NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	214902 SDN1
Priority or Standard	Standard
Submit Date(s)	01-Oct-20
Received Date(s)	01-Oct-20
PDUFA Goal Date	01-Aug-21
Division/Office	Dermatology and Dentistry
Review Completion Date	1-Jun-21
Established/Proper Name	Tretinoin and benzoyl peroxide cream, 0.1%/3%
(Proposed) Trade Name	Twyneo
Pharmacologic Class	Retinoid/oxidizing agent
Code name	
Applicant	Sol-Gel Technologies Ltd
Dosage form	Cream
Applicant proposed Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	11381005 |Acne vulgaris (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4) Adults and adolescents 9 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	11381005 |Acne vulgaris (disorder)|
Recommended Dosing Regimen	Apply a thin layer of TWYNEO to the affected areas once daily on clean and dry skin.

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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

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANCOVA	analysis of covariance
AR	adverse reaction
ASD	acne sign and symptom domain
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BPO/ATRA	benzoyl peroxide and encapsulated tretinoin
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GEE	generalized estimating equations
GRMP	good review management practice
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MCMC	Markov Chain Monte Carlo
MI	multiple imputation

MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRS	numeric rating scale
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PRE-FACE	Patient-Reported Evaluation of Facial Acne
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

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1.1. Product Introduction

The Applicant, Sol-Gel Technologies Ltd., is seeking approval for Twyneo cream, a fixed dose combination topical drug product that contains tretinoin (0.1%) and benzoyl peroxide (3%) for the topical treatment of acne vulgaris, under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The listed drug (LD) is Retin-A® (tretinoin) cream, 0.1% (new drug application (NDA) 017340), which was approved January 26, 1973. The Applicant relied on information provided from the over-the-counter (OTC) monograph and literature for the safety and efficacy of the benzoyl peroxide component of the combination product.

Both active ingredients have been approved individually in various formulations for marketing in the United States for the indication of treatment of acne vulgaris. This application is for a novel combination topical cream containing benzoyl peroxide (oxidizing agent) and tretinoin (retinoid), "encapsulated" in silica-based microcapsules to protect components in the formulation from interacting with one another. The proposed dose and administration is a thin layer applied to the affected areas once daily for the indication of topical treatment of acne vulgaris in patients 9 years of age and older.

The Agency concluded that the proposed proprietary name, Twyneo, was acceptable from both a promotional and safety perspective (Proprietary Name Review by Madhuri R. Patel, PharmD, Division of Medication Error Prevention and Ananlysis dated December 15, 2020).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials (SGT-65-04 and SGT-65-05) which provided evidence of effectiveness of tretinoin/benzoyl peroxide cream, 0.1%/3%, for the topical treatment of acne vulgaris in the target population. Both trials assessed the changes from baseline to Week 12 for the following co-primary efficacy endpoints:

- Proportion of subjects who achieved the primary measure of success at Week 12, defined as a 2-grade improvement in the Investigator Global Assessment (IGA) score from baseline, with the IGA score equating to clear or almost clear
- Absolute change from baseline in inflammatory lesion count
- Absolute change from baseline in non-inflammatory lesion count

Tretinoin/benzoyl peroxide cream, 0.1%/3%, was statistically superior to vehicle on the coprimary efficacy endpoints in both trials. The Applicant has demonstrated that tretinoin/benzoyl peroxide cream, 0.1%/3%, is effective for its intended use and has met the

evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126(a)(b) to support approval.

Upon review of the benefits and risks, the review team recommends approval in subjects 9 years of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Sol-Gel Technologies Ltd submitted a new drug application (NDA) 214902 for Twyneo (tretinoin and benzoyl peroxide) topical cream, 0.1%/3%, under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed indication is the topical treatment of acne vulgaris in patients 9 years of age and older. Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. Twyneo is a new fixed dose combination product that contains tretinoin (0.1%) and benzoyl peroxide (3%). The formulation uses silica (silicon dioxide) to separately "encapsulate" the benzoyl peroxide and tretinoin components to limit interactions with the two ingredients. The Applicant established a clinical bridge to the listed drug (LD) Retin-A cream, 0.1% (NDA 017340, approved January 26, 1973) in order to rely on the Agency's findings of safety for nonclinical toxicology for the LD. The Applicant relied on the literature for safety and efficacy for the benzoyl peroxide component of the combination.

In two, multicenter, randomized, double-blind, vehicle-controlled clinical trials enrolling 858 subjects age 9 years and older with acne vulgaris, benzoyl peroxide and tretinoin, 3%/0.1%, cream was statistically superior to vehicle for the treatment of acne vulgaris. The co-primary efficacy endpoints were the absolute change from baseline in non-inflammatory lesion count, absolute change from baseline in inflammatory lesion count, and the proportion of subjects with treatment success, defined as an IGA score of 0 ("clear") or 1 ("almost clear"), and at least a two-grade improvement (decrease) from baseline at Week 12.

The safety profile for tretinoin/benzoyl peroxide cream, 0.1%/3%, was adequately characterized during the drug development program. There were no deaths or drug-related serious adverse events (SAEs) in the phase 3 trials SGT-65-04 and SGT-65-05. In the phase 3 trials pooled safety analysis set, SAEs occurred in 0.2% of subjects in the tretinoin/benzoyl peroxide cream, 0.1%/3%, group and in 0.4% of subjects in the vehicle group. Adverse reactions (ARs) occurred at a higher frequency in the tretinoin/benzoyl peroxide cream group compared to the vehicle cream group (29% vs. 0.2%). Active assessment of cutaneous safety and tolerability assessment (erythema, scaling, pigmentation, itching, burning and stinging) indicated that the percentage of subjects who reported signs and symptoms at any post-baseline visit was greater in the tretinoin/benzoyl peroxide group cream group than the vehicle cream group. The most common ARs occurred at the application site and included the following ARs in the tretinoin/benzoyl peroxide cream group, compared to the vehicle cream group: pain (10.6% vs. 0.4%), dryness (4.9% vs. 0.4%), exfoliation (4.1% vs. 0), erythema (4% vs. 0), dermatitis (1.3% vs. 0.4%), pruritis (1.3% vs. 0), and irritation (1.1% vs. 0.4%). Although there were no severe hypersensitivity reactions during the development program for Twyneo cream, literature suggests that rare but severe hypersensitivity reactions may occur following the use of benzoyl peroxide-containing products. Therefore, labeling pertaining to hypersensitivity reactions should be included in Section 4 CONTRAINDICATIONS. Review of the data supports including the potential for skin

irritation and increased sun sensitivity in Section 5 WARNINGS AND PRECAUTIONS of labeling.

Tretinoin/benzoyl peroxide cream, 0.1%/3%, provides an additional treatment option for acne vulgaris. The available evidence of safety and efficacy supports the approval of Twyneo (tretinoin/benzoyl peroxide) Cream, 0.1%/3%, 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 that 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 impairment of quality of life.	Acne is a common chronic disorder with a range of disease severities which may impact quality of life.
Current Treatment Options	Many topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antibiotics and antimicrobials (e.g., sarecycline, 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, the severity of disease, and patient preferences.	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of acne vulgaris in adolescents and adults. The response to treatment varies with the lesion type, severity of the disease and compliance with the treatment regimen. Combination topical therapy is recommended for the management of patients with acne to enhance efficacy and treatment compliance. Although both benzoyl peroxide and topical retinoids are mainstays of treatment, combination of the two active ingredients in a single formulation has previously been limited

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		by the fact that storage of the two agents together results in degradation of tretinoin. Additional combination benzoyl peroxide and retinoid formulations may promote compliance by addressing patient preferences.
Benefit	Data from two adequate and well-controlled trials (SGT-65-04 and SGT-65-05) provided substantial evidence of the effectiveness of tretinoin/benzoyl peroxide cream, 0.1%/3%. These trials enrolled 858 subjects age 9 years and older with acne vulgaris. Tretinoin/benzoyl peroxide cream, 0.1%/3%, was statistically superior to vehicle cream in both trials for the co-primary efficacy endpoints of absolute change in noninflammatory lesion count, absolute change in inflammatory lesion count and IGA success (defined as an IGA score of 0 ("clear") or 1 ("almost clear"), and at least a two-grade improvement (decrease) from baseline) at Week 12. Review of the safety data from clinical trials SGT-65-04 and SGT-65-05 did not identify any new safety signals associated with the use of benzoyl peroxide and tretinoin in the treatment of acne. Tretinoin/benzoyl peroxide cream, 0.1%/3%, was generally well tolerated in all evaluated subgroups.	Tretinoin/benozyl peroxide cream, 0.1%/3% provides an effective and safe treatment option for patients with acne vulgaris.
Risk and Risk Management	The primary safety database included 832 subjects enrolled in the two pivotal phase 3 studies who received treatment with tretinoin/benzoyl peroxide cream (n=555) or vehicle cream (n=277) 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 in Twyneo cream group, and more frequent than in vehicle cream group, was localized to the application site and included the following: pain (10.6%), dryness (4.9%),	The risks associated with the use of tretinoin/benzoyl peroxide cream, 0.1%/3%, are primarily at the site of application. Local effects such as pain, dryness, scaling, erythema, itching and irritation may occur but are primarily mild to moderate in severity with a few severe reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exfoliation (4.1%), erythema (4%), dermatitis (1.3%), pruritus (1.3%), and irritation (1.1%). Active assessment of local adverse reactions indicated that most were mild or moderate. Labeling: Prescription labeling adequately addresses the known risks associated with the moieties and identified during product development. No issues require further assessment with a post-marketing requirement or post-marketing commitment (PMR/PMC). A risk evaluation and mitigation strategy (REMS) does not appear necessary and is not recommended.	Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	X	Clinical outcome assessment (COA) data, such as		
		☐	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 was not submitted as part of this application.**			

2 Therapeutic Context

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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).

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:

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

Both lesion types develop from microcomedones (Dawson et al, 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. These variants are typically excluded from clinical trial populations.

The clincal 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 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 of the FDA-approved therapies belong to the following pharmacologic classes: antibiotics and antimicrobials (e.g., erythromycin, clindamycin, benzoyl peroxide, dapsone); hormonal agents (e.g., ethinyl estradiol/norgestimate); and retinoids (e.g., tretinoin, tazarotene, isotretinoin). Other treatment options which are used less frequently include: physical modalities (e.g., chemical peels, intralesional corticosteroids and laser therapy), complementary/alternative therapies (e.g., tea tree oil, herbal supplements and biofeedback) and dietary management (e.g., low glycemic index diets and low calcium diets.) Factors which influence the choice of treatment are lesion type(s), disease severity, personal preference, and individual patient characteristics (e.g., age, sex, skin sensitivity, predisposition for hyperpigmentation/scarring.) Topical products such as benzoyl peroxide, retinoids and antibiotics are indicated for acne of mild to moderate severity, whereas, oral formulations of isotretinoin are indicated for severe, recalcitrant, nodulo-cystic acne. Topical products may contain a single active ingredient or two active ingredients which may address different lesion types. Categories of drug products and examples of topical and systemic therapies currently approved for the treatment of acne vulgaris are presented in Table 1, Table 2 and Table 3, below.

Table 1: Categories of Drug Products for Acne Treatment

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

Source: Modified from Table 1, NDA 211882, Clinical Review by Hamid Tabatabai, MD
*Over-the-counter monograph approved products
[a]: Azithromycin/erythromycin, ampicillin/amoxicillin used off-label
[b]: Spironolactone, flutamide, corticosteroids used off-label

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

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
Antimicrobials				
AMZEEQ (minocycline) foam, 4% (2019)	Topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.	Apply to affected areas once daily	3, 12-week, R, DB, VC trials in 2418 subjects: Active vs. vehicle Trial one: • IGA success: 8% vs. 5% • Mean absolute CFB Inflam: 14 vs. 11 Trial two: • IGA success: 16% vs. 8% • Mean absolute CFB Inflam: 14 vs. 11 Trial three: • IGA 31% vs. 20% • Mean absolute CFB Inflam: 16 vs. 13	AR: headace W&P: flammability, (from oral minocycline): teratogenicity, tooth discoloration, inhibition of bone growth, Clostridium difficile associated diarrhea, hepatotoxicity; azotemia, hyperphosphatemia, and acidosis (w/ renal impairment), lightheadedness, dizziness or vertigo (CNS effects), Intracranial hypertension, autoimmune syndromes, photosensitivity, hypersensitivity reactions (anaphylaxis, SJS, DRESS, EM), tissue hyperpigmentation, potential for drug-resistant bacteria
ACZONE (dapsone) Gel, 7.5%, NDA 207154 (2016)	Topical treatment of acne vulgaris in patients 12 years of age and older (expanded to ≥9 years of age in 9/2019)	Apply a pea-sized amount in a thin layer to the entire face once daily	2, 12-week R, DB, VC trials in 4340 subjects Active vs. vehicle Trial one: • GAAS: 30% vs. 21% • Inflam: 56% vs. 49% • Noninflam: 45% vs. 39% Trial two: • GAAS: 30% vs. 21% • Inflam: 54% vs. 48% • Noninflam: 46% vs. 41%	AR: application site dryness and pruritus W&P: Methemoglobinemia, Hemolysis, Peripheral neuropathy, Skin reactions

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
EVOCLIN (clindamycin phosphate) foam, 1% NDA 050801 (2004)	Acne vulgaris in patients 12 years and older	Apply once daily to affected areas	A 12-week R, DB, VC trial in 513 subjects with mild to moderate acne. Active vs. vehicle: • IGSA: 31% vs. 18% • Inflam:49% vs. 35% • Noninflam: 38% vs. 27%	AR: headache, application site burning, application site pruritus, application site dryness, application site reactions W&P: colitis, irritation
AZELEX (azelaic acid) cream, 20% NDA 020428 (1995)	Topical treatment of mild to moderate inflammatory acne vulgaris	Apply a thin film to affected areas twice daily	Not included	AR: pruritus, burning, stinging, and tingling W&P: hypopigmentation, sensitivity, or irritation
Retinoids				
AKLIEF (trifarotene) cream, 0.005% NDA 211527 (2019)	Topical treatment of acne vulgaris in patients 9 years of age and older	Apply a thin layer to the affected areas of the face and/or trunk once a day, in the evening, on clean and dry skin	2, 12-week R, DB, VC trials in 2,420 subjects Active vs. vehicle: Trial one: • IGA: 29.4% vs. 19.5% • Inflam: 54.4% vs. 44.8% • Noninflam: 49.7% vs. 35.7% Trial two: • IGA: 42.3% vs. 25.7% • Inflam: 66.2% vs. 51.2% • Noninflam: 57.7% vs. 43.9%	AR: application site irritation, application site pruritus, and sunburn W&P: skin irritation, UV light and environmental exposure
ARAZLO (tazarotene) lotion, 0.045% NDA 211882 (2019)	Topical treatment of acne vulgaris in patients 9 years of age and older	Apply a thin layer to affected areas once daily	2, 12-week R, DB, VC trials in 1,624 subjects Active vs. vehicle: Trial one: • EGSS: 25.5% vs. 13% • Noninflam: 51.4% vs. 41.5% • Inflam: 55.5% vs. 45.7% Trial two:	AR: application site pain, dryness, exfoliation, erythema and pruritus W&P: embryofetal toxicity, skin irritation, photosensitivity and risk for sunburn

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
			• EGSS: 29.6% vs. 17.3% • Noninflam: 60% vs. 41.6% • Inflam: 59.5% vs. 49%	
ALTRENO (tretinoin) Lotion, 0.05% NDA 209353 (2018)	Topical treatment of acne vulgaris in patients 9 years of age and older	Apply a thin layer to affected areas once daily	2, 12-week R, DB, VC trials in 1,640 subjects Active vs. vehicle: Trial one: • EGSS: 17% vs. 7% • Noninfl: 48% vs. 27% • Inflam: 51% vs. 40% Trial two: • EGSS 20% vs. 13% • Noninfl: 46% vs. 32% • Inflam: 53% vs. 42%	AR: application site dryness, pain, erythema, irritation, exfoliation W&P: Skin irritation, UV light and environmental exposure, fish allergies
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 <u>Active vs. vehicle</u> <u>Trial one:</u> • IGA: 29% vs. 16% • Inflam: 58% vs. 45% • Noninfl: 55% vs. 33% • Total: 56% vs. 39% Trial two: • 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

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
DIFFERIN (adapalene) Lotion, 0.1% NDA 022502 (2010)	Topical treatment of acne vulgaris in patients 12 years and older	Apply a thin film to the entire face and other affected areas of the skin once daily, after washing gently with a mild soap less cleanser	2, 12-week R, DB, VC trials in 2,141 subjects <u>Active vs. vehicle</u> Trial one: • IGA: 26% vs. 17% • Inflam: 55% vs. 40% • Noninfl: 50% vs. 36% • Total: 52% vs. 37% Trial two: • 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
Androgen Receptor Inhibitors				
WINLEVI (clascoterone) cream, 1% NDA 213433 (2020))	Topical treatment of acne vulgaris in patients 12 years of age and older	Apply a thin layer to affected area twice daily	2, 12-week R, DB, VC trials in 1,421 subjects Active vs. vehicle: Trial one: • IGA: 18.8% vs. 8.7% • Noninflam: 32.6% vs. 21.8% • Inflam: 44.6% vs. 36.3% Trial two: • IGA: 20.9% vs. 6.6% • Noninflam: 29.6% vs. 15.7% • Inflam: 47.1% vs. 29.7%	AR: erythema/reddening, pruritis, and scaling/dryness W&P: local irritation, hypothalamic-pituitary-adrenal (HPA) axis suppression, hyperkalemia

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
Combination Products				
EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% NDA 207917 (2015)	Topical treatment of acne vulgaris	Apply a thin layer 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% vs 19.7%	AR: skin irritation, eczema, atopic dermatitis, and skin burning sensation. W&P: UV light exposure, local cutaneous reactions
ACANYA (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/2.5% NDA 050819 (2008)	Topical treatment of acne vulgaris in patients 12 years or older	Pea-sized amount 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: Trial one: • EGSS: 0/1: 29% vs. 14% • 2 grade: 33% vs. 19% • Inflam: 55% vs. 35% • Noninfl: 45% vs. 29% Trial two: • 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

Source: Modified from Table 2, NDA 211882, Clinical Review by Hamid Tabatabai, MD, MD; Updated by reviewer from "Drugs at FDA" accessed January 7, 2021.

