 596)	-19	-15.6	-3.4

Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
8366	(7, 9)	-16.4	-17.4	1
8367	(11, 8)	-11	-5.4	-5.6
8370	(6, 6)	-22.8	-14.2	-8.6
8420	(6, 10)	-15.3	-15	-0.3
8456	(16, 14)	-14.9	-12.1	-2.7
8507	(6, 8)	-28	-26	-2
8509	(8, 4)	-29.2	-18.8	-10.5
8522	(6, 7)	-12.9	-16.2	3.2
8528	(10, 8)	-4.1	-10	5.9
8529	(6, 7)	-15.8	-18.2	2.4
8542	(5, 8)	-17	-14.6	-2.4
8543	(7, 7)	-18.7	-20.3	1.6
8544	(17, 16)	-23.1	-19.8	-3.4
8567	(5, 7)	-13.6	-13.7	0.1
8571	(16, 14)	-13.4	-5.4	-8.1
8577	(9, 9)	-22.6	-20.6	-2
8579	(14, 15)	-24.4	-26.4	2
8580	(11, 9)	-30.2	-24	-6.2
8582	(8, 8)	-9.6	-4.6	-5.1
8585	(7, 8)	-19.6	-19.5	-0.1
8586	(8, 9)	-14.5	1.3	-15.8
8592	(16, 16)	-26.6	-20	-6.6
Overall	(612, 596)	-19	-15.6	-3.4

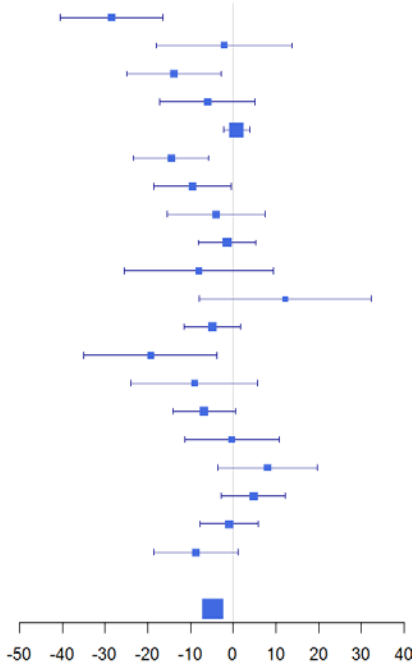


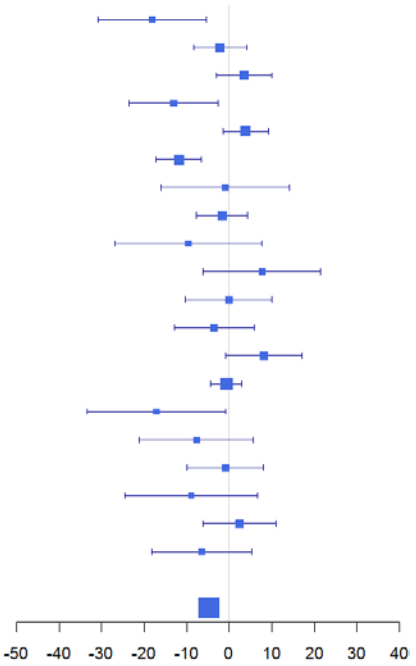
Source: Reviewer's analysis
Missing data imputed using multiple imputation and results combined from 50 imputed datasets

Figure 30. Change From Baseline in Facial Inflammatory Lesion Count at Week 12 by Site, Study 18252

Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
5004	(5, 9)	-34.2	-5.7	-28.5
5005	(15, 13)	-30.2	-28.1	-2.1
5006	(15, 15)	-24.7	-10.9	-13.9
5011	(15, 13)	-24.9	-18.8	-6
5013	(20, 20)	-10.4	-11.2	0.8
5014	(14, 16)	-28.8	-14.2	-14.5
5016	(14, 12)	-24.7	-15.2	-9.5
5018	(10, 9)	-20.9	-16.9	-4.1
5030	(16, 18)	-44.4	-42.9	-1.5
5036	(5, 7)	-32.4	-24.3	-8.1
5264	(18, 16)	-24.8	-37.1	12.2
5300	(10, 8)	-22.4	-17.5	-4.9
5346	(7, 6)	-38.7	-19.3	-19.4
5375	(22, 13)	-35.2	-26.2	-9.1
5532	(27, 28)	-24.9	-18.1	-6.8
5550	(7, 7)	-15.6	-15.2	-0.3
5711	(12, 12)	-15.6	-23.6	8
5715	(6, 8)	-21.7	-26.5	4.8
5764	(8, 7)	-16.7	-15.7	-1
5770	(10, 7)	-30.2	-21.4	-8.8
Overall	(602, 610)	-24.2	-19.4	-4.8

Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
5772	(14, 16)	-40.7	-22.6	-18.1
5773	(8, 10)	-18	-15.8	-2.2
5777	(7, 13)	-29.7	-33.2	3.4
5778	(16, 13)	-28.9	-15.7	-13.2
5784	(16, 14)	-27.4	-31.3	3.8
5790	(21, 16)	-20.9	-9	-11.9
5791	(11, 7)	-15.5	-14.6	-0.9
5816	(13, 14)	-19.3	-17.6	-1.7
5818	(15, 12)	-31.2	-21.5	-9.7
5859	(13, 9)	-20.7	-28.3	7.6
6008	(10, 12)	-24.3	-24.2	-0.1
8150	(8, 10)	-22.5	-18.9	-3.6
8184	(5, 11)	-10.8	-18.9	8.1
8255	(12, 23)	-23.9	-23.2	-0.7
8302	(8, 9)	-14.9	2.2	-17.1
8447	(11, 19)	-28.3	-20.5	-7.8
8519	(12, 10)	-22.6	-21.7	-0.9
8535	(6, 8)	-24	-15	-9
8536	(8, 6)	-25.1	-27.5	2.4
8537	(9, 14)	-17.5	-11.1	-6.5
Overall	(602, 610)	-24.2	-19.4	-4.8

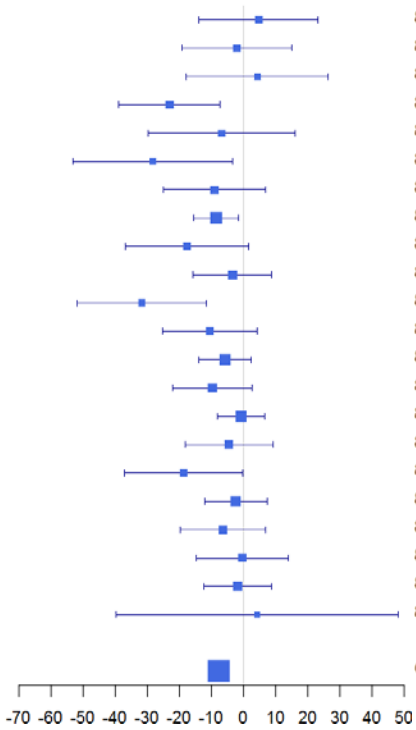




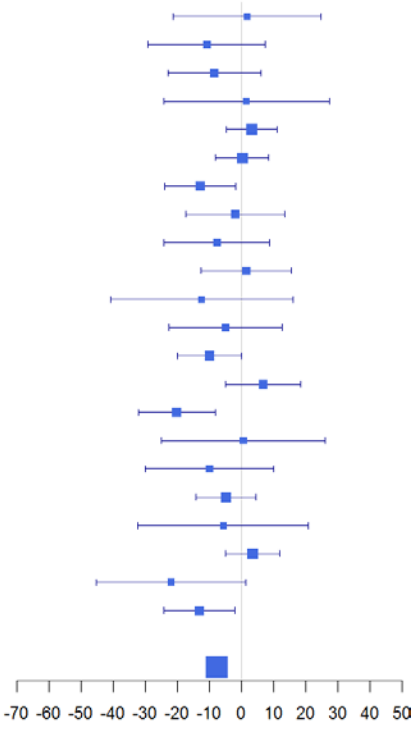
Source: Reviewer's analysis
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets

Figure 31. Change From Baseline in Facial Noninflammatory Lesion Count at Week 12 by Site, Study 18251

Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
5263	(8, 7)	-26.9	-31.6	4.7
5566	(15, 15)	-31.7	-29.6	-2.1
5567	(6, 6)	-48.1	-52.4	4.3
5604	(9, 9)	-35.9	-12.8	-23.1
5635	(10, 11)	-55.3	-48.4	-6.9
5750	(18, 18)	-33.7	-5.4	-28.3
5802	(8, 7)	-17.4	-8.2	-9.2
5811	(10, 10)	-25.9	-17.4	-8.5
5812	(6, 7)	-50.3	-32.7	-17.6
8026	(8, 7)	-18.1	-14.7	-3.5
8027	(6, 7)	-31.9	-0.1	-31.7
8060	(6, 9)	-28.3	-17.8	-10.5
8092	(6, 6)	-24.7	-18.8	-5.8
8135	(7, 7)	-23.7	-14	-9.8
8143	(20, 20)	-15.7	-14.9	-0.8
8160	(6, 6)	-20.5	-16	-4.5
8168	(6, 9)	-23.7	-5	-18.7
8195	(18, 12)	-29.7	-27.2	-2.4
8215	(7, 7)	-26.1	-19.8	-6.4
8224	(7, 8)	-13.5	-13.1	-0.4
8259	(22, 22)	-25.1	-23.2	-1.9
8338	(10, 4)	-48.8	-53	4.2
Overall	(612, 596)	-26	-18.3	-7.7



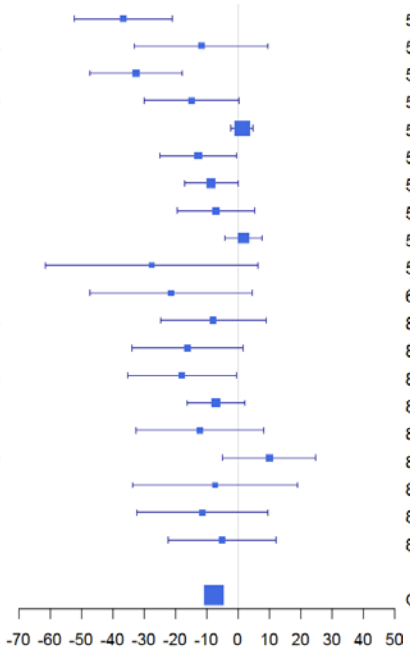
Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
8366	(7, 9)	-20.7	-22.5	1.7
8367	(11, 8)	-16.5	-5.6	-10.9
8370	(6, 6)	-20.4	-11.9	-8.5
8420	(6, 10)	-17.7	-19.2	1.5
8456	(16, 14)	-15.3	-18.4	3.1
8507	(6, 8)	-28.2	-28.4	0.2
8509	(8, 4)	-28.2	-15.2	-13
8522	(6, 7)	-18.5	-16.5	-1.9
8528	(10, 8)	-11.1	-3.4	-7.7
8529	(6, 7)	-24.5	-25.9	1.4
8542	(5, 8)	-33.6	-21.1	-12.5
8543	(7, 7)	-25.8	-20.7	-5.1
8544	(17, 16)	-33.6	-23.6	-10
8567	(5, 7)	-12.4	-19.1	6.7
8571	(16, 14)	-20.1	0.1	-20.2
8577	(9, 9)	-33.4	-33.9	0.5
8579	(14, 15)	-36.9	-26.8	-10
8580	(11, 9)	-27.3	-22.5	-4.9
8582	(8, 8)	-18.9	-13.1	-5.7
8585	(7, 8)	-18.6	-22	3.4
8586	(8, 9)	-13.6	8.4	-22
8592	(16, 16)	-31.8	-18.6	-13.2
Overall	(612, 596)	-26	-18.3	-7.7