Abbreviations: AR=adverse reaction, CFB=change from baseline, CNS=central nervous system, DB=double blind, DRESS=drug reaction with eosinophilia and systemic symptoms, EM= erythema multiforme, EGSS=Evaluator's Global Severity Score, GAAS=Global Acne Assessment Score, IGA=Investigator Global Assessment, IGSA=Investigator Global Static Assessment, Inflam=inflammatory, Noninflam=noninflammatory, R=randomized, SJS=Stevens-Johnson syndrome, UV=ultraviolet, VC=vehicle controlled, W&P=Warnings and Precautions

Table 3: Examples of Systemic Acne Products

Generic Name	Brand Name	Formulations	Appplicant	Indication
Oral Antibiotics				
Sarecycline	SEYSARA	Tablets: 60 mg, 100 mg, 150 mg	Almirall	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.
Minocycline Hydrochloride	SOLODYN	Extended release tablets: 55mg, 65 mg, 105 mg, 115 mg	Medicis	Only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.
Doxycycline hyclate	DORYX MPC	Delayed release tablets: 60 mg & 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 mg, 75 mg, 100 mg	Aqua Pharms	
Tetracycline Hydrochloride	Tetracycline Hydrochloride	Capsules: 250 mg, 500 mg	Heritage Pharms Inc	
Isotretinoin	ABSORICA	Capsules: 10 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg	Sun Pharmaceutical Industries, Inc.	Severe recalcitrant nodular acne in patients 12 years of age and older
	ABSORICA LD	Capsules: 8 mg, 16 mg, 20 mg, 24 mg, 28 mg and 32 mg	Sun Pharmaceutical Industries, Inc.	
	AMNESTEEM Generic	Capsules: 10 mg, 20 mg, 40 mg	Mylan Pharmaceuticals Inc	
	CLARAVIS Generic	Capsules: 10 mg, 20 mg, 30 mg, 40 mg	Teva Pharmaceuticals USA, Inc	
	MYORISAN Generic	Capsules: 10 mg, 20 mg, 30 mg, 40 mg	Versapharm Incorporated	
	ZENATANE Generic	Capsules: 10 mg, 20 mg, 30 mg, 40 mg	Dr. Reddy's Laboratories Limited	
Hormonal Therapies				
Drospirenone 3 mg/ethinyl estradiol 0.02 mg	YAZ	Tablets	Bayer Healthcare	Moderate acne for women at least 14 years old only if patient desires an oral contraceptive for birth control

Generic Name	Brand Name	Formulations	Appplicant	Indication
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

Source: Modified from Table 3, NDA 211882, Clinical Review by Hamid Tabatabai, MD, MD; Updated by reviewer from "DAILYMED" accessed January 7, 2021.

3 Regulatory Background

[Do not insert text here]

3.1. U.S. Regulatory Actions and Marketing History

The proposed product, Twyneo (tretinoin and benzoyl peroxide) cream, 0.1%/3%, is not approved in the U.S. or any other jurisdiction. Therefore, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 125961 was submitted on January 19, 2016, for the proposed indication of the topical treatment of acne vulgaris. The IND-opening study was a phase 2 study entitled: *A Phase 2 Randomized, Multicenter, Double-Blind, Active and Vehicle Controlled Parallel-group Study Evaluating the Efficacy, Safety, and Tolerability of Products S6G5T-1 and S6G5T-3 for the Treatment of Acne Vulgaris for 12 Weeks*. A Study May Proceed letter was issued on March 2, 2016.

On April 12, 2016, the Agency issued an advice letter, recommending that the Sponsor evaluate the product's potential to induce ocular irritation and phototoxicity.

On May 9, 2018, an End-of-Phase (EOP) 2 meeting was held with the Sponsor to discuss their phase 3 development program including sample size, dosage strength, proposed efficacy endpoints including Patient Reported Outcomes (PROs), requirements for safety monitoring, and PREA requirements.

On June 22, 2018, the Sponsor submitted a request for a Special Protocol Assessment (SPA) for the phase 3 development program. On August 8, 2018, the Agency issued a Special Protocol – Agreement letter. The letter conveyed the Agency's agreements regarding the Sponsor's proposed phase 3 trial designs, co-primary efficacy endpoints, secondary endpoints, and analysis plan.

On July 6, 2018, the Sponsor submitted an initial Pediatric Study Plan (iPSP). On May 1, 2019, the Agency sent an iPSP Written Response letter to the Sponsor following discussion of the iPSP at a PeRC meeting held on April 17, 2019. On May 6, 2020, the Sponsor submitted an Agreed iPSP, which was reviewed by DDD on May 13, 2020 and discussed at a PeRC meeting on May 19, 2020. On May 27, 2020, the Agency sent an Agreed iPSP – Agreement letter to the Sponsor.

On October 5, 2018, the Agency issued an Advice letter in response to the Sponsor's Information Request containing questions related to the PRO instruments. Per recommendations from the Clinical Outcomes Assessment (COA) team, the Advice letter stated that certain items in the Sponsor's PRO (i.e., PRE-FACE Item 5 -- embarrassment) did not appear to be fit-for-purpose for the pediatric population based on the submitted qualitative data. On September 2, 2020, the Agency issued an Advice letter containing Post Meeting Responses to questions related to PRO data that were not addressed during the Pre-NDA meeting held on March 16, 2020.

On June 12, 2018, the Sponsor submitted a Request for a Proprietary Name Review. On November 30, 2018, the Agency reviewed the Sponsor's proposed proprietary name, (b) (4) and on December 6, 2018, the Agency issued a Proprietary Name Request – Unacceptable letter, stating that the proposed proprietary name, (b) (4) may be confused with the product, (b) (4) On April 29, 2019, the sponsor submitted a new complete Request for a Proprietary Name Review. On October 21, 2019, the Agency reviewed the Sponsor's proposed proprietary name, Twyneo, and on October 22, 2019, the Agency issued a Proprietary Name Request – Conditionally Acceptable letter for the proposed proprietary name, Twyneo. A request for proprietary name review for Twyneo was submitted under NDA 214902 on October 6, 2020. The Agency reviewed the proprietary name proposal on December 15, 2020, and on December 17, 2020, the Agency issued a Proprietary Name Request – Conditionally Acceptable letter for Twyneo under NDA 214902.

On August 6, 2019, a Type C meeting was held to obtain CMC guidance on product-related issues, including in-process control tests, release and stability specifications, and QC methods, and characterization plan.

On March 16, 2020, a Pre-NDA meeting was held with the Sponsor, and the following issues were discussed:

- Regulatory:
  - The organization of the eCTD NDA
  - Agreed that the information provided from the OTC monograph and literature for benzoyl peroxide is sufficient to address the non-clinical requirements to support a 505(b)(2) NDA
- Clinical Pharmacology:
  - The design of the maximal use PK study and its adequacy to support a clinical bridge with the listed drug

    - Reiterated that additional long-term systemic safety data may not be necessary if the systemic exposure of tretinoin observed in the maximal use PK study does not exceed that observed for other marketed topical tretinoin products
    - Agreed with Sponsor's proposal to submit a waiver request for QT/QTc assessment
- Clinical/Biostatistics
    - Agreed that the clinical study reports and datasets from the IND studies are adequate to support NDA filing
    - The safety data gleaned from the four dermal safety studies; the Agency stated that the adequacy of these data would be a review issue
    - Agreed that the propose Study Data Standardization Plan (SDSP) is acceptable
    - Agreed with the Sponsor's plan for pooling data from the two phase 3 clinical trials

On March 18, 2020, a Pre-NDA meeting was held with the Sponsor to discuss CMC content, and the following issue were discussed:

- CMC:
    - Request for categorical exclusion according to 21 CFR 25.31(a)
    - Adequacy of the QC method
    - Adequacy of the characterization data
    - Hold-time studies
    - Adequacy of product specification
    - Adequacy of release and stability specification
    - Recommendations regarding microbial limit test (MLT) and testing for specific organisms, including BCC
    - Exemption from 21 CFR 820 requirements
    - Process validation

On October 1 2020, the Applicant submitted NDA 214902 for tretinoin/benzoyl peroxide cream, 0.1%/3% (Twyneo), under the 505(b)(2) regulatory pathway, for the topical treatment of acne vulgaris in patients nine years of age and older. The Applicant referenced Retin-A® (tretinoin) cream, 0.1% (NDA 017340) as the LD and relied on information provided from the over-the-counter (OTC) monograph and literature for the safety and efficacy of the benzoyl peroxide component of the combination.

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

[Do not insert text here]

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The Division requested that the Office of Scientific Invesigations conduct clinical inspections of 4 domestic sites. The sites were were selected based on enrollment numbers and the noted difference in IGA scores and absolute change in lesions.

Table 4: Planned Clinical Site Inspections

Investigator Name, Address	**Site Number**	**Protocol ID**	**Number of Subjects**	**Study Title**
Clark-Loeser, Lesley 8399 West Oakland Park Blvd. Sunrise, FL 33351	505	SGT-65-05	21	A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris
Draelos, Zoe 2444 North Main Street High Point, NC 27262	408	SGT-65-04	15	A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris
Katz, Bruce 60 E 56th Street New York, NY 10022	412	SGT-65-04	15	A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris
Reed, Ann 1001 NW 13th Street Boca Raton, FL 33486	521	SGT-65-05	21	A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment

of Acne Vulgaris

Source: Reviewer's Table with data from CDER's Clinical Investigator Site Selection Tool Generated October 30, 2020 and OSI Review by Christian Shounda, MD. Key to Compliance Classifications -Abbreviations: NAI = No Action Indicated, VAI = Voluntary Action Indicated, OAI = Official Action Indicated

Timely conduct of clinical site inspections proved difficult due to limitations imposed by the Covid 19 pandemic. In order to allow timeline completion for the anticipated PDUFA goal date, the two clinical sites recommended for inspection with smaller enrollment sizes (sites 412 and 408) were not inspected during the review cycle. Selection of trial sites was influenced primarily on enrollment size and not for data integrity concerns or other for-cause issues related to trial conduct. Additionally, neither of the two active ingredients were novel and had previously been well characterized for the treatment of acne.

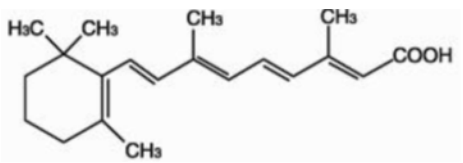
Clinical investigator inspections for Drs. Lesley Clark-Loeser (site 505) and Ann Reed (site 521) were conducted via a Remote Regulatory Assessment (RRA). Based on the results of these RRAs, Protocol SGT-65-05 appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication. As sites were selected primarily related to study site enrollment size, and inspections of the two larger enrollment sites did not identify any issues of concern, and statistical analysis by center also did not present any concerns, clinical site inspections of two sites was deemed adequate for this application.

4.2. Product Quality

The drug product, TWYNEO® cream is fixed-dose combination containing two active ingredients, tretinoin and benzoyl peroxide.

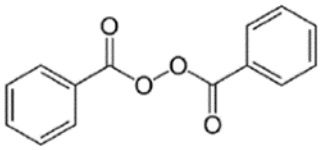
1. Drug substance
   A. Tretinoin: The active ingredient, tretinoin is a compendial drug substance and it has been classified as a retinoid. It was first approved in 1973 as the active ingredient of RETIN-A topical cream for the treatment of acne vulgaris. Since its original approval multiple brand name and generic drug products.

      It is a yellow to yellow-orange crystalline powder with melting range of 182ºC with decomposition and it is very sparingly soluble in water. Tretinoin has the chemical name, all trans (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonate traenoic acid, a chemical formula of $C_{20}H_{28}O_2$, a molecular weight of 300.44 g/mol, and the chemical structure provided below:



Tretinoin, USP for this application is manufactured in accordance to the current good manufacturing practices (cGMP) requirements by (b) (4) (b) (4) It is tested, released, and accepted according to the USP compliant specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of (b) (4) months. The details of the manufacturing process, packaging, release testing, and stability for tretinoin produced by (b) (4) is provided in Drug Master File (DMF) (b) (4) which has been reviewed and found to be adequate to support the approval of this application.

B. Benzoyl Peroxide: The active ingredient, benzoyl peroxide, is a compendial drug substance and has been classified as an oxidizing agent. Benzoyl peroxide has been marketed for more than 50 years as the active ingredient of topical over-the-counter products for the treatment of acne vulgaris. It has also been used as the active ingredient of multiple approved combination drug products for topical use. Benzoyl peroxide is a white granular powder with a melting range of 103°C to 106°C and no observed polymorphic forms. It is sparingly soluble in water or alcohol and soluble in benzene, chloroform, and ether. The chemical name for benzoyl peroxide is benzoyl benzenecarboperoxoate. It has a molecular formula of $C_{14}H_{10}O_4$, a molecular weight of 242.23g/mol, and the chemical structure provided below:



Benzoyl peroxide, USP for this application is manufactured in accordance to the cGMP requirements by (b) (4) It is tested, released, and accepted according to the USP compliant specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its currently assigned retest date of (b) (4) months. The detailed manufacturing process for benzoyl peroxide produced by (b) (4) have been provided in DMF (b) (4) which has been reviewed and found to be adequate to support this new drug application.

2. Drug Product

The drug product, TWYNEO® (tretinoin/benzoyl peroxide) cream, 0.1%/3% is a non-sterile yellow cream packaged as 50g in a 50-mL (commercial drug product) and as 6g in a 30-mL (physician sample) high-density polyethylene (HDPE) bottles with (b) (4) pumps and transparent caps. This drug product is intended for topical administration as a thin layer to dry and clean affected skin areas for the treatment of acne vulgaris in patients 9 years of age and older.

Each gram of TWYNEO® cream contains 1 mg of tretinoin and 30 mg of benzoyl peroxide

as the active ingredients and polyquaternium-7, silicon dioxide, cetrimonium chloride, (S)-lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, white wax, tetraethyl ortho silicate, squalane, butylated hydroxytoluene, glycerin, macrogol stearate, cetyl alcohol, mono and di-glycerides, edetate disodium, cyclomethicone, imidurea, carbomer homopolymer type C and purified water as inactive ingredients.

The active ingredients, tretinoin and benzoyl peroxide in this drug product are first separately encapsulated into microcapsules consisting of silica (b) (4)

The encapsulation enables (b) (4) inclusion of the two active ingredients in the cream product. It provides for the slow migration of the active ingredients through the microcapsules' shells leading to continuous release of this active ingredient over time and delivery to the affected skin area.

TWYNEO® cream is manufactured (b) (4) for Sol-Gel in accordance to the cGMP requirements. It is tested and released according to a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. Sufficient stability data in support of expiration dating period of the drug product has been submitted.

This drug product should be stored at 2ºC – 8ºC (36ºF – 46ºF) prior to dispensing to patients and at 20ºC – 25ºC (68ºF – 77ºF) for up to 12 weeks after dispensing. The unused drug product should be discarded 30 days after opening. The physician sample should be discarded 5 days after opening.

4.3. Clinical Microbiology

[Insert text here.]

4.4. Devices and Companion Diagnostic Issues

[Insert text here]

5 Nonclinical Pharmacology/Toxicology

[Do not insert text here]

5.1. Executive Summary

The Applicant submitted a 505(b)(2) application for the fixed-dose combination drug product, benzoyl peroxide (BPO)/ tretinoin (ATRA) cream 3%/0.1%, for the treatment of acne vulgaris in patients 9 years of age and older. BPO/ATRA cream was originally licensed by Medicis Pharmaceutical Corporation (Medicis). The Applicant, Sol-Gel Technologies, now holds exclusive ownership of the nonclinical studies for which Medicis is listed as the Sponsor.

For the nonclinical safety assessment of the BPO component of the combination product, the Applicant is relying on literature data available for benzoyl peroxide and the OTC monograph for benzoyl peroxide (2.5 – 10%) for the treatment of acne. A 13-week repeat-dose dermal toxicity study in minipigs with BPO cream (5 and 10%) was also included in the NDA submission.

For the nonclinical safety assessment of the ATRA component of the combination product, the Applicant is relying on the Agency's previous findings of safety for the listed drug (LD), Retin-A® cream, 0.1% (NDA 017340, approved January 26, 1973). The Applicant established a clinical bridge to the LD in order to rely on the Agency's findings of safety for nonclinical toxicology for the LD.

The following pivotal toxicology studies have been conducted with the combination product BPO/ATRA cream, 6%/0.1% or 3%/0.1% in support of the NDA.

- 14-day dermal tolerability study in minipigs (BPO/ATRA cream, 6%/0.1%)
- 13-week repeat-dose dermal toxicity study in minipigs (BPO/ATRA cream, 6%/0.1%)
- Guinea pig sensitization study (BPO/ATRA cream, 6%/0.1%)
- Rabbit phototoxicity study (BPO/ATRA cream, 3%/0.1%)
- Bovine corneal opacity and permeability study (BPO/ATRA cream, 3%/0.1% and 3%/0.05%)

The results from these nonclinical data provided in the submission did not reveal any new or unique toxicities that had not been previously observed with either active ingredient alone.

In addition, in the response to the initial pediatric study plan provided 01 May 2019, the FDA agreed that a juvenile toxicity study was not needed for the drug product.

There are no safety issues associated with the use of the following noncompendial excipients in the proposed topical drug product.

- (b) (4) The

proposed level of silicon dioxide is qualified based on the Inactive Ingredient Database (IID) and the 13-week dermal toxicity study in minipigs with BPO/ATRA cream.

- Cetyl trimethyl ammonium chloride (CTAC), [(b) (4)%] and [(b) (4)] [(b) (4)] are two noncompendial excipients [(b) (4)] [(b) (4)] They were considered to be qualified by the pivotal toxicology studies in animals at higher concentrations of CTAC ([(b) (4)%) and [(b) (4)] Therefore the specifications for CTAC and [(b) (4)] provided in the NDA submission are acceptable from a Pharmacology/Toxicology perspective.

There are no safety issues associated with the impurities identified in the drug product. The levels of two impurities identified, [(b) (4)] [(b) (4)] along with individual unknown impurities are consistent with ICH Q3B(R2).

In summary, the nonclinical assessment do not identify any safety concerns for the applicant's BPO/ATRA cream formulation. This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

Retin-A® cream, 0.1%, NDA 017340 approved on January 26, 1973.

5.3. Pharmacology

Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects. However, the mechanism of action [(b) (4)] is unknown.

Tretinoin is a metabolite of vitamin A that binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus. Tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation. It has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both.

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

The above information supports the statements contained in Section 12.1 of labeling.

5.4. ADME/PK

The toxicokinectics of BPO/ATRA cream, 6%/0.1%, was evaluated in the 13-week dermal toxicity study in minipigs. Benzoyl peroxide is converted in the skin to benzoic acid and

hydrogen peroxide. Therefore, BPO cannot be directly measured due to its rapid conversion to benzoic acid. Plasma concentrations of benzoic acid, 13-cis retinoic acid, 4-keto 13-cis retinoic acid, all-trans retinoic acid and all-trans-4-keto retinoic acid from samples collected at multiple timepoints on Days 1 and 90 were determined. Analysis of the data indicated that repeated daily applications of BPO/ATRA cream, 6%/0.1%, to minipig skin for 13 weeks did not demonstrate measurable systemic exposure to benzoic acid above its endogenous levels, or tretinoin (all-trans retinoic acid) and its metabolites above the LLOQ (lower limit of quantitation).

5.5. Toxicology

5.5.1. General Toxicology

The pivotal general toxicology studies provided in the NDA submission include 3 formulations:

(1) BPO/ATRA cream, 3%/0.1% (clinical formulation)
(2) BPO/ATRA cream, 6%/1% (Formulation (b) (4))
(3) BPO cream, 5% and 10%

The "E" in E-EPO or E-ATRA in some of the nonclinical study reports stands for encapsulated.

Study title/number: Formulation (b) (4) and Formulation (b) (4): 14-Day Cumulative Skin Irritation Study in Minipigs with a 14-Day Recovery / 1256-007

- Mild erythema and edema were observed with the treatment of both Formulations (b) (4) (b) (4) at the end of the 14-day dosing period. They were resolved during the recovery period.
- Formulation (b) (4) were less irritating than the comparator products (DIFFERIN® Gel, 0.3%; TAZORAC® (tazarotene) cream, 0.1%; EPIDUO (adapalene /benzoyl peroxide, 0.1%/2.5% Gel; tretinoin cream, 0.1%), with the exception of RETIN-A MICRO, 0.1% (which exhibited no irritation).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Formulation (b) (4) (6% E-BPO/0.1% E-ATRA), Formulation (b) (4) (6% E-BPO/0.1% E-ATRA) Epiduo (Adapalene 0.1% + 2.5% E-BPO), 0.1% Tazarotene Differin 0.3% gel (Adapalene) Tretinoin cream 0.1% RETIN-A MICRO Gel, 0.1% Once daily

Route of administration:	Topical
Formulation/Vehicle:	No vehicle group
Species/Strain:	Minipig/Gottingen
Number/Sex/Group:	5
Age:	3.5-5.5 months of age
Satellite groups/ unique design:	Topically applied test article at a fixed dose of 1 g/site to one of seven 2 x 2 inch sites on the shaved backs of each minipig
Deviation from study protocol affecting interpretation of results:	No deviations affected the integrity of the study.

Observations and Results: changes from control

Parameters	Major findings
Mortality	No treatment related effects.
Clinical Signs	No treatment related effects for clinical signs. Very slight to well-defined erythema was observed in all treatment groups. The 6% E-BPO and the 6% E-BPO/ 0.1% E-ATRA combination product appeared to be less irritating than the 0.1% E-ATRA formulation.
Body Weights	No treatment related effects.

Study title/ number: 6% E-BPO + 0.1% E-ATRA Combination Product, 0.1% E-ATRA, and 6% E-BPO: A 13-Week Dermal Toxicity Study in Gottingen Minipigs Followed by a 4-Week Recovery Period / 1256-012

- Erythema were observed at the site of application with all three test articles, 6% E-BPO + 0.1% E-ATRA combination product, 0.1% E-ATRA, or 6% E-BPO.
- Microscopic findings were limited to the sites of administration and included minimal to mild epidermal surface exudate (ATRA cream, 0.1% only), hyperkeratosis, epidermal hyperplasia, and sub-acute/chronic inflammation.
- No systemic exposure to benzoic acid, 13-cis retinoic acid, 4-keto 13-cis retinoic acid, all-trans retinoic acid and all-trans-4-keto retinoic acid was noted.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Untreated control, placebo control (cream vehicle), 6% E-BPO + 1% E-ATRA (combination product, also known as Formulation (b) (4) or E-BPO/E-ATRA), 0.1% E-ATRA, and 6% E-BPO, twice daily (two doses with 8 hours apart)
Route of administration:	Topical
Formulation/Vehicle:	Clinical vehicle

Species/Strain:	Minipig/Gottingen
Number/Sex/Group:	6
Age:	3.5-5.5 months of age
Satellite groups/ unique design:	Topically applied vehicle or test article to 10% body surface area (BSA) at a rate of 8µL/cm^2 (0.25 mL/kg of formulation per application)
Deviation from study protocol affecting interpretation of results:	No deviations affected the integrity of the study.

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	No treatment related effects.
Clinical Signs	No treatment related effects for clinical signs. Very slight to well-defined erythema was observed for in all treatment groups. The 6% E-BPO and the 6% E-BPO/ 0.1% E-ATRA combination product appeared to be less irritating than the 0.1% E-ATRA formulation.
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.
Gross Pathology	No treatment related effects.
Organ Weights	No treatment related effects.
Histopathology Adequate battery: Yes	Test article-related microscopic findings at the terminal necropsy were limited to the treated skin sites and included epidermal surface exudate (E-ATRA cream, 0.1% only), hyperkeratosis, epidermal hyperplasia, and subacute/chronic inflammation.

General toxicology; additional studies
Study title/ number: Encapsulated Benzoyl Peroxide Gel: A 13-Week Dermal Toxicity Study in Gottingen Minipigs / 1611-002

This study was reviewed by Dr. Barbara Hill under NDA (b) (4). The summary provided below are the key findings of the study.

- The nomenclature for benzoyl peroxide gel was subsequently changed to benzoyl peroxide cream.
- No systemic exposure to benzoic acid was noted after 13-weeks of daily topical application of BPO cream, 5% or 10% to minipig skin.
- BPO cream, 5% or 10% only caused minimal hyperkeratosis at the treatment site.

The no-observed-adverse-effect-level (NOAEL) was 10% BPO cream, the highest concentration evaluated in this study.

5.5.2. Genetic Toxicology

BPO:
A review of literature information available for the genetic toxicity of BPO indicates that a variety of genetic toxicity studies have been conducted with BPO. The results of these studies have sometimes been positive and sometimes been negative.

Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests (i.e., Ames assay) by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

ATRA:
The mutagenic potential of tretinoin was evaluated in in an in vitro bacterial reversion test (i.e., Ames assay) and an in vivo mouse micronucleus assay. Both tests were negative.

The above genetic toxicity information supports nonclinical statements contained in Section 13.1 of labeling.

5.5.3. Carcinogenicity

There are no carcinogenicity studies conducted with BPO/ATRA cream.

BPO:
For BPO safety information, the Applicant references the OTC monograph for BPO (2.5-10%) for the treatment of acne (21 CFR 333.310; 56 FR 37622, August 7, 1991; 21 CFR 201.66). The Consumer Health Products Association conducted topical carcinogenicity studies in rodents with an aqueous carbopol gel formulation of BPO. The results from these topical carcinogenicity studies in rodents is contained in the final rule for the OTC monograph for BPO posted on March 4, 2010 with an effective date of March 4, 2011 (75 FR 9767). The Applicant references these topical carcinogenicity studies in Section 13.1 of the submitted labeling for BPO/ATRA cream.

No significant increase in tumor formation was observed in rats treated topically with a 15 to 25% BPO carbopol gel for two years. Similar results were obtained in mice topically treated with 25% BPO gel for 56 weeks followed by intermittent treatment with 15% BPO gel for rest of the 2 years study period and in mice topically treated with 5% BPO gel for two years.

The carcinogenicity of BPO has been investigated in a number of literature studies. However, most of the studies have not been of two years duration and have not used daily application. In most studies, BPO applied alone did not produce skin tumors. In a study conducted by the National Toxicology Program, BPO was shown to promote tumor formation in the skin initiated by dimethylbenzathracene or methylnitro-nitrosoguanidine in B6C3F$_1$, Swiss CD-1 and SENCAR

mice (NTP TR 441, 1996). In this study the initiator was administered once and BPO was administered weekly for 52 weeks. The results from these literature studies clearly show that BPO is a tumor promoter and tumor progression agent in the skin in several animal models.

ATRA

The following information concerning dermal carcinogenic potential associated with tretinoin is provided in the listed drug, Retin-A cream, labeling.

In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are two and four times the maximum human systemic dose, when adjusted for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.1 times the maximum human systemic dose, adjusted for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose is defined as 1 gram of 0.1% RETIN-A applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

There is a description of a photocarcinogenicity study conducted with topical administration of tretinoin in hairless mice in the listed drug label. However, we are no longer recommending conduct of photocarcinogenicity studies because these studies are not predictive of human risk (refer to the ICH M3(R2) guidance, *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*). Therefore, this photocarcinogenicity study description will not be included in the BPO/ATRA cream labeling.

The above carcinogenicity information supports nonclinical statements contained in Section 13.1 of labeling.

5.5.4. Reproductive and Developmental Toxicology

There are no reproductive and developmental toxicology studies conducted with BPO/ATRA cream.

BPO:
The Applicant submitted literature data that describes reproductive and developmental toxicology studies conducted with BPO that were basically negative. However, the validity of these studies is questionable due to the rapid breakdown of BPO to benzoic acid. It is not clear if the fetus would ever be exposed to BPO in a reproductive and developmental toxicology

study due to the short half-life of BPO. Therefore, reproductive and developmental toxicology information for BPO is not included in the labeling.

ATRA:
The following information concerning reproductive and developmental toxicity associated with tretinoin after topical and oral administration is provided in the listed drug, Retin-A cream, labeling.

Pregnancy: Teratogenic effects. Pregnancy Category C. Oral tretinoin has been shown to be teratogenic in rats, mice, hamsters, and subhuman primates. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (8 times the maximum human systemic dose adjusted for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which metabolically is closer to humans for tretinoin than the other species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (83 times the maximum human systemic does adjusted for total body surface area), although increased skeletal variations were observed at all doses. A dose-related increase in embryolethality and abortion was reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose adjusted for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied.

There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (3.3 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animals studies have shown that dermally applied tretinoin may be fetoxic, but not overly teratogenic in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (8 times the maximum human systemic does adjusted for total body surface area in both species).

Nonteratogenic effects:
Topical tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (8 times the maximum human systemic dose adjusted for total body surface area). Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death in rats when administered 2.5 mg/kg/day (20 times the maximum human systemic dose adjusted for total body surface area).

The above reproductive and developmental toxicity information supports nonclinical statements contained in Section 8.1 and 13.1 of labeling.

5.5.5. Other Toxicology Studies

In vivo phototoxicity:

Study title / number: Phototoxicity Test in Rabbits with S6G5T-3 / 0432LS89.002
Aliquots (0.1 ml) of S6G5T-3 (E-BPO/E-ATRA 3%/0.1% cream), vehicle control (S6G5T-8), positive control (1% 8-methoxypsoralen in ethanol) or negative control (100% ethanol) were topically administered to rabbits on duplicate symmetrical intact skin sites (to the left and right of the midline) on six rabbits (3/sex). One additional site on each side of all rabbits remained untreated. One set of treated sites was exposed to UV light (~281-600 nm) for 60 minutes (approximately 16 J/cm^2/hr) and the other set of treated sites were non-irradiated. Based upon the results of this study, erythema and edema were not observed at any sites receiving irradiation with test article (S6G5T-3) or vehicle (S6G5T-8) applied. Therefore E-BPO/E-ATRA 3%/0.1% cream did not display evidence of phototoxicity potential under the conditions of this study.

Bovine Corneal Opacity and Permeability Test:

Study title / number: OECD Bovine Corneal Opacity and Permeability Test (BCOP)/ MB-1524099.09

Three bovine corneas per group were dosed with 0.75 ml of S6G5T-9 (P3149-00115, a combination of 3% E-BPO and 0.1% E-ATRA), S6G5T-10 (P3156-00315, a combination of 3% E-BPO and 0.05% E-ATRA), Minimal Essential Media (MEM) (negative control), or 100% Ethanol (positive control). Following a 10-minute exposure in the 32^{0}C incubator for each group of dosed corneas, opacity measurements and sodium fluorescein permeability were determined by a spectrophotometer as the optical density at 490 nm. Based on an In Vitro Irritation Score of less than 3, no category can be assigned for the test articles, as defined in OECD Guideline #437. In conclusion, E-BPO/E-ATRA cream, 3%/0.1% and E-BPO/E-ATRA cream, 3%/0.05% were considered to be non-irritants.

Skin Sensitization Study:

Study title / number: Skin Sensitization (Buehler Method) Study of Formulation (b) (4) and Formulation (b) (4) in Guinea Pigs / 1256-008
The two test articles [Formulation (b) (4) and Formulation (b) (4), 6% (E-BPO)/0.1% E-ATRA], the positive control (α-hexylcinnamaldehyde HCA), and negative control (untreated) were administered to the guinea pigs once per week for 3 weeks during the Induction Phase, and once during the Challenge Phase two weeks later. The guinea pigs were divided into 5/sex for control groups and 10/sex for the test article groups.

On Days 1, 8, and 15, the animals received one 0.4 mL (positive control) or 0.4 g (both test groups) application of the appropriate treatment (100% HCA, Formulation (b) (4), or Formulation (b) (4), respectively) to the test site for at least 6 hours but no more than 6.5 hours.

On Day 29, the animals received one 0.4 mL (positive control) or 0.4 g (control and both test groups) application of the appropriate treatment (50% HCA, Formulation (b) (4) on the left flank/Formulation (b) (4) on the right flank, Formulation (b) (4), or Formulation (b) (4), respectively) to the test site(s). During the Challenge Phase, the test sites were scored at approximately 24 and 48 (±1) hours after removal (from the completion time of the dermal wash) of the positive control or test articles. The skin at the site was compared with the surrounding skin for signs of dermal irritation.

No dermal irritation was observed in any control animal when challenged with Formulation (b) (4) or Formulation (b) (4). One test article animal dosed with Formulation (b) (4) showed very faint erythema at 48 hours post-challenge. Three test article animals dosed with Formulation (b) (4) exhibited irritation, two with very faint erythema at 24 and 48 hours post-challenge and one with faint erythema at 48 hours post-challenge. Under the condition of the study, the test article Formulation (b) (4) is classified as a non-sensitizer while the test article Formulation (b) (4) is classified as a weak sensitizer.

5.5.6. Other nonclinical considerations related to excipients and impurities

Excipients:

(b) (4) The proposed level of silicon dioxide ((b) (4)%) is qualified based on the Inactive Ingredient Database (IID) and the 13-week dermal toxicity study in minipigs with BPO/ATRA.

All other excipients are present at levels at or below those found in FDA-approved drug products except cetrimonium chloride [also known as cetyl trimethyl ammonium chloride (CTAC), (b) (4)%] and (b) (4) CTAC and (b) (4) are two noncompendial excipients (b) (4) These two excipients were (b) (4) considered to be qualified by the pivotal toxicology studies in animals at higher concentrations of CTAC ((b) (4)%) and (b) (4) and supplemented by literature searches to locate additional nonclinical safety information. There are no safety issues associated with the use of the CTAC and (b) (4) excipients in this topical drug product.

Impurities:
Two impurities were identified, (b) (4) The level of these impurities in the drug product along with the level of individual unknown impurities are consistent with ICH Q3B(R2).

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant, Sol-Gel Technologies Ltd., submitted a new drug application (NDA) via the 505(b)(2) regulatory pathway on October 01, 2020. The proposed drug product is a topical dermal cream containing benzoyl peroxide (3%) and tretinoin (0.1%) (This product is referred to as S6G5T-3 in the review).

Benzoyl peroxide at concentrations of 2.5 to 10% is generally recognized as safe (GRAS) as an active ingredient in over-the-counter (OTC) topical products for the topical treatment of acne. Benzoyl peroxide is metabolized into benzoic acid with approximately 5% benzoic acid being systemically absorbed and eliminated unchanged in the urine. The Agency has waived PK assessment of benzoic acid and, hence, establishment of a PK bridge to a listed product for benzoic acid is not required.

Tretinoin is the active ingredient in several FDA-approved topical drugs for the treatment of acne. The clinical pharmacology program for Twyneo consists of a maximal usage trial (MUsT) in acne patients age 9+ years to establish a clinical bridge to the listed drug, Retin-A® 0.1% (tretinoin) cream, using the relative bioavailability approach (Study SGT-65-03). Study SGT-65-03 results demonstrated that Twyneo has similar total exposure of tretinoin compared to the listed drug, Retin-A cream 0.1% in adolescents and adults after 14 days of topical administration (steady-state conditions) under maximal use conditions. Therefore, an adequate PK bridge to the listed drug has been established.

Recommendation: This NDA is approvable from a clinical pharmacology perspective..

Post-marketing requirement/post-marketing commitment: None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The PK results of tretinoin, and its two metabolites (4-keto-13-cis retinoic acid and 13-cis-retinoic-acid) from the maximal use study (SGT-65-03) are summarized in Table 5. For the other two metabolites of tretinoin, all-trans 4-keto retinoic acid and 9-cis-retinoic acid, the PK parameters could not be calculated because their plasma concentrations were below the lower limit of quantification.