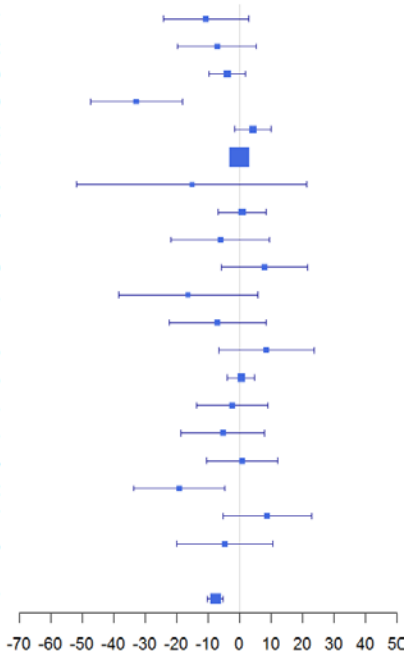
Source: Reviewer's analysis
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets

Figure 32. Change From Baseline in Facial Noninflammatory Lesion Count at Week 12 by Site, Study 18252

Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
5004	(5, 9)	-44.6	-7.9	-36.7
5005	(15, 13)	-40.3	-28.5	-11.8
5006	(15, 15)	-39.9	-7.1	-32.7
5011	(15, 13)	-32.7	-17.8	-14.9
5013	(20, 20)	-7.9	-9.2	1.2
5014	(14, 16)	-37.9	-25.1	-12.7
5016	(14, 12)	-25.3	-16.7	-8.6
5018	(10, 9)	-22.2	-15.1	-7.1
5030	(16, 18)	-31.4	-33.1	1.7
5036	(5, 7)	-52.6	-24.9	-27.7
5264	(18, 16)	-50.4	-28.9	-21.5
5300	(10, 8)	-31.1	-23.1	-8
5346	(7, 6)	-41.7	-25.6	-16.1
5375	(22, 13)	-40	-22.1	-18
5532	(27, 28)	-24	-16.9	-7.1
5550	(7, 7)	-30.4	-18.2	-12.2
5711	(12, 12)	-19.7	-29.6	9.9
5715	(6, 8)	-38.9	-31.5	-7.4
5764	(8, 7)	-36.6	-25.1	-11.4
5770	(10, 7)	-56.5	-51.3	-5.2
Overall	(602, 610)	-30	-22.3	-7.7



Site ID	(n[T], n[V])	Trifarotene	Vehicle	Difference
5772	(14, 16)	-39.3	-28.6	-10.7
5773	(8, 10)	-30.2	-23.1	-7.2
5777	(7, 13)	-28	-24.1	-3.9
5778	(16, 13)	-51.3	-18.5	-32.9
5784	(16, 14)	-27.6	-31.7	4.2
5790	(21, 16)	-2.7	-2.6	-0.2
5791	(11, 7)	-44.8	-29.6	-15.3
5816	(13, 14)	-11.5	-12.3	0.8
5818	(15, 12)	-27.6	-21.5	-6.1
5859	(13, 9)	-17.8	-25.8	7.9
6008	(10, 12)	-51.3	-34.9	-16.4
8150	(8, 10)	-26.3	-19.2	-7.1
8184	(5, 11)	-26	-34.5	8.5
8255	(12, 23)	-26.6	-27.1	0.5
8302	(8, 9)	-22.4	-20	-2.4
8447	(11, 19)	-43	-37.7	-5.4
8519	(12, 10)	-22.5	-23.3	0.8
8535	(6, 8)	-38.7	-19.4	-19.2
8536	(8, 6)	-21.8	-30.5	8.7
8537	(9, 14)	-19.2	-14.4	-4.8
Overall	(602, 610)	-30	-22.3	-7.7



Source: Reviewer's analysis
Missing data imputed using multiple imputation, and results combined from 50 imputed datasets

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/s/

DAWN WILLIAMS
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