Table 5: Summary of Clinical Pharmacology Review

<table>
<tr><th>Issue</th><th>Conclusions/Comments</th></tr>
<tr><td>Baseline levels</td><td>In adult subjects, the mean plasma concentration of tretinoin at baseline (endogenous) was 1.12 ng/mL for S6G5T-3 and 0.998 ng/mL for Retin-A cream, 0.1%. In adolescent subjects, the baseline values were 0.958 ng/mL for S6G5T-3 and 0.907 ng/mL for Retin-A cream, 0.1%. For children, the baseline concentration of S6G5T-3 was 0.928 ng/m. Baseline (engdogenous) values were obtained from subjects from a single PK sample prior to dosing on Day 1. Diurnal characteristics of endogenous tretinoin and its metabolites are unknown and were not explored by this applicant. Diurnal variation is unlikely to impact the PK parameters obtained in this study since all PK samples were collected from subjects at approximately the same time in the evening on both Day 1 and Day 14.</td></tr>
<tr><td>Systemic exposure</td><td>The table below presents the baseline-corrected PK parameters of tretinoin and its two metabolites following topical administration of S6G5T-3 for 14 days.
<table>
<tr><th>Age (years)</th><th>Compound</th><th>Mean (± SD) Cmax (ng/mL)</th><th>Mean (± SD) AUC0-24 (ng*h/mL)</th></tr>
<tr><td>≥ 18</td><td>tretinoin</td><td>0.15 ± 0.17</td><td>0.63 ± 0.95</td></tr>
<tr><td></td><td>4-keto 13-cis RA</td><td>0.27 ± 0.29</td><td>2.88 ± 3.61</td></tr>
<tr><td></td><td>13-cis RA</td><td>0.21 ± 0.19</td><td>1.99 ± 2.90</td></tr>
<tr><td>12 to 17</td><td>tretinoin</td><td>0.19 ± 0.18</td><td>1.56 ± 1.97</td></tr>
<tr><td></td><td>4-keto 13-cis RA</td><td>0.32 ± 0.28</td><td>2.39 ± 3.05</td></tr>
<tr><td></td><td>13-cis RA</td><td>0.28 ± 0.35</td><td>1.79 ± 2.79</td></tr>
<tr><td>9 to 11</td><td>tretinoin</td><td>0.18 ± 0.22</td><td>2.06 ± 3.96</td></tr>
<tr><td></td><td>4-keto 13-cis RA</td><td>0.34 ± 0.36</td><td>2.89 ± 3.17</td></tr>
<tr><td></td><td>13-cis RA</td><td>0.13 ± 0.09</td><td>0.96 ± 1.36</td></tr>
</table>
There was no accumulation of tretinoin or any of the metabolites in all age groups; all values for Day 14/Day 1 C_{max} and AUC_{0-24} ratios were approximately equal to 1.</td></tr>
<tr><td>Relative Exposure</td><td>The relative exposure of tretinoin and metabolites following 14 days topical administration of S6G5T-3 and Retin-A cream 0.1% was measured in adult and adolescent subjects. The 90% confidence intervals of the geometric mean ratios (GMRs) for C_{max} and AUC_{0-24} were within 80-125% for tretinoin and its 2 metabolites, with the exception of the C_{max} for 13-cis RA in adults, which had a upper 90% CI of 127%. This slight increased C_{max} on a single metabolite is not considered clinically relevant.</td></tr>
</table>

Terminal half-life	Terminal half-life ($t_{1/2}$) could not be calculated since for the majority of concentration-time profiles since PK samples were not collected for a sufficient duration post-dose to adequately assess the elimination phase and estimate $t_{1/2.}$
Clinical trial formulation	The PK study SGT-65-03 used the final to-be-marketed formulation of Twyneo (S6G5T-3).
Pediatric subjects	Pediatric subjects aged 9-11 years (n=8) and 12-17 years (n=15) were included in the PK study.
Drug interactions	Evaluation of drug-drug interactions were not performed as this is a 505(b)(2) application.
Bioanalytical methods	The full validation reports were submitted and the bioanalytical method was adequately validated. Due to limited sample volume, incurred sample reanalysis of the study samples was not performed. However, while this limits the reliability of drug concentrations obtained, the application is still considered approvable for the following reasons: • The bioavailability of tretinoin were comparable between the listed drug and the new drug. • The bioanalytical method is well validated, hence, the PK data is considered accurate. • Tretinoin is not a new drug. The listed drug was approved in 1973 and there are years of marketing experience which have not suggested any significant systemic safety concerns. • The indication between the listed drug and the new drug is the same – acne vulgaris. • The maximal use study was well designed and the drug was applied to max body surface area (BSA) and application to higher BSA is not anticipated during normal use. • This sponsor has conducted phase 3 trials to obtain the new product safety data. .

Reviewer comments: ISR analysis is an integral part to support the validation of a bioanalytical method. The lack of ISR is considered acceptable in this case due to the aforementioned reasons and such approach should not be extrapolated to support the approval of other products.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant has proposed a dosing regimen of application of a thin layer of TWYNEO to the affected areas once daily on clean and dry skin.

This dosing regimen is similar to other approved topical tretinoin formulations and is supported by safety from the maximal use study (SGT-65-03) and efficacy and safety data from the two phase 3 trials (SGT-65-04 and SGT-65-05). Refer to Section 7 and Section 8 for efficacy and safety determinations.

Therapeutic Individualization

Therapeutic individualization was not evaluated.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The maximal use study (SGT-65-03) was designed as an open-label, parallel-group study where subjects were randomized to receive either Twyneo (n=35) or the listed drug, Retin-A cream 0.1% (n=27). Patients age 9 to <12 years were randomized to only receive Twyneo, while adolescents (age 12 to 17 years) and adults could receive either Twyneo or Retin-A cream, 0.1%.

The assigned study treatment was topically applied to the face (cheeks, forehead, nose, and chin), shoulders, back and upper chest once daily for 14 days by the study staff in the clinic. The mean study drug usage at day 14 was 25.5 g S6G5T-3 (mean daily dose of 1.82 g) and 20.7 g Retin-A® cream 0.1% (mean daily dose of 1.48 g). The mean daily usage of S6G5T-3 in Study SGT-65-03 exceeds the study drug use in the phase 3 studies for all age groups and is therefore reflective of maximal use conditions in terms of dose.

Table 6: Mean daily use of Twyneo in Study SGT-65-03

Age Group (years)	Mean Daily Use of S6G5T-3 (g) (min – max)	
	MUsT Study (SGT-65-03)	Pooled phase 3 (SGT-65-04 and SGT-65-05)
9 to <12 years	1.85 (0.78 – 2.36)	0.55 (0.15 – 1.15)
12 to 18 years	1.75 (0.14 – 2.43)	0.79 (0.03 – 2.13)
>18 years	1.9 (0.36 – 2.07)	0.81 (0.03 – 1.98)

(Source: Reviewer-created table, modified from Sponsor table 14.3.0.1.AH1 IR Response on 11/23/20, Link \\CDSESUB1\

evsprod\NDA214902\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-acne-vulgaris\5353-rep-analys-data-more-one-stud\sgt-65-iss)

Summary of Demographics

Demographics of enrolled subjects are presented in Table 7.

Table 7: Summary of Demographics

	S6G5T-3 (N=35)		Retin-A 0.1% cream (N=27)		Total (N=62)	
Age (years)						
n	35		27		62	
Mean	17.7		18.8		18.2	
SD	8.28		5.56		7.19	
Median	16.0		17.0		17.0	
Min. to Max.	9 to 46		12 to 33		9 to 46	
9 to < 12 Years	8	(22.9%)	0		8	(12.9%)
12 to < 18 Years	15	(42.9%)	15	(55.6%)	30	(48.4%)
≥ 18 Years	12	(34.3%)	12	(44.4%)	24	(38.7%)
Sex						
n	35		27		62	
Female	19	(54.3%)	11	(40.7%)	30	(48.4%)
Male	16	(45.7%)	16	(59.3%)	32	(51.6%)
Ethnicity						
n	35		27		62	
Hispanic or Latino	9	(25.7%)	8	(29.6%)	17	(27.4%)
Not Hispanic or Latino	26	(74.3%)	19	(70.4%)	45	(72.6%)
Not Reported/Unknown	0		0		0	
Race						
n	35		27		62	
American Indian or Alaska Native	0		0		0	
Asian	0		0		0	
Black or African American	11	(31.4%)	7	(25.9%)	18	(29.0%)
Native Hawaiian or Other Pacific Islander	0		0		0	
White	22	(62.9%)	19	(70.4%)	41	(66.1%)
Mult ple/Other	2	(5.7%)	1	(3.7%)	3	(4.8%)

(Source: Clinical Study Report Body SGT-65-03, page 77, Table 10, Link \\CDSESUB1\evsprod\NDA214902\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\sgt-65-03\sgt-65-03-report-body.pdf)

PK Sampling

Plasma concentration of tretinoin, 4-keto-14-cis RA, and 13-cis RA were collected on days 1 and 14 prior to treatment administration and at 2, 6, 12, 24, 48 and 72 hours post-treatment.

PK Results

Day 1 mean concentration-time profiles for each age group are displayed in Figure 1, Figure 2, and Figure 3. Day 14 mean concentration-time profiles are shown in Figure 4, Figure 5, and Figure 6. The relatively flat concentration-time profiles for all age groups on day 14 indicates that steady-state was achieved. Additionally, there was no accumulation of tretinoin or any of the metabolites in all age groups; all values for Day 14/Day 1 C_{max} and AUC_{0-24} ratios were approximately equal to 1.

Figure 1. Concentration (ng/mL) vs Time (hour) for Adults on Day 1

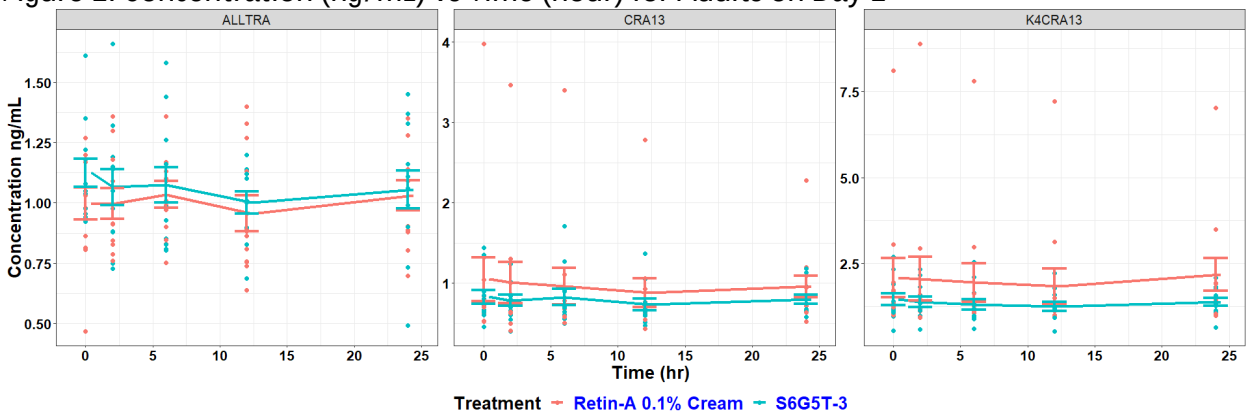


Figure 2. Concentration (ng/mL) vs Time (hour) for Subjects Age 12-17 years on Day 1

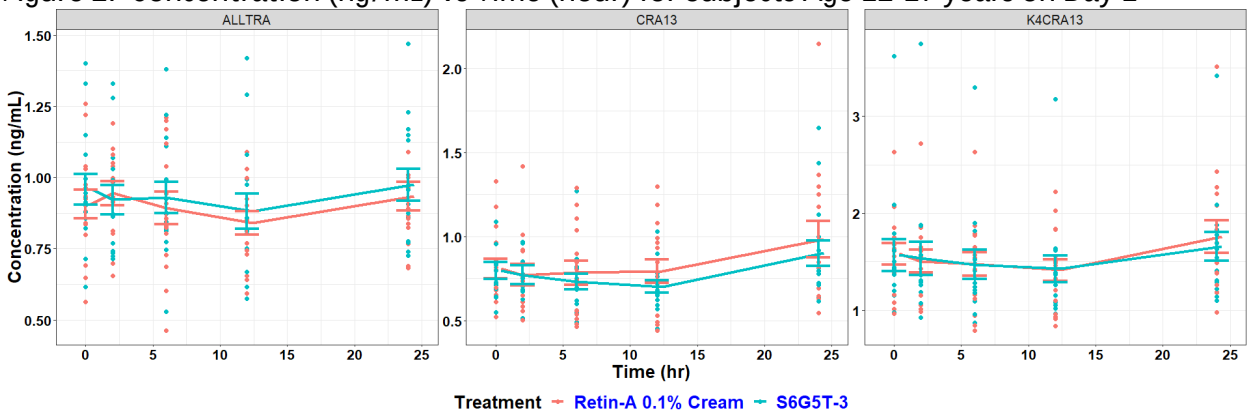


Figure 3. Concentration (ng/mL) vs Time (hour) for Subjects Age 9 to <12 years on Day 1

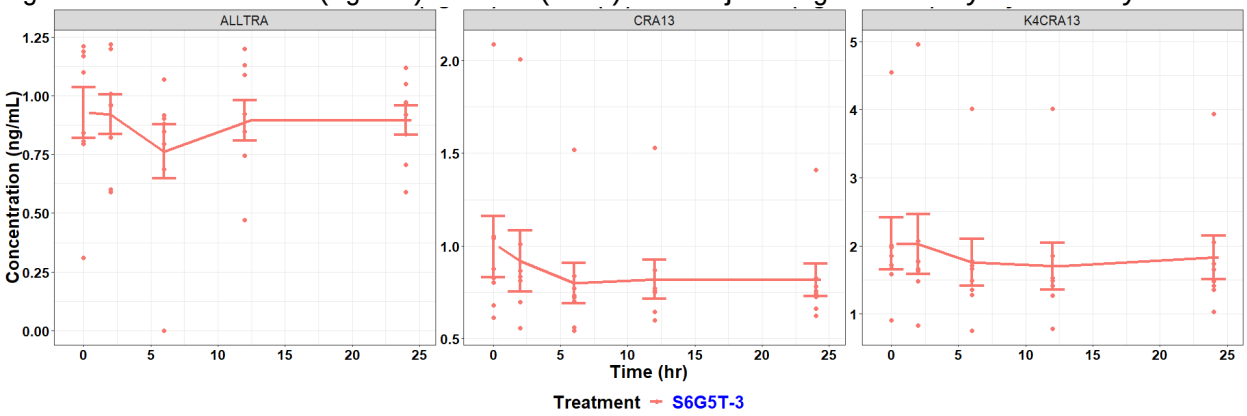


Figure 4. Concentration (ng/mL) vs Time (hour) for Adult Subjects on Day 14

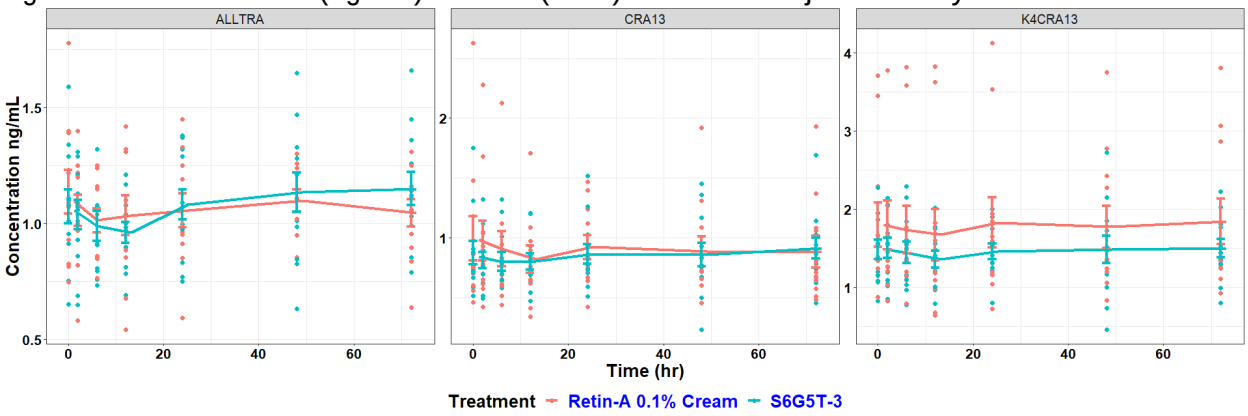


Figure 5. Concentration (ng/mL) vs Time (hour) for Subjects Age 12 to 17 years on Day 14

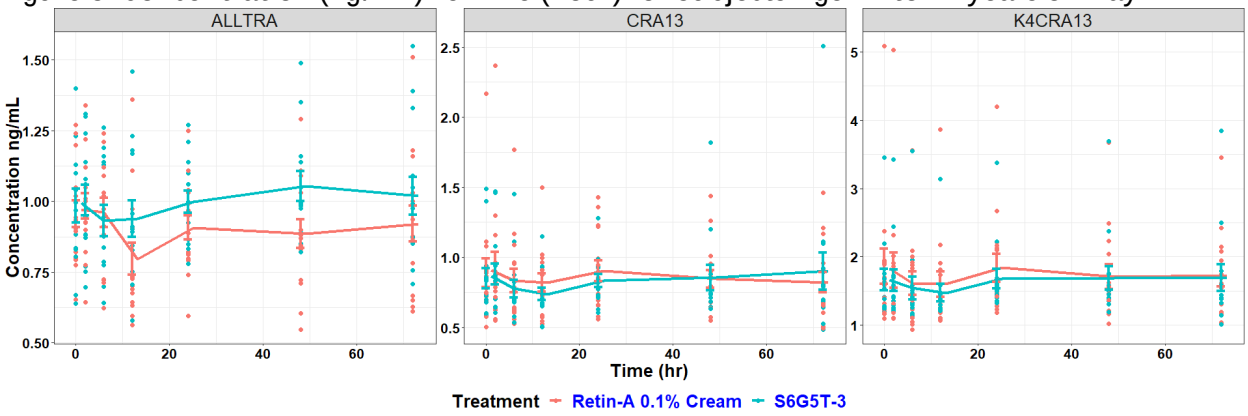
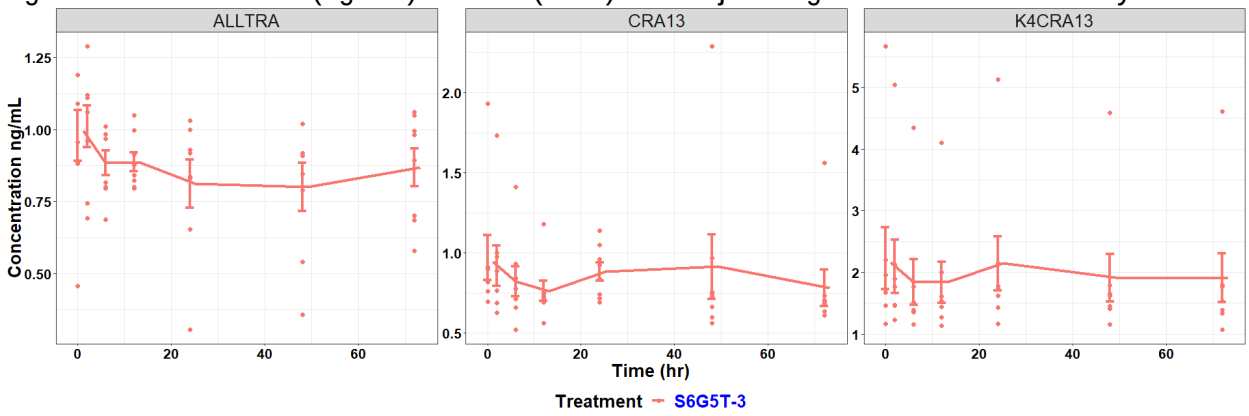


Figure 6 Concentration (ng/mL) vs Time (hour) for Subjects Age 9 to <12 Years on Day 14



(Source for Figures X-X: Reviewer-created plots using datasets from SGT-65-03, Link \\CDSESUB1\evsprod\NDA214902\0001\m5\datasets\sgt-65-03)

Table 8 and Table 9 present comparisons of exposure for Twyneo and Retin-A cream 0.1% in adults and adolescent patients. In Table 8, the PK parameters for tretinoin and metabolites were calculated using baseline-corrected systemic concentration data to account for endogenous levels of tretinoin and metabolites. The day 14 baseline-corrected concentration values were calculated as the day 14 total concentrations at each timepoint minus the day 1 baseline (pre-dose) value. Day 14 baseline-corrected concentrations that resulted in negative values were set to zero for the PK parameter assessments.

Comparison of the baseline-corrected PK parameters shows significantly lower C_{max} and AUC_{0-24} for tretinoin in adults (GMR of 37% and 14%, respectively) with S6G5T-3 compared to Retin-A cream 0.1%. In adolescent subjects, however, exposure of tretinoin was higher following administration of S6G5T-3 with GMRs of 102% and 172% for C_{max} and AUC_{0-24}, respectively. Baseline correction of the total systemic concentrations resulted in negative values for a large proportion of the data. The resulting exposure comparison has high variability as shown by the wide confidence interval.

For the comparison of Twyneo with Retin-A cream 0.1% in adults and adolescents by using the total concentration data (not baseline-corrected), the 90% confidence intervals of the geometric mean ratios for C_{max} and AUC_{0-24} were within 80-125% for all values except one; the upper 90% confidence interval of Cmax for 13-cis RA in adults only was 127% (Table 9). This slightly higher value is not considered clinically relevant as the product is topically administered at the target site (i.e. skin). Also it is noted that for tretinoin (all-trans RA), the lower limit of 90% confidence interval was 79.09%. This will not be an issue because the sponsor has conducted phase 3 safety and efficacy trials for their product.

Table 8: Baseline-Corrected Comparison of the Cmax and AUCs of All-Trans RA and its Metabolites, 4-Keto 13-Cis RA and 13-Cis RA in Patients with Acne Vulgaris on Day 14

Group	Analyte	PK Parameter	Geometric Mean		%Ratio[a]	CI 90% Lower[b]	CI 90% Upper[c]	Diff DF
			Retin-A®	S6G5T-3				
Adult	All-trans RA	C_{max}, ng/mL	0.318	0.119	37.40	20.14	69.45	18
		$AUC_{(0-T)}$, ng·h/mL	7.00	2.02	28.92	10.13	82.53	17
		$AUC_{(0-24)}$, ng·h/mL	2.22	0.314	14.17	4.57	43.88	17
	4-keto 13-cis RA	C_{max}, ng/mL	0.286	0.201	70.33	26.42	187.18	16
		$AUC_{(0-T)}$, ng·h/mL	6.08	5.28	86.78	20.34	370.19	16
		$AUC_{(0-24)}$, ng·h/mL	1.30	2.89	221.98	56.86	866.60	14
	13-cis RA	C_{max}, ng/mL	0.167	0.172	103.17	52.01	204.63	17
		$AUC_{(0-T)}$, ng·h/mL	3.91	3.14	80.36	23.93	269.86	17
		$AUC_{(0-24)}$, ng·h/mL	1.56	0.820	52.41	13.65	201.20	16
Adolescent	All-trans RA	C_{max}, ng/mL	0.160	0.163	101.87	59.50	174.39	25
		$AUC_{(0-T)}$, ng·h/mL	1.82	3.65	200.09	81.22	492.93	25
		$AUC_{(0-24)}$, ng·h/mL	0.865	1.50	172.90	80.45	371.61	22
	4-keto 13-cis RA	C_{max}, ng/mL	0.420	0.229	54.54	25.42	117.03	21
		$AUC_{(0-T)}$, ng·h/mL	15.5	6.34	40.81	14.46	115.14	19
		$AUC_{(0-24)}$, ng·h/mL	4.05	1.07	26.37	7.27	95.61	19
	13-cis RA	C_{max}, ng/mL	0.175	0.215	122.63	60.01	250.62	22
		$AUC_{(0-T)}$, ng·h/mL	3.84	3.63	94.43	26.02	342.77	21
		$AUC_{(0-24)}$, ng·h/mL	1.19	1.24	103.80	31.49	342.18	20

[a] %Ratio of analyte geometric means following S6G5T to Retin-A®
[b] Lower levels of the 90% CI
[c] Upper levels of the 90% CI
[d] %The relative bioavailability of analyte exposure parameter following S6G5T is equivalent to that following Retin-A®

(Source: MCR18-033 Report Amendment 1 (June 1, 2021), Response to Clinical Pharmacology Information Request Sent 5/24/21, Appendix E, Table 2, page 11)

Table 9: Comparison of the Cmax and AUCs of All-Trans RA and its Metabolites, 4-Keto 13-Cis RA and 13-Cis RA in Patients with Acne Vulgaris on Day 14 (Without Baseline Correction)

Group	Analyte	PK Parameter	Geometric Mean		%Ratio[a]	CI 90% Lower[b]	CI 90% Upper[c]
			S6G5T-3	Retin-A®			
Adult	All-trans RA	C_{max}, ng/mL	1.17	1.30	89.59	79.09	101.48
		$AUC_{(0-24)}$, ng·h/mL	23.8	24.7	96.31	85.03	109.10[d]
		$AUC_{(0-72)}$, ng·h/mL	77.0	75.8	101.62	90.11	114.59[d]
		$AUC_{(0-T)}$, ng·h/mL	77.0	75.8	101.62	90.11	114.59[d]
	4-keto 13-cis RA	C_{max}, ng/mL	1.55	1.76	88.11	66.35	117.02
		$AUC_{(0-24)}$, ng·h/mL	33.0	36.7	89.96	67.02	120.74
		$AUC_{(0-72)}$, ng·h/mL	101	115	87.85	65.78	117.32
		$AUC_{(0-T)}$, ng·h/mL	101	115	87.85	65.78	117.32
	13-cis RA	C_{max}, ng/mL	0.920	0.970	95.08	71.04	127.26
		$AUC_{(0-24)}$, ng·h/mL	19.1	19.7	96.69	75.30	124.14
		$AUC_{(0-72)}$, ng·h/mL	58.8	59.5	98.89	76.01	128.64
		$AUC_{(0-T)}$, ng·h/mL	58.8	59.5	98.89	76.01	128.64
Adolescent	All-trans RA	C_{max}, ng/mL	1.09	1.06	102.62	92.55	113.79[d]
		$AUC_{(0-24)}$, ng·h/mL	22.8	21.0	108.43	96.90	121.33[d]
		$AUC_{(0-72)}$, ng·h/mL	71.2	63.5	112.14	100.47	125.17
		$AUC_{(0-T)}$, ng·h/mL	71.2	63.5	112.14	100.47	125.17
	4-keto 13-cis RA	C_{max}, ng/mL	1.73	1.85	93.65	75.77	115.75
		$AUC_{(0-24)}$, ng·h/mL	36.3	38.1	95.45	78.34	116.31
		$AUC_{(0-72)}$, ng·h/mL	114	117	97.22	79.91	118.28
		$AUC_{(0-T)}$, ng·h/mL	114	117	97.22	79.91	118.28
	13-cis RA	C_{max}, ng/mL	0.920	0.960	95.83	78.99	116.27
		$AUC_{(0-24)}$, ng·h/mL	18.6	19.7	94.27	79.63	111.61
		$AUC_{(0-72)}$, ng·h/mL	58.3	59.3	98.31	83.11	116.28[d]
		$AUC_{(0-T)}$, ng·h/mL	58.3	59.3	98.31	83.11	116.28[d]

[a] %Ratio of analyte geometric means following S6G5T to Retin-A®
[b] Lower levels of the 90% CI
[c] Upper levels of the 90% CI
[d] %The relative bioavailability of analyte exposure parameter following S6G5T is equivalent to that following Retin-A®

(Source: Clinical Study Report Body 2 SGT-65-03, page 31, 10, Link \\CDSESUB1\evsprod\NDA214902\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\sgt-65-03\sgt-65-03-report-body-2.pdf)

Conclusions

- *The study SGT-65-03 was appropriately designed to assess the exposure of Twyneo in patients with acne vulagaris > 9 years old and the relative exposure of Twyneo compared to Retin-A cream, 0.1% in adolescents and adults with acne vulgaris. Additionally, the*

exposure, as measured by the mean daily study drug used, exceeds the exposure of the Phase 3 studies.

- *Study SGT-65-03 adequately establishes a clinical bridge between Twyneo and Retin-A cream 0.1%. This conclusion is based on the similar total systemic concentrations of tretinoin and metabolites in adults and adolescent subjects 12 to 17 years old after 14 days of topical administration (steady-state conditions) under maximal use conditions.*
  - *The purpose of this clinical bridge is to cross reference systemic safety of S6G5T-3 from the listed drug (Retin-A cream) by demonstrating that the total exposures (endogenous plus drug-related) of tretinoin and metabolites are reasonable and do not significantly exceed that of the listed drug. The use of total systemic concentrations (i.e. endogenous + those produced following drug application) to support establishment of clinical bridge to cross reference safety is a reasonbale approach. Efficacy of S6G5T-3 was established independently through Phase 3 efficacy studies.*
  - *Comparison of the total systemic exposure in adults (Error! Reference source not found.) in adults and adolescent subjects shows C_{max} and AUC_{0-24} 90% CI were generally within the no effect boundary of 80-125%.*
  - *Due to high variability in the baseline-corrected PK parameters due to several concentrations being negative, this data would not be considered to support establishment of a clinical bridge. However, this data will be essential for labeling as it reprenents the systemic exposure produced by application of the drug.*

Bioanalytical Method Validation and Performance
Tretinoin (all-trans retinoic acid), 4-keto 13-cis retinoic acid, and 13-cis retinoic acid were measured in human plasma using a validated HPLC-MS/MS method for the maximal use study (SGT-65-03). This method was developed and validated by (b) (4) (b) (4) The method was shown to be precise, accurate and sensitive over the validated range. The validation parameters and method performance for Study SGT-65-03 are summarized in Error! Reference source not found..

Due to limited sample volume, incurred sample reanalysis was not performed. In general, incurred sample reanalysis should be performed to verify the reliability of the reported study sample analyte concentrations (See FDA Bioanalytical Method Validation Guidance for Industry (2018)). In the context of this development program, the purpose of the maximal use study is to demonstrate that tretinoin and metabolite concentrations following Twyneo administration do not exceed that of a listed drug, Retin-A cream 0.1%. Following 14 days of similar mean daily use of Twyneo and Retin-A cream 0.1%, very similar exposures (C_{max} and AUC_{0-24}) were obtained, as demonstrated by the point estimates of the GMRs of exposure near 1 (See Table 9). Additionally, the daily usage in study SGT-65-03 is greater than 2-fold higher than real-world usage, as shown by comparison to the actual study drug usage in the phase 3 studies (Table 6). While the lack of incurred sample reanalysis may limit the reliability of the drug concentrations,

it is not expected that this is a significant safety concern given that safety and efficacy were also independently established in Phase 3 studies SGT-65-04 and SGT-65-05.

Table 10: Summary of Bioanalytical Method Validation and Study Performance

Validation parameters	Method validation summary	
Calibration curve performance during accuracy & precision	Number of standard calibrators from 0.200 to 10.0 ng/mL	10 (concentration levels)
	Cumulative accuracy (%bias [%Dev]) from 0.200 to 10.0 ng/mL All-Trans Retinoic Acid 13-Cis Retinoic Acid 4-Keto 13-Cis Retinoic Acid	 -6.00 to 5.00% -7.50 to 5.14% -2.10 to 2.20%
	Cumulative precision (%CV) from 0.200 to 10.0 ng/mL All-Trans Retinoic Acid 13-Cis Retinoic Acid 4-Keto 13-Cis Retinoic Acid	 ≤8.50% ≤6.36% ≤9.27%
QC performance during accuracy & precision	Cumulative accuracy (%bias) in 42 QCs: QCs: 0.200, 0.600, 5.00, 8.00 ng/mL All-Trans Retinoic Acid 13-Cis Retinoic Acid 4-Keto 13-Cis Retinoic Acid	 -5.00 to 3.00% -8.50 to 1.60% -3.50 to -0.875%
	Inter-batch %CV QCs: 0.200, 0.600, 5.00, 8.00 ng/mL All-Trans Retinoic Acid 13-Cis Retinoic Acid 4-Keto 13-Cis Retinoic Acid	 ≤13.4% ≤8.77% ≤8.50%
Selectivity & matrix effect	Charcoals Scrubbed Human Plasma: 10 lots, 100% Passed Untreated Human Plasma: 6 lots, 100% Passed	
Interference & specificity	Charcoals Scrubbed Human Plasma: 10 lots, 100% Passed Untreated Human Plasma: 6 lots, 100% Passed Concomitant met non-interference	
Hemolysis effect	All-Trans Retinoic Acid: 1 lot, -6.75 to -2.50%, -0.400% with higher low QC concentration 13-Cis Retinoic Acid: 1 lot, -18.2 to -8.50%, -4.80% with higher low QC concentration 4-Keto 13-Cis Retinoic Acid: 1 lot, -7.38 to 8.83%, 0.00% with higher low QC concentration	
Lipemic effect	All-Trans Retinoic Acid: 1 lot, -7.50 to -1.17%, -3.60% with higher low QC concentration 13-Cis Retinoic Acid: 1 lot, -9.50 to 19.8%, 1.20% with higher low QC concentration 4-Keto 13-Cis Retinoic Acid: 1 lot, -7.25 to 22.7%, -2.40% with higher low QC concentration	
Dilution linearity & hook effect	Not Applicable	
Benchtop/process stability	Bench-top Storage (Room Temperature) for 6 Hours Reinjection Integrity at 10 ± 5°C for 7 Day Processed Extracts Stored Refrigerated at 10 ± 5°C for 7 Day	

	Thawed in an Ice Bath for 25 Hours.
Freeze-Thaw stability	5 Freeze/Thaw (-70°C/Ice Bath) Cycles
Long-term storage	Frozen Storage (-70°C) for 381 Days
Whole blood stability	At Room Temperature and Ice Bath for 60 minutes
Parallelism	Not Applicable
Carry over	Pass, no carry over observed
Method performance in Study SGT-65-03	
Assay passing rate	60/69 runs = 87% pass rate
Standard curve performance	All-Trans Retinoic Acid • Cumulative bias range: -6.50 to 4.57% (MN18069); -0.800 to 3.50% (MN19108) • Cumulative precision: ≤10.1% CV (MN18069); ≤8.95% CV (MN19108) 13-Cis Retinoic Acid • Cumulative bias range: -6.50 to 4.67% (MN18069); -8.50 to 5.33% (MN19108) • Cumulative precision: ≤10.1% CV (MN18069); ≤11.5% CV (MN19108) 4-Keto 13-Cis Retinoic Acid • Cumulative bias range: -1.00 to 1.20% (MN18069); -3.20 to 4.80% (MN19108) • Cumulative precision: ≤5.00% CV (MN18069); ≤13.0% CV (MN19108)
QC performance	All-Trans Retinoic Acid • Cumulative bias range: -3.13 to 0.600% (MN18069); -2.40 to -1.50% (MN19108) • Cumulative precision: ≤14.4% CV (MN18069); ≤7.64% CV (MN19108) 13-Cis Retinoic Acid • Cumulative bias range: -4.50 to 0.600% (MN18069); 0.00 to 0.875% (MN19108) • Cumulative precision: ≤9.01% CV (MN18069); ≤13.1% CV (MN19108) 4-Keto 13-Cis Retinoic Acid • Cumulative bias range: -3.00 to -0.375% (MN18069); -2.20 to 1.67% (MN19108) • Cumulative precision: ≤4.10% CV (MN18069); ≤13.6% CV (MN19108)
Method reproducibility	Incurred sample reanalysis was not performed due to limited sample volume
Study sample analysis/ stability	Frozen Storage (-70°C) for 381 Days

(Source: Modified from Clinical Pharmacology Response to Information Request submitted 12/01/2020, Link, \\CDSESUB1\evsprod\NDA214902\0005\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\sgt-65-03)

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy evaluated in the two phase 3 trials and was not evaluated in the phase 1 Study (SGT-65-03). See Sections 7 and 8 efficacy results and determinations.

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

Based on the results from the maximal use study and efficacy and safety results from the phase 3 trials, the proposed dosing regimen is appropriate.

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

The systemic exposure of tretinoin between adult and pediatric subjects aged 9 years and older were comparable following once daily application of Twyneo. Impact of other intrinsic factors was not evaluated by the applicant as this is a 505(b)(2) application.

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

Drug interactions were not evaluated. This 505(b)(2) relies on metabolism and DDI information for the listed drug.

7 Sources of Clinical Data and Review Strategy

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7.1. Table of Clinical Studies

The clinical development program for Twyneo cream for the topical treatment of acne vulgaris included the following 8 studies:

- Phase 3 Trials (SGT-65-04 and SGT-65-05)
- Phase 2 Dose-Ranging, Safety and Efficacy Study (SGT-54-02)
- Phase 1b PK/Bioavailability Maximal Use Study (SGT-65-03)
- Phase 1 Provocative Dermal Safety Studies
    - Cumulative Contact Irritation(Study SGT-65-06)
    - Contact Sensitization (Study SGT-65-07)
    - Phototoxicity (Study SGT-65-08)
    - Photoallergy (Study SGT-65-09)

Table 11: Clinical Trials in the NDA 214902 Development Program

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
SGT-65-04	Phase 3, multicenter, double-blind, randomized, parallel-group, vehicle-controlled, pivotal study	Tretinoin/benzoyl peroxide cream, 0.1%/3% or vehicle cream applied topically to face once daily	3 co-primary efficacy endpoints: • Proportion of subjects who achieved the primary measure of success at Week 12, defined as a 2-grade improvement in the Investigator Global Assessment (IGA) score from baseline, with the IGA score equating to clear or almost clear • Absolute change from baseline in inflammatory lesion count • Absolute change from baseline in noninflammatory lesion count	12 weeks (84 days)	N = 424 T/BP: 281 : 143	Male/female subjects ≥ 9 years of age with moderate or severe acne including ≥ 30 and ≤ 150 noninflammatory and ≥ 20 and ≤ 100 inflammatory lesions with ≤ 2 cysts/nodules	US: 32

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
SGT-65-05	Phase 3, multicenter, double-blind, randomized, parallel-group, vehicle-controlled, pivotal study	Tretinoin/benzoyl peroxide cream, 0.1%/3% or vehicle cream applied topically to face once daily	3 co-primary efficacy endpoints: • Proportion of subjects who achieved the primary measure of success at Week 12, defined as a 2-grade improvement in the Investigator Global Assessment (IGA) score from baseline, with the IGA score equating to clear or almost clear • Absolute change from baseline in inflammatory lesion count • Absolute change from baseline in noninflammatory lesion count	12 weeks (84 days)	N = 434 TBP0.1/3: 290 C: 144	Male/female subjects ≥ 9 years of age with moderate or severe acne including ≥ 30 and ≤ 150 noninflammatory and ≥ 20 and ≤ 100 inflammatory lesions with ≤ 2 cysts/nodules	US: 31

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
SGT-65-02	Phase 2, multicenter, double-blind, randomized, parallel-group, active- and vehicle-controlled study	Eligible subjects were randomized in a 1:1:1:1:1:1 ratio to receive one of the following study drugs: • Benzoyl peroxide cream 3% • Tretinoin cream 0.1% • Tretinoin cream 0.05% • Tretinoin/benzoyl peroxide cream, 0.1%/3% • Tretinoin/benzoyl peroxide cream 0.05%/3% • Vehicle Cream Study drug was applied once daily for 12 weeks	3 co-primary efficacy endpoints: • Proportion of subjects who achieved the primary measure of success at Week 12, defined as a 2-grade improvement in the Investigator Global Assessment (IGA) score from baseline, with the IGA score equating to clear or almost clear • Absolute change from baseline in inflammatory lesion count • Absolute change from baseline in noninflammatory lesion count	12 weeks (84 days)	N = 702 TBP0.1/3: 114 TBP0.05/3: 117 BPO: 118 T0.1: 117 T0.05: 120 C: 116	Male/female subjects ≥ 9 years of age with moderate or severe acne including ≥ 25 and ≤ 100 noninflammatory and ≥ 20 and ≤ 50 inflammatory lesions with ≤ 2 cysts/nodules	US: 35
Studies to Support Safety							

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
SGT-65-06	Phase 1, single-center, evaluator-blinded, randomized, controlled, within-subject comparison study	Subjects were exposed to the following study drugs: • Tretinoin/benzoyl peroxide cream, 0.1%/3% • Vehicle cream • Positive control (sodium lauryl sulfate, 0.5%) • Negative control (saline, 0.9%) Each study drug was applied to one side of the infrascapular area of the back using semi-occlusive patches and worn for 24 hours and replaced daily for 21 days	• Comparison with controls of the potential to cause skin irritation after repeated application under occlusion • Assessment of local safety by evaluation of AEs	21 days	N = 38	Healthy adult subjects with any skin type	US: 1
SGT-65-07	Phase 1, single-center, evaluator-blinded, randomized, controlled, within-subject comparison study	Tretinoin/benzoyl peroxide cream, 0.1%/3%, vehicle cream, and negative control (saline, 0.9%) applied topically to back	Proportion of subjects with evidence of sensitization after repeated application under occlusion	Induction: 3 times weekly (3 weeks) Challenge: once (48 hours) Rechallenge: once (48 hours)	N = 240	Healthy adult subjects with any skin type	US: 1
SGT-65-08	Phase 1, single-center,	Tretinoin/benzoyl peroxide cream, 0.1%/3%, and	Comparison with controls of the phototoxic response	4 days	N = 33	Healthy adult subjects with ligher skin types	US: 1

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
	double-blinded, randomized, controlled, within-subject comparison study	vehicle cream applied topically once daily to infrascapular region of back	to tretinoin/benzoyl peroxide cream, 0.1%/3%				
SGT-65-09	Phase 1, single-center, double-blinded, randomized, controlled, within-subject comparison study	Tretinoin/benzoyl peroxide cream, 0.1%/3% and vehicle cream applied topically to one side of back using semi-occlusive patches and irradiated multiple times during induction and challenge phases	Comparison with controls of the photoallergic response to tretinoin/benzoyl peroxide, 0.1%/3% cream	Induction: twice weekly (3 weeks) Challenge: once (24 hours) Rechallenge: once (24 hours)	N = 62	Healthy adult subjects with lighter skin types	US: 1
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
SGT-65-03	Phase 1b, multicenter, open-label, randomized, parallel-group, active-controlled, maximal use systemic exposure study	Tretinoin/benzoyl peroxide cream, 0.1%/3% or Retin-A cream, 0.1% applied topically to face, shoulders, back and chest once daily for 14 days	PK of tretinoin/benzoyl peroxide cream, 0.1%/3%, compared to the listed drug, Retin-A cream, 0.1%, when applied topically once daily for 14 days under maximal use conditions	2 weeks (14 days)	N = 62 TBP0.1/3: 35 Retin-A Cream, 0.1%: 27	Male/female subjects ≥ 9 years of age with moderate or severe acne	US: 2

Source: Adapted from Applicant's submission, Section 2.5 (Clinical Overview), ,Table 2.5-1, Pages 7-10.
Abbreviations: TBP0.1/3 = tretinoin/benzoyl peroxide cream, 0.1%/3%, TBP0.05/3 = tretinoin/benzoyl peroxide cream, 0.05%/3%, BPO = benoxyl peroxide cream, T0.1 = tretinoin cream, 0.1%, T0.05 = tretinoin cream, 0.05%, VC = vehicle cream

7.2. Review Strategy

7.2.1 Data Sources

The data sources used for the evaluation of the efficacy and safety of Twyneo cream included the Applicant's clinical study reports (CSRs), datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model and analysis datasets were submitted. The analysis datasets used in this review are archived at: \\CDSESUB1\evsprod\NDA214902\0001

7.2.2 Data and Analysis Quality

The statistical and clinical teams evaluated data fitness. The databases for the study requiredminimal data management before performing analyses. In general, the data submitted by the Applicant to support the safety and efficacy of tretinoin/benzoyl peroxide cream, 0.1%/3%, for the proposed indication appeared adequate. The finalized Statistical Analysis Plans were submitted to the Agency; they are discussed in more detail in section 8.1.2 of this review.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design and Endpoints

The Applicant conducted two identically designed phase 3 trials (SGT-65-04 and SGT-65-05). Both were randomized, multicenter, double-blind, vehicle-controlled, parallel-group trials to evaluate the efficacy and safety of benzoyl peroxide and tretinoin (BPO/ATRA), 3%/0.1% cream.

For enrollment, the protocols specified the following key inclusion criteria:

- Male or female, 9 years of age or older
- Diagnosis of facial acne with 20-100 inflammatory lesions and 30-150 non-inflammatory lesions
- Have 2 or fewer cysts or nodules
- Have Investigator's Global Assessment (IGA) score of 3 ('moderate') or greater; see Table 12 for details on the IGA scale

Each trial was designed to enroll and randomize approximately 420 subjects from approximately 25 centers in a 2:1 ratio to receive either BPO/ATRA, 3%/0.1% cream (N=280) or Vehicle cream (N=140). Randomization was stratified by center.

Subjects applied study product once daily in the evening for 12 weeks. The protocol specified subjects to use a "pea-size" amount for each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead). Study product was to be spread as a thin layer, avoiding the eyes, lips, inside the nose, mouth and all mucous membranes. Subjects had the following study visits: screening, baseline (Day 1), and Weeks 2, 4, 8, and 12.

Table 12: Investigator's Global Assessment (IGA) Scale

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

Source: Protocol for Trial SGT-65-04; page 41

For both trials, the protocols/SAPs specified the following co-primary efficacy endpoints:

- Proportion of subjects with an assessment of 'clear' or 'almost clear' and with at least a 2-grade improvement in IGA from baseline at Week 12
- Absolute change from baseline in inflammatory lesion counts at Week 12
- Absolute change from baseline in non-inflammatory lesion counts at Week 12

The protocols/SAPs specified the following as secondary efficacy endpoints:

1. Percent change from baseline in non-inflammatory lesion counts at Week 12
2. Percent change from baseline in inflammatory lesion counts at Week 12
3. Proportion of subjects achieving at least a 4-point reduction on Item 1 (pimples) of the Patient-Reported Evaluation of Facial Acne (PRE-FACE) from baseline to Week 12
4. Proportion of subjects achieving at least a 4-point reduction on Item 5 (embarrassment) of the PRE-FACE from baseline to Week 12
5. Absolute change from baseline in non-inflammatory lesion count at Week 8
6. Absolute change from baseline in inflammatory lesion count at Week 8
7. Absolute change from baseline in non-inflammatory lesion count at Week 4
8. Absolute change from baseline in inflammatory lesion count at Week 4

Patient-Reported Evaluation of Facial Acne (PRE-FACE)

According to the protocols, the PRE-FACE is a seven-item patient reported outcome (PRO) questionnaire that assesses acne vulgaris-related signs, symptoms and impacts. The acne sign and symptom domain (ASD) consists of 4 items and assesses the severity of acne vulgaris-related pimples, whiteheads, blackheads, and redness, at their worst, in the 24 hours prior to administration of treatment based on an 11-point numeric rating scale (NRS) ranging from 0 ("no [Concept] at all") to 10 ("[Concept] as bad as you can imagine"). The acne impact domain

(AID) consists of three items and assesses acne vulgaris-related embarrassment, self-consciousness, and sadness in the seven days prior to administration of the treatment based on an 11-point NRS ranging from 0 ("not [Concept] at all) to 10 ("extremely [Concept]"). R

Regarding the PRE-FACE Item 1 (Pimple severity), the Agency recommended (advice letter dated 10/5/2018) that the Applicant provides more clarification around the actual concept that they intend to assess in the item stem to standardize patient responses. Regarding PRE-FACE Item 5 (Embarrassment), the Agency noted (advice letter dated 10/5/2018) that this item appears not to be fit-for-purpose for the context of this drug development program, among other limitations, and therefore this concept may be measured for exploratory purposes. At the Pre-NDA meeting (meeting minutes dated 3/18/2020), the Agency noted that the endpoint of at least a 4-point reduction on Item 1 (pimples) of the PRE-FACE from baseline to Week 12 failed to show statistical significance in one of the two phase 3 trials, while the endpoint of at least a 4-point reduction on Item 5 (embarrassment) of the PRE-FACE from baseline to Week 12 failed to show statistical significance in both phase 3 trials. Replication of study findings for the endpoint based on PRE-FACE Item 1 was not achieved.

The protocols also specified 'supportive efficacy endpoints', and 'exploratory' endpoints based on Patient Reported Outcomes (PROs); however, as these endpoints were not included in the multiplicity testing strategy, the results of these endpoints are considered exploratory and are not included in this review.

8.1.2. Statistical Methodologies

Analysis Populations:
The protocol-specified primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all subjects randomized who were dispensed study product.

The protocols/SAPs also specified conducting supportive efficacy analyses using the per-protocol (PP) population. The PP population is defined as all subjects in the ITT population who complete the 12-week evaluation without noteworthy study protocol violations. Subjects who met any of the following violations were not included in the PP population:

- Failed any of the inclusion/exclusion criteria
- Have taken any interfering concomitant medications
- Did not attend the Week 12 visit
- Missed more than 1 post baseline study visit prior to Week 12
- Have not been compliant with the dosing regimen (i.e., Subjects may not miss more than five consecutive days of dosing and must take 80-120% of expected doses. The number of expected doses will be determined for each subject based on the length of their participation in the study)
- Out of visit window at the Week 12 visit by ±5 days

According to the protocols/SAPs, subjects that discontinue from the trials due to an adverse event related to study treatment or documented lack of treatment effect were to be included in the PP population. Data for these subjects were not imputed by multiple imputation but rather their data were imputed with values consistent with their status as treatment failures (see details under 'Handling of Missing Data' in this section).

Methods for analyzing the co-primary endpoints:
The protocols/SAPs specified analyzing the IGA success (i.e., clear or almost clear with at least a 2-grade improvement) at Week 12 using logistic regression with treatment group and analysis center as factors in the model.

The protocols/SAPs specified analyzing the absolute change in lesion counts (inflammatory and non-inflammatory) at Week 12 using analysis of covariance (ANCOVA) with treatment group and analysis center as factors, and respective baseline value as a covariate. The treatment-by-analysis center interaction was specified to be included in the ANCOVA model if it is significant at the 0.10 level; otherwise it was removed. The protocols/SAPs specified applying Zar's skewness test to the residuals of the ANCOVA. The protocols/SAPs specified conducting the ANCOVA using the rank-transformed data if the two-sided p-value for the skewness test is significant at the 0.01 level.

Methods for analyzing the secondary endpoints:
The protocols/SAPs specified analyzing the secondary efficacy endpoints of percent change in lesion counts (inflammatory and non-inflammatory) using the same methods as for the co-primary endpoints of the absolute change in lesion counts (i.e., ANCOVA models, ranked or un-ranked, depending on result of a skewness test). The proportion of subjects with at least a 4-point reduction on Items 1 (pimples) and 5 (embarrassment) of the PRE-FACE were to be analyzed using the same approach as for the analysis of the IGA (i.e., logistic regression).

Multiplicity adjustment plan:
To control the overall Type I error rate for testing multiple secondary efficacy endpoints, the protocols/SAPs specified analyzing the secondary efficacy endpoints using a sequential gatekeeping approach. The secondary endpoints were specified to be analyzed in the order listed in Section Error! Reference source not found. and the testing will stop once a non-statistically significant value is observed (i.e., p-value ≥ 0.05). It should be noted that the SAPs excluded the last listed secondary endpoint (i.e., absolute change from baseline in inflammatory lesion count at Week 4) from the testing hierarchy.

Pooling Algorithm for Centers:
The protocols/SAPs specified that the trials were to be conducted in a manner such that a minimum of 15 subjects are randomized and included in the ITT population (i.e., at least 10 subjects in the active treatment group and 5 subjects in the vehicle treatment group) for any center. Centers that do not enroll a minimum of 15 subjects were specified in the SAPs to be

pooled by ordering these centers and combining the smallest with the largest, second smallest with second largest, and so on. These combined centers are termed “analysis centers”.

Center-to-center Variability:

The protocols/SAPs specified that the consistency of treatment response across analysis centers for the co-primary efficacy endpoints will be investigated using the treatment-by-analysis center interaction in the primary efficacy analysis. If the p-value for the interaction is significant at the 0.10 level, then the protocol specified that a sensitivity analysis will be conducted where analysis centers with “extreme” efficacy results will be excluded. Otherwise, the conclusions from the pooled data were to be considered free of the impact of extreme analysis centers. Extreme analysis centers were to be identified by analyzing all the possible subsets that can be created by excluding one analysis center. Each data subset will be analyzed to see if the interaction between treatment and analysis center remains significant at the 0.10 level. If one or more of the subsets result in an interaction p-value greater than or equal to 0.10, then the analysis center excluded that resulted in the largest interaction p-value is deemed to be the extreme analysis center. If all subset interaction p-values are less than 0.10, then the process will continue with all subsets that can be created by excluding two analysis centers. The process of identifying the extreme analysis centers will continue in stepwise manner (excluding one, two, three, etc.) until the p-value of the interaction exceeds 0.10.

The protocols/SAPs specified investigating the center-to-center variability prior to pooling. Specifically, the SAPs specified:

> “Prior to pooling, change from baseline in inflammatory and non-inflammatory lesions will be analyzed with an ANCOVA (unranked or ranked) with factors of treatment group, investigational site, and treatment group by investigational site interaction, and the respective baseline lesion count variable as a covariate. The dichotomized primary endpoint will be analyzed with a logistic regression with factors of treatment group, investigational site, and the interaction term of treatment group by investigational site. If any of the analyses are not computationally feasible due to some investigational sites having very few subjects enrolled, the low-enrolling investigational sites will be excluded from the analysis.”

Handling of Missing Data

The protocol-specified primary method of handling the missing data is the multiple imputation (MI). The protocols/SAPs specified that missing data will be imputed 5 times within each treatment group independently using the Markov Chain Monte Carlo (MCMC) method. According to the SAPs, data for subjects that discontinue from the study due to an AE related to study treatment were not to be imputed by multiple imputation or LOCF but rather their data were to be imputed with values consistent with their status as treatment failures. For these subjects, values for lesion count and IGA are imputed such that change from baseline is zero, meaning the values will be set to the baseline value. This imputation is done after the data for all subjects has been through the MI process.

The SAPs specified the following sensitivity analyses:

- Observed Data: observed data will be analyzed using repeated measures approaches. Absolute change in lesion counts (inflammatory and non-inflammatory) from baseline to Week 12 will be analyzed using a repeated measures ANCOVA with treatment group, analysis center, visit, and treatment-by-visit interaction as factors, and baseline value as a covariate. IGA success at Week 12 will be analyzed using a repeated measures logistic regression (i.e., generalized estimating equations [GEE]) with treatment group, analysis center, visit, treatment-by-visit interaction as factors in the model.
- Model-Based Multiple Imputation: missing data will be imputed 5 times using the model-based MI approach. For absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, the imputation model will include treatment group, analysis center, and baseline lesion count. For IGA success at Week 12, the imputation model will include treatment group and analysis center. The following random seeds were pre-specified: inflammatory lesion count seed =1098696156, non-inflammatory lesion count seed =1003722056, IGA seed =1857263794.
- Tipping Point Analysis:
    - Lesion Counts: the multiple imputation datasets used for the primary analyses are used for the tipping point analyses for lesion counts. To perform the tipping point analysis, the imputed values from the multiple imputation datasets for only the BPO/ATRA cream group are adjusted, by adding a constant (shift value) to the lesion counts. Change from baseline is then be recalculated with the changed imputed values. The shifted multiple imputed datasets are then analyzed as described in the 'Methods for analyzing the co-primary endpoints' section. This is repeated by adding the constant again to create another new shifted multiple imputed dataset and that dataset was analyzed. The resulting point estimates and p-values associated with each shift value are used to assess the magnitude of the shift value required to "tip" the p-value greater than 0.05.
    - IGA: To perform the tipping point analysis for the dichotomized IGA, all combinations for the number of imputed successes for the non-respondents in the BPO/ATRA cream group and the vehicle group are analyzed to identify the points that would indicate a treatment failure using a p-value greater than 0.05. The resulting points of treatment failure are plotted with the average number of successes in each treatment group from the primary multiple imputation analysis overlaid. The tipping points are identified as the points where the particular combinations of imputed successes change the treatment success to a treatment failure.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial SGT-65-04 enrolled and randomized a total of 424 subjects (281 to BPO/ATRA and 143 to vehicle) from 32 centers in the United States. Of note, among the 32 centers, Center 430, did not have any subjects being randomized to the trial due to subjects being screen failures. Trial

SGT-65-05 enrolled and randomized a total of 434 subjects (290 to BPO/ATRA and 144 to vehicle) from 31 centers in the United States. Table 13 presents the disposition of subjects for Trials SGT-65-04 and SGT-65-05. The discontinuation rate was slightly higher in the BPO/ATRA group compared to the vehicle group in both trials. In addition, the discontinuation rate was slightly higher in Trial SGT-65-05 compared to Trial SGT-65-04 in the BPO/ATRA group. The most common reasons for discontinuation were lost to follow-up and subject withdrawal in both treatment groups and both trials.

Table 13: Disposition of Subjects – Trials SGT-65-04 and SGT-65-05 (ITT[1])

	Trial SGT-65-04		Trial SGT-65-05	
	BPO/ATRA Cream (N=281)	**Vehicle Cream (N=143)**	**BPO/ATRA Cream (N=290)**	**Vehicle Cream (N=144)**
Discontinued, n (%)	32 (11%)	12 (8%)	48 (17%)	12 (8%)
Adverse Event (AE)	4 (1%)	0 (0%)	12 (4%)	0 (0%)
Lost to Follow-up	10 (4%)	7 (5%)	15 (5%)	7 (5%)
Pregnancy	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Protocol Deviation	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Physician Decision	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Withdrawal by Parent/Guardian	4 (1%)	1 (1%)	4 (1%)	0 (0%)
Withdrawal by Subject	9 (3%)	4 (3%)	14 (5%)	5 (3%)
Other	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

The demographics and baseline disease characteristics for Trials SGT-65-04 and SGT-65-04 are presented in Table 14. The demographics were generally balanced across the treatment groups within each trial and were similar in terms of age and sex between the two trials. Trial SGT-65-04 had a slightly higher proportion of subjects identified as Asian compared to Trial SGT-65-05.

The baseline disease characteristics were generally balanced across the treatment groups within each trial and were similar in terms of baseline IGA score between the two trials. The mean inflammatory and non-inflammatory lesion counts at baseline were slightly higher in Trial SGT-65-04 compared to Trial SGT-65-05.

Table 14: Demographics and Baseline Disease Characteristics - Trials SGT-65-04 and SGT-65-05 (ITT[1])

	Trial SGT-65-04		Trial SGT-65-05	
	BPO/ATRA Cream (N=281)	**Vehicle Cream (N=143)**	**BPO/ATRA Cream (N=290)**	**Vehicle Cream (N=144)**
Age (years)				
Mean (SD)	20.9 (8.5)	21.4 (8.6)	20.1 (7.0)	20.3 (6.7)
Median	18	18	18	18.5
Range	11 – 67*	10 – 57	10 – 51	9 – 42
Categories, n (%)				
9 to 11	5 (2%)	4 (3%)	5 (2%)	4 (3%)
12 to 17	121 (43%)	56 (39%)	133 (46%)	60 (42%)
≥18	155 (55%)	83 (58%)	152 (52%)	80 (56%)

	Trial SGT-65-04		Trial SGT-65-05	
	BPO/ATRA Cream (N=281)	Vehicle Cream (N=143)	BPO/ATRA Cream (N=290)	Vehicle Cream (N=144)
Sex, n (%)				
Male	106 (38%)	60 (42%)	117 (40%)	67 (47%)
Female	175 (62%)	83 (58%)	173 (60%)	77 (53%)
Race, n (%)				
White	194 (69%)	109 (76%)	212 (73%)	110 (76%)
Black or African American	53 (19%)	20 (14%)	52 (18%)	18 (12%)
American Indian or Alaska Native	1 (<1%)	1 (1%)	2 (1%)	2 (1%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	2 (1%)	1 (<1%)	1 (1%)
Asian	26 (9%)	10 (7%)	12 (4%)	6 (4%)
Multiple	6 (2%)	1 (1%)	7 (2%)	6 (4%)
Other	0 (0%)	0 (0%)	4 (1%)	1 (1%)
IGA, n (%)				
3 – Moderate	251 (89%)	132 (92%)	262 (90%)	133 (93%)
4 – Severe	30 (11%)	11 (8%)	28 (10%)	10 (7%)
Inflammatory Lesion counts				
Mean (SD)	33.5 (14.6)	33.5 (14.7)	28.2 (8.7)	27.5 (8.5)
Median	28	28	25	25
Range	20 – 92	20 – 90	2 – 62	20 – 75
Non-inflammatory Lesion counts				
Mean (SD)	48.6 (20.2)	47.1 (20.0)	44.6 (18.0)	44.9 (18.8)
Median	42	41	39	38
Range	30 – 148	30 – 140	23 – 149	30 – 123

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product
* Only one subject abve the age of 65 years old was enrolled in the trial.
Note: Subject (b) (6) in Trial SGT-65-05 was missing IGA score at baseline.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

8.1.4. Results of the Co-Primary Efficacy Endpoints

Table 15 presents the results of the co-primary efficacy endpoints for the ITT population. The final primary analyses for the primary endpoints are driven by the results of a skewness test (lesion count endpoints only) and whether the treatment-by-analysis center interactions were significant. Zar's test for skewness was statistically significant for both change in lesion count endpoints (non-inflammatory and inflammatory) in both trials (p-values < 0.001). Thus, the non-parametric method (i.e., based on the ranks) was considered the primary analysis for the lesion count endpoints. Treatment-by-analysis center interaction was significant only for the inflammatory lesion count endpoint in Trial SG-65-04 (both ranked and unranked ANCOVA analyses). For both trials, BPO/ATRA cream was statistically superior to vehicle cream on all three co-primary efficacy endpoints (p-values < 0.025). The results in the PP population (not shown) were similar to those in the ITT population.

As can be seen in Table 15Error! Reference source not found., the efficacy results for all three co-primary endpoints in Trial SGT-65-04 were much higher compared to Trial SGT-65-05. It should be noted that the higher efficacy results in Trial SGT-65-04 compared to Trial SGT-65-05 appear to be attributed to the active group; results in the vehicle group are consistent across the two trials. An additional sensitivity analysis investigating the effect of extreme analysis

centers can be found in Section 8.1.6.2. It should be noted that the Applicant excluded Subject (b) (6) from the analysis of IGA success in Trial SG-65-05 because the IGA was not performed at baseline. The statistical reviewer decided to keep Subject (b) (6) in the IGA analysis (and maintain the FAS population) since IGA was performed for all post-baseline visits and was consistent with lesion count values. Results for the IGA success endpoint using the Applicant's approach are very close to those presented in Table 15 (see Appendix 14.3 of the review).

Table 15: Results of the Co-Primary Endpoint at Week 12 - Trials SGT-65-04 and SGT-65-05 (ITT; MI[1])

	Trial SGT-65-04		Trial SGT-65-05	
	BPO/ATRA Cream (N=281)	**Vehicle Cream (N=143)**	**BPO/ATRA Cream (N=290)**	**Vehicle Cream (N=144)**
IGA Success[2]				
Proportion[3]	39.9%	14.3%	26.8%	15.1%
Difference (95% CI)	25.7% (17.1%, 34.2%)		11.6% (3.6%, 19.7%)	
Adjusted Proportion[4]	38.5%	11.5%	25.4%	14.3%
Difference (95% CI)[4]	26.9% (17.8%, 36.0%)		11.1% (2.8%, 19.5%)	
P-Value[4]	<0.001		0.009	
Absolute Change from Baseline in Inflammatory Lesion Counts				
Mean[3]	-21.5	-14.7	-16.4	-13.9
LS mean[5]	-21.6	-14.8	-16.2	-14.1
Difference (95% CI)[5]	-6.8 (-9.1, -4.6)		-2.1 (-3.9, -0.4)	
P-Value (unranked data)[5]	<0.001		0.018	
P-Value (ranked data)[6]	<0.001		0.021	
Absolute Change from Baseline in Noninflammatory Lesion Counts				
Mean[3]	-30.0	-19.1	-24.5	-18.0
LS mean[5]	-29.7	-19.8	-24.2	-17.4
Difference (95% CI)[5]	-9.9 (-13.0, -6.8)		-6.8 (-9.9, -3.7)	
P-Value (unranked data)[5]	<0.001		<0.001	
P-Value (ranked data)[6]	<0.001		<0.001	

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
[2] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[3] Average over the five imputed datasets.
[4] Adjusted proportions, difference (95% CI), and p-value are based on logistic regression with factors of treatment group and analysis center. For Trial SGT-54-05, the logistic regression used the Firth's penalized likelihood due to quasi-complete separation of the data.
[5] Least square (LS) means, difference (95% CI) and p-value are based on ANCOVA with factors of treatment group and analysis, and baseline value as a covariate. For the inflammatory lesion count analysis in Trial SGT-65-04, the interaction of treatment by analysis center was included in the model.
[6] P-value is based on a ranked ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate. For the inflammatory lesion count analysis, the interaction of treatment by analysis center was included in the model.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

For Trial SGT-54-05, the standard logistic regression did not converge due to quasi-complete separation of the data; quasi-complete separation in a logistic regression happens when the outcome variable separates a predictor variable or a combination of predictor variables to

certain degree. Therefore, the Applicant used the Firth's penalized likelihood for this trial. As a sensitivity analysis, the statistical reviewer analyzed the coprimary efficacy endpoint of IGA success at Week 12 using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis centers. For both trials, the CMH test produced statistically significant results (i.e., p-values < 0.01). Table 16 presents the estimated treatment effect (i.e., difference [95% CI]) by the various analysis approaches.

Table 16: Treatment Effect on IGA Success[1] at Week 12 by Analysis Approach (ITT; MI[2])

	Trial SGT-54-04	Trial SGT-54-05
Unadjusted[3]		
Difference from Vehicle (95% CI)	25.7% (17.1%, 34.2%)	11.6% (3.6%, 19.7%)
Logistic Regression – Standard[4]		
Difference from Vehicle (95% CI)	26.9% (17.8%, 36.0%)	NA
Logistic Regression – Firth's[5]		
Difference from Vehicle (95% CI)	26.5% (17.4%, 35.7%)	11.1% (2.8%, 19.5%)
CMH (Sensitivity Analysis)[6]		
Difference from Vehicle (95% CI)	25.5% (17.2%, 33.8%)	11.5% (3.6%, 19.4%)

[1] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[3] Average over the five imputed datasets.
[4] Adjusted difference in proportions is based on logistic regression with factors of treatment group and analysis center. For Trial SGT-54-01, the logistic regression did not converge due to quasi-complete separation of the data.
[5] Adjusted difference in proportions is based on logistic regression using the Firth's penalized likelihood with factors of treatment group and analysis center.
[6] Adjusted difference in proportions is the weighted average of the treatment differences across analysis center with the Cochran-Mantel-Haenszel (CMH) weights.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Table 17 presents the number of subjects with missing data for the co-primary efficacy endpoints along with the results of the co-primary efficacy endpoints across the various prespecified imputation methods. The proportion of subjects with missing data was slightly higher in Trial SGT-65-05 compared to Trial SGT-65-04. The results were generally similar across the various prespecified methods.

Table 17: Results for the Co-primary Efficacy Endpoints with Different Approaches for Handling Missing Data - Trials SGT-65-04 and SGT-65-05 (ITT[1])

	Trial SGT-65-04			Trial SGT-65-05		
	BPO/ATRA Cream (N=281)	Vehicle Cream (N=143)	Difference (P-Value)	BPO/ATRA Cream (N=290)	Vehicle Cream (N=144)	Difference (P-Value)
Subject with Missing Data	31 (11%)	12 (8%)		46 (16%)	12 (8%)	
IGA Success[2] at Week 12						
MI-MCMC (primary)[3]	38.5%	11.5%	26.9% (<0.001)	25.4%	14.3%	11.1% (0.017)
MI-Model[3]	40.0%	12.9%	27.1% (<0.001)	27.1%	14.6%	12.5% (0.008)
Observed[4]	40.2%	12.7%	27.5% (<0.001)	26.9%	12.6%	14.3% (0.002)

	Trial SGT-65-04			Trial SGT-65-05		
	BPO/ATRA Cream (N=281)	Vehicle Cream (N=143)	Difference (P-Value)	BPO/ATRA Cream (N=290)	Vehicle Cream (N=144)	Difference (P-Value)
Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12						
MI-MCMC (primary)[5]	-21.6	-14.8	-6.8 (<0.001)	-16.2	-14.1	-2.1 (0.021)
MI-Model[6]	-21.8	-15.3	-6.5 (<0.001)	-16.0	-14.0	-2.0 (0.038)
Observed[7]	-22.3	-15.3	-7.0 (<0.001)	-17.1	-14.3	-2.8 (0.015)
Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12						
MI-MCMC (primary)[5]	-29.7	-19.8	-9.9 (<0.001)	-24.2	-17.4	-6.8 (<0.001)
MI-Model[6]	-30.5	-20.0	-10.5 (<0.001)	-23.8	-17.4	-6.4 (<0.001)
Observed[7]	-31.3	-20.5	-10.8 (<0.001)	-25.8	-18.0	-7.9 (<0.001)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product.
[2] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[3] Proportions and p-values are based on a logistic regression with factors of treatment group and analysis center.
[4] Proportions and p-value are based on a repeated measures logistic regression (i.e., generalized estimating equations) with factors of treatment group, analysis center, visit, and treatment-by-visit interaction.
[5] Least square (LS) means, difference (95% CI) and p-value are based on ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate. For the inflammatory lesion count analysis in Trial SGT-65-04, the interaction of treatment by analysis center was included in the model.
[6] Least square (LS) means and p-value are based on ANCOVA with factors of treatment group, analysis center and baseline value as a covariate.
[6] Least square (LS) means and p-value are based on a repeated measures ANCOVA with factors of treatment group, analysis center, visit, and treatment-by-visit interaction, and baseline value as a covariate.
Note: For Trial SGT-54-05, the logistic regression used the Firth's penalized likelihood due to quasi-complete separation of the data.
Note: P-values for lesion counts are based on ranked data since skewness test p-values were <0.001
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADEFF.xpt

The Applicant also conducted tipping point analyses for the co-primary efficacy endpoints. For these analyses, the missing lesion counts in the BPO/ATRA cream group were adjusted by adding shift values to the lesion counts and the change from baseline was re-calculated with adjusted imputed values. This process was repeated for several shift values to identify the magnitude of the shift value required to "tip" the p-value greater than 0.05. The resulting point estimates and p-values associated with each shift value are provided in Appendix 14.3 of this review. For Trial SG-65-04, a 'tipping' point was not identified for either the inflammatory or non-inflammatory lesion counts. For Trial SG-65-05, the values for BPO/ATRA cream group would need to be shifted by 2.25 inflammatory lesions in order to reach a non-significant p-value; whereas for the non-inflammatory lesion count analysis the imputed values would need to be shifted by 140 lesions in order to have a non-significant p-value.

For the tipping point analyses of the IGA success, all combinations for the number of imputed successes for the non-respondents in the BPO/ATRA cream group and the vehicle group are analyzed to identify the points that would indicate a treatment failure using a p-value greater than 0.05. These points are plotted in Figure 10 and

Figure 11 in Appendix 14.3 of the review. All combinations in Trial SG-65-04 and the majority of the combinations in Trial SG-65-05 for the number of imputed successes for the non-respondents in the BPO/ATRA cream group and the vehicle group showed treatment successes using a p-value of ≤ 0.05.

8.1.5. Results of the Secondary Efficacy Endpoints

Table 18 presents the results for the secondary efficacy endpoints for the ITT population in the order tested per the multiplicity testing process described in Section 8.1.2.

For both trials, BPO/ATRA cream was statistically superior to vehicle cream on percent change from baseline in lesion counts. However, BPO/ATRA cream failed to show statistical superiority to vehicle cream on the endpoint of at least a 4-point reduction on Pre-FACE Item 1 (pimples) from baseline to Week 12 in Trial SGT-65-05, while BPO/ATRA cream failed to show statistical superiority to vehicle cream on the endpoint of at least a 4-point reduction on PRE-FACE Item 5 (embarrassment) from baseline to Week 12 in both phase 3 trials. Therefore, absolute change in lesion counts at Weeks 8 and 4 cannot be tested per the multiplicity testing plan. It should be noted that for the analyses of the endpoints based on the Pre-FACE, the statistical reviewer excluded subjects with baseline score of <4, while the Applicant considered such subjects as non-responders (Applicant's results not presented here). In both analyses, results were similar and conclusions remained the same. The reader is also referred to Section 8.1.1 for more information on Agency's comments regarding the PRO of PRE-FACE.

Table 18: Results for the Secondary Efficacy Endpoints - Trials SGT-65-04 and SGT-65-05 (ITT; MI[1])

	Trial SGT-65-04		Trial SGT-65-05	
	BPO/ATRA Cream (N=281)	**Vehicle Cream (N=143)**	**BPO/ATRA Cream (N=290)**	**Vehicle Cream (N=144)**
Percent Change from Baseline in Inflammatory Lesion Counts at Week 12				
Mean[2]	-65.6%	-43.4%	-58.1%	-51.0%
LS mean[3]	-66.1%	-43.5%	-57.6%	-50.8%
Difference (95% CI)[3]	-22.6% (-29.2%, -16.0%)		-6.8% (-13.1%, -0.5%)	
P-Value (unranked data)[3]	<0.001		0.033	
P-Value (ranked data)[4]	<0.001		0.014	
Percent Change from Baseline in Noninflammatory Lesion Counts at Week 12				
Mean[2]	-61.5%	-40.4%	-55.0%	-42.2%
LS mean[3]	-61.6%	-40.9%	-54.4%	-41.5%
Difference (95% CI)[3]	-20.7% (-27.2%, -14.2%)		-13.0% (-19.6%, -6.4%)	
P-Value (unranked data)[3]	<0.001		<0.001	
P-Value (ranked data)[4]	<0.001		<0.001	
Pre-FACE Item 1 (pimples) Success[5] at Week 12	**N=259**	**N=126**	**N=261**	**N=128**
Proportion[2]	42.4%	22.2%	41.5%	33.6%
Difference (95% CI)	20.2% (10.5%, 29.9%)		7.9% (-2.4%, 18.1%)	
Adjusted Proportion[6]	42.2%	21.2%	39.2%	30.7%
Difference (95% CI)[6]	21.0% (11.1%, 30.9%)		8.5% (-2.2%, 19.2%)	
P-Value[6]	<0.001		0.1199	
Pre-FACE Item 5 (embarrassment) Success[5] at Week 12	**N=196**	**N=95**	**N=195**	**N=104**
Proportion[2]	60.6%	49.3%	52.3%	52.9%
Difference (95% CI)	11.3% (-1.0%, 23.7%)		-0.5% (-13.1%, 12.0%)	
Adjusted Proportion[6]	65.2%	53.4%	53.2%	53.3%
Difference (95% CI)[6]	10.1% (-<0.1%, 20.3%)		-0.2% (-13.6%, 13.2%)	
P-Value[6]	0.0971		*	
Absolute Change from Baseline in Inflammatory Lesion Counts at Week 8				
Mean[2]	-17.0	-12.4	-14.1	-12.1
LS mean[3]	-17.1	-12.5	-14.0	-12.5
Difference (95% CI)[3]	-4.6 (-6.9, -2.2)		-1.5 (-3.2, 15.4)	
P-Value (unranked data)[3]	*		*	
P-Value (ranked data)[4]	*		*	
Absolute Change from Baseline in Noninflammatory Lesion Counts at Week 8				
Mean[2]	-24.4	-16.0	-20.2	-13.1
LS mean[3]	-24.4	-16.9	-20.0	-12.8
Difference (95% CI)[3]	-7.5 (-10.7, -4.4)		-7.2 (-10.4, -4.0)	
P-Value (unranked data)[3]	*		*	
P-Value (ranked data)[4]	*		*	
Absolute Change from Baseline in Noninflammatory Lesion Counts at Week 4				
P-Value (unranked data)[3]	-18.6	-12.7	-14.7	-11.1
P-Value (ranked data)[4]	-18.5	-13.4	-14.6	-10.8
Difference (95% CI)[3]	-5.1 (-7.9, -2.4)		-3.8 (-6.7, -0.9)	
P-Value (unranked data)[3]	*		*	
P-Value (ranked data)[4]	*		*	

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
[2] Average over the five imputed datasets.
[3] Least square (LS) means, difference (95% CI) and p-value are based on ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate. For the inflammatory lesion count analysis, the interaction of treatment by analysis center was included in the model.
[4] P-value is based on a ranked ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate. For the inflammatory lesion count analysis, the interaction of treatment by analysis center was included in the model.
[5] Success is defined at least 4 point reduction in Item 1/Item 5 of the PRE-FACE from baseline; subjects with baseline score of <4 are excluded from the analysis.
[6] Adjusted proportions, difference (95% CI), and p-value are based on logistic regression with factors of treatment group and analysis center.
* Testing stops per the multiplicity tes ing plan.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

8.1.6. Findings in Special/Subgroup Populations

8.1.6.1. Sex, Race, Age, and Baseline Disease Severity

The results for IGA success at Week 12 by sex, age, race, and baseline IGA score for Trials SGT-54-04 and SGT-54-05 are presented in Table 19 and Table 20 respectively. The results for absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 by sex, age, race, and baseline IGA score for Trials SGT-54-04 and SGT-54-05 are presented inTable 21, Table 22, Table 23 and Table 24 respectively.

The sample size in the subgroups of subjects between 9 and 11 years old and subjects with severe IGA score at baseline was small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

For race, the treatment effect tended to be higher in subjects who identify as White compared to those who identify as non-White for the three co-primary endpoints in both trials, except for the IGA success in Trial SGT-65-04; however, twice the number of enrolled subjects in the two trials were identified as White compared to non-White.

Table 19: IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA Score - Trial SGT-65-04 (ITT; MI[1])

Subgroups (n[E], n[V])	BPO/ATRA Cream (N=281)	Vehicle Cream (N=143)	Difference	95% CI
Sex				
Males (106, 60)	40.6%	12.0%	28.6%	(14.9%, 42.3%)
Females (175, 83)	39.5%	15.9%	23.6%	(12.7%, 34.6%)
Age (years)				
9-11 (5, 4)	60.0%	0%	60.0%	(17.1%, 100%)
12-17 (121, 56)	38.8%	12.5%	26.3%	(12.5%, 40.2%)
18+ (155, 83)	40.1%	16.1%	24.0%	(12.6%, 35.4%)
Race				
White (194, 109)	40.9%	16.7%	24.2%	(14.1%, 34.3%)
Non-White (87, 34)	37.7%	6.5%	31.2%	(17.2%, 45.3%)
Baseline IGA				
3 – Moderate (251, 132)	40.6%	14.2%	26.4%	(17.7%, 35.1%)
4 – Severe (30, 11)	34.0%	14.6%	19.5%	(-13.1%, 52.0%)
Overall	39.9%	14.3%	25.7%	(17.1%, 34.2%)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Table 20: IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA Score - Trial SGT-65-05 (ITT; MI[1])

Subgroups (n[E], n[V])	BPO/ATRA Cream (N=290)	Vehicle Cream (N=144)	Difference	95% CI
Sex				
Males (117, 67)	26.7%	9.6%	17.1%	(6.1%, 28.1%)
Females (173, 77)	26.9%	20.0%	6.9%	(-5.0%, 18.9%)
Age (years)				
9-11 (5, 4)	40.0%	0%	40.0%	(-2.9%, 82.9%)
12-17 (133, 60)	24.8%	10.7%	14.1%	(2.9%, 25.4%)
18+ (152, 80)	28.2%	19.3%	8.9%	(-2.6%, 20.4%)
Race				
White (212, 110)	29.0%	12.9%	16.1%	(7.0%, 25.1%)
Non-White (78, 34)	21.0%	22.3%	-1.3%	(-19.6%, 17.0%)
Baseline IGA				
3 – Moderate (262, 133)	28.3%	16.2%	12.1%	(3.4%, 20.7%)
4 – Severe (28, 10)	12.9%	2.0%	10.9%	(-10.1%, 32.5%)
Overall	26.8%	15.1%	11.6%	(3.6%, 19.7%)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Table 21: Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12 by Sex, Age, Race, and Baseline IGA Score - Trial SGT-65-04 (ITT; MI[1])

Subgroups (n[E], n[V])	BPO/ATRA Cream (N=281)	Vehicle Cream (N=143)	Difference	95% CI
Sex				
Males (106, 60)	-22.1	-13.9	-8.2	(-11.9, -4.4)
Females (175, 83)	-22.1	-15.5	-5.6	(-8.6, -2.5)
Age (years)				
9-11 (5, 4)	-26.0	-14.5	-7.6	(-21.6, 6.4)
12-17 (121, 56)	-21.8	-11.9	-9.6	(-13.3, -5.8)
18+ (154, 83)	-21.2	-16.5	-4.9	(-8.0, -1.8)
Race				
White (194, 109)	-23.0	-14.9	-8.1	(-10.9, -5.3)
Non-White (87, 34)	-17.9	-14.8	-3.1	(-7.5, 1.3)
Baseline IGA				
3 – Moderate (251, 132)	-19.8	-13.5	-6.3	(-8.7, -3.9)
4 – Severe (30, 11)	-37.2	-26.5	-10.7	(-21.9, 0.5)
Overall	-21.6	-14.8	-6.8	(-9.1, -4.6)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Abbreviations: CI: Confidence Interval; n[E] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Note: Values displayed are the least square (LS) means based on analysis of covariance (ANCOVA) with treatment group as a factor and baseline value as a covariate.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Table 22: Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12 by Sex, Age, Race, and Baseline IGA Score - Trial SGT-65-05 (ITT; MI[1])

Subgroups (n[E], n[V])	BPO/ATRA Cream (N=290)	Vehicle Cream (N=144)	Difference	95% CI
Sex				
Males (117, 67)	-17.0	-13.4	-3.5	(-6.5, -0.6)
Females (173, 77)	-15.8	-14.8	-1.0	(-3.4, 1.4)
Age (years)				
9-11 (5, 4)	-20.4	-13.0	-10.1	(-13.3, -6.9)
12-17 (133, 60)	-16.3	-13.2	-3.2	(-6.3, -0.2)
18+ (152, 80)	-16.4	-14.4	-1.2	(-3.5, 1.2)
Race				
White (212, 110)	-16.3	-13.5	-2.8	(-5.0, -0.6)
Non-White (78, 34)	-16.5	-15.8	-0.6	(-4.0, 2.7)
Baseline IGA				
3 – Moderate (262, 133)	-15.7	-13.7	-2.0	(-3.9, 0.0)
4 – Severe (28, 10)	-22.7	-19.1	-3.6	(-10.2, 3.0)
Overall	-16.2	-14.1	-2.1	(-3.9, -0.4)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Abbreviations: CI: Confidence Interval; n[E] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Note: Values displayed are the least square (LS) means based on analysis of covariance (ANCOVA) with treatment group as a factor and baseline value as a covariate.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Table 23: Absolute Change in Non-Inflammatory Lesion Counts from Baseline to Week 12 by Sex, Age, Race, and Baseline IGA Score - Trial SGT-65-04 (ITT; MI[1])

Subgroups (n[E], n[V])	BPO/ATRA Cream (N=281)	Vehicle Cream (N=143)	Difference	95% CI
Sex				
Males (106, 60)	-30.0	-17.6	-12.4	(-18.1, -6.7)
Females (175, 83)	-29.5	-21.1	-8.4	(-12.6, -4.1)
Age (years)				
9-11 (5, 4)	-59.2	-19.4	-14.9	(-36.6, 6.8)
12-17 (121, 56)	-30.5	-15.0	-14.1	(-20.0, -8.0)
18+ (154, 83)	-28.6	-21.8	-6.9	(-10.7, -3.1)
Race				
White (194, 109)	-30.8	-19.8	-11.0	(-15.3, -6.7)
Non-White (87, 34)	-27.1	-19.6	-7.5	(-12.7, -2.2)
Baseline IGA				
3 – Moderate (251, 132)	-28.1	-18.1	-10.0	(-13.4, -6.6)
4 – Severe (30, 11)	-44.9	-34.1	-10.8	(-27.0, 5.1)
Overall	-29.7	-19.8	-9.9	(-13.0, -6.8)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Abbreviations: CI: Confidence Interval; n[E] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Note: Values displayed are the least square (LS) means based on analysis of covariance (ANCOVA) with treatment group as a factor and baseline value as a covariate.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Table 24: Absolute Change in Non-Inflammatory Lesion Counts from Baseline to Week 12 by Sex, Age, Race, and Baseline IGA Score - Trial SGT-65-05 (ITT; MI[1])

Subgroups (n[E], n[V])	BPO/ATRA Cream (N=290)	Vehicle Cream (N=144)	Difference	95% CI
Sex				
Males (117, 67)	-24.4	-16.2	-8.1	(-13.5, -2.8)
Females (173, 77)	-24.9	-18.9	-6.1	(-10.1, -2.0)
Age (years)				
9-11 (5, 4)	-27.8	19.0	-47.1	(-85.5, -8.7)
12-17 (133, 60)	-26.4	-17.2	-9.8	(-15.4, -4.2)
18+ (152, 80)	-22.8	-20.4	-2.6	(-6.0, 0.8)
Race				
White (212, 110)	-25.6	-15.8	-9.9	(-13.9, -5.9)
Non-White (78, 34)	-21.7	-24.7	3.0	(-2.2, 8.1)
Baseline IGA				
3 – Moderate (262, 133)	-24.1	-17.6	-6.5	(-9.9, -3.0)
4 – Severe (28, 10)	-30.6	-17.9	-12.7	(-26.2, 0.9)
Overall	-24.2	-17.4	-6.8	(-9.9, -3.7)

[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Abbreviations: CI: Confidence Interval; n[E] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Note: Values displayed are the least square (LS) means based on analysis of covariance (ANCOVA) with treatment group as a factor and baseline value as a covariate.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

8.1.6.2. Results by Center

Trial SGT-65-04 randomized a total of 424 subjects (281 to BPO/ATRA cream and 143 to vehicle cream) from 31 centers in the United States. Trial SGT-54-05 randomized a total of 434 subjects (290 to BPO/ATRA cream and 144 to vehicle) from 31 centers in the United States. The SAP specified a pooling strategy for centers that enrolled less than 15 subjects. These centers were pooled by ordering and combining the smallest with the largest. The process repeated until all centers had at least 15 subjects. For Trial SGT-65-04, 13 out of the 31 centers enrolled less than 15 subjects and the pooling process yielded 23 analysis centers (18 un-pooled and 5 pooled). For Trial SGT-65-05, 14 out of the 31 centers enrolled less than 15 subjects and the pooling process yielded 24 analysis centers (17 un-pooled and 7 pooled).

Figure 7 presents the results for IGA success at Week 12 by analysis centers for Trials SGT-65-04 and SGT-65-05. Figure 8 and Figure 9 present the results for absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 for Trials SGT-65-04 and SGT-65-05, respectively. In both trials, most analysis centers had higher efficacy with BPO/ATRA cream than vehicle cream for all three co-primary efficacy endpoints. Larger deviations from the means are observed in Trial SGT-65-04 compared to Trial SGT-65-05. In addition, it is noted that in Trial SGT-65-05, the vehicle group has better IGA response rates than the active group in 6 analysis centers and similar IGA response rates with the active group in 3 analysis centers (i.e., total of 9 out 24 analysis centers; 154/434 [35%] subjects were enrolled in these analysis centers), but only 2 analysis centers had higher response rates in the vehicle compared to the active group in Trial SGT-65-04. Similarly, the vehicle arm has similar or better results compared

to the active group in 8 analysis centers for the inflammatory lesion counts in Trial SGT-65-05, compared to 5 analysis centers in Trial SGT-65-04 and 8 analysis centers for the inflammatory lesion counts in Trial SGT-65-05, compared to 2 analysis centers in Trial SGT-65-04.

The SAPs specified investigation of the consistency of results across analysis centers by testing the treatment-by-analysis center interaction in the logistic regression model for IGA success and in the ANCOVA model for change in lesion counts. The SAPs also specified evaluation of the interactions prior to pooling (i.e., treatment-by-center interaction). If the interaction was significant at the 0.10 level, the protocol specified a sensitivity analysis where the data were to be analyzed excluding one analysis center (or center) at a time to identify the impact of each analysis center (or center) on the overall results.

For IGA success, the p-values for the treatment-by-analysis center interaction were 0.953 and 0.961 for Trials SGT-65-04 and SGT-65-05, respectively. The p-values for the treatment-by-center interaction for IGA success were 0.990 and 0.978 for Trials SGT-65-04 and SGT-65-05, respectively.

For absolute change in inflammatory lesion counts, the p-values for the treatment-by-analysis center interaction and the treatment-by-center interaction were significant at the 0.10 level (i.e., p-values ≤ 0.06 using ranked analysis) in Trial SG-65-04. Applicant's sensitivity analysis identified three analysis centers with extreme results in inflammatory lesion counts: analysis center #13 (sites 415 and 418), analysis center #17 (site 422) and analysis center #20 (site 427). The removal of these analysis centers did not affect the overall conclusions for the co-primary efficacy endpoints (i.e., p-values remained < 0.001; see also

Table 25). In Trial SG-65-05 no treatment-by-analysis center or treatment-by-center interaction was observed for the inflammatory lesion counts (p=values=0.0334 and 0.095, respectively, using ranked data).

For absolute change in non-inflammatory lesion counts, the p-values for the treatment-by-analysis center interaction were 0.163 and 0.241 for Trials SGT-65-04 and SGT-65-05, respectively, using ranked data. The p-values for the treatment-by-center interaction were 0.336 and 0.341 for the non-inflammatory lesion counts for Trials SGT-65-04 and SGT-65-05, respectively.

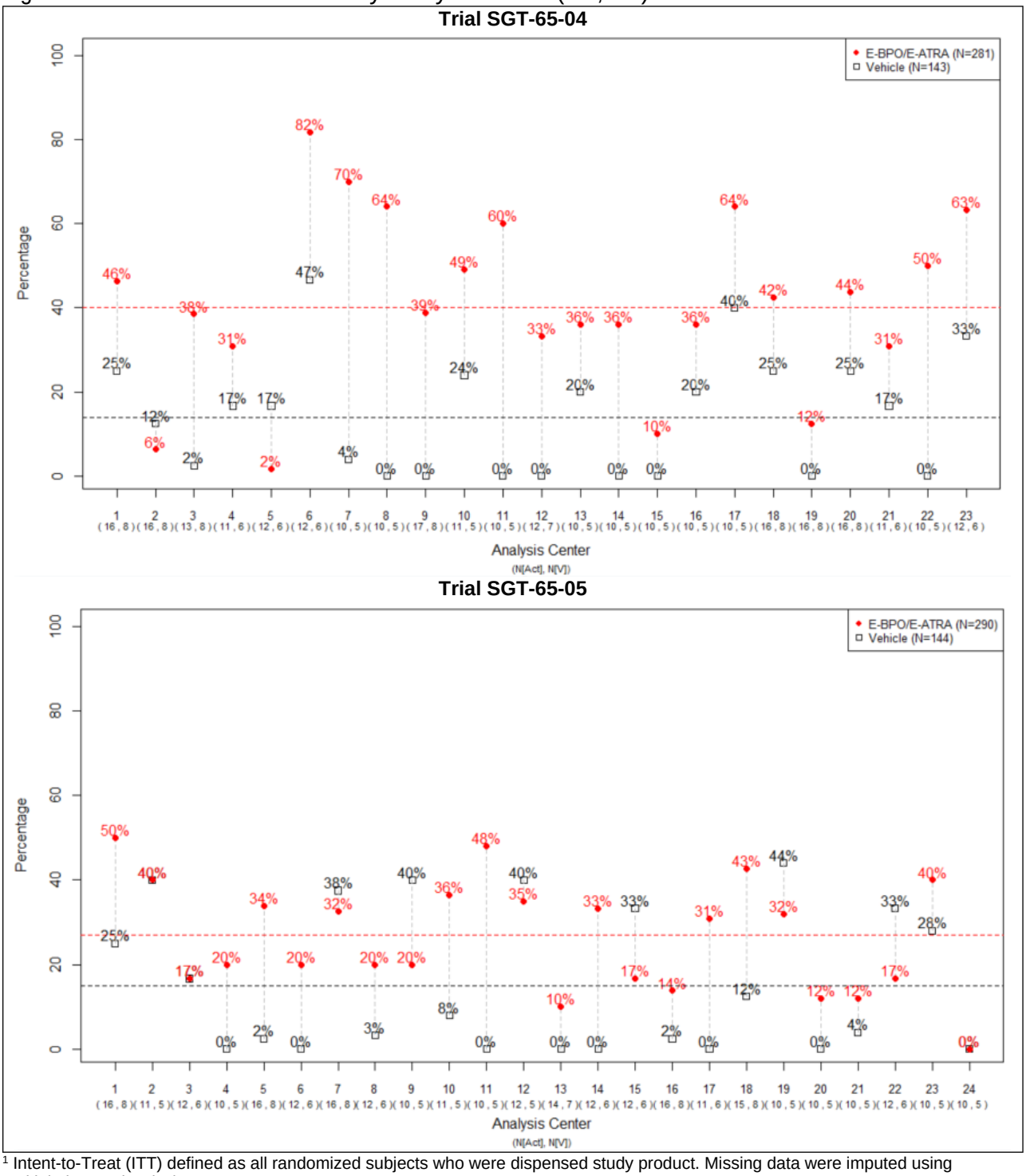
Table 25 presents the co-primary efficacy endpoints results for each identified extreme centers in Trial SG-65-04. The table also presents the results for both the combined extreme centers and with the extreme centers removed. A total of 54 subjects (36 BPO/ATRA and 18 vehicle) are included in the extreme centers, which amounts to approximately 13% of the total sample size in the trial. By removing the extreme centers, the results for all three only slightly decreased in both treatment groups with the treatment effect remaining similar.

Table 25: Sensitivity Analysis for the Co-Primary Efficacy Endpoints at Week 12 Based on Extreme Centers – Trial SG-65-04 (ITT;MI[1])

	IGA Success[2]		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
	BPO/ATRA Cream (N=281)	**Vehicle Cream (N=143)**	**BPO/ATRA Cream (N=281)**	**Vehicle Cream (N=143)**	**BPO/ATRA Cream (N=281)**	**Vehicle Cream (N=143)**
Extreme Centers						
415 (N_A=3, N_V=1)	33.3%	0.0%	-29.0	-20.0	-51.0	-23.0
418 (N_A=7, N_V=4)	37.1%	25.0%	-16.7	-26.0	-21.2	-19.5
422 (N_A=10, N_V=5)	64.0%	40.0%	-25.5	-28.6	-21.5	-36.8
427 (N_A=16, N_V=8)	43.8%	25.0%	-24.4	-31.0	-49.5	-43.6
Results for Extreme Centers						
Response[3,4]	47.2%	27.8%	-23.4	-26.8	-36.8	-35.0
Difference	19.4%		3.4		-1.8	
Results Excluding Extreme Centers						
Response[3,4]	38.9%	12.3%	-21.3	-13.0	-28.7	-17.5
Difference	26.5%		-8.4		-11.2	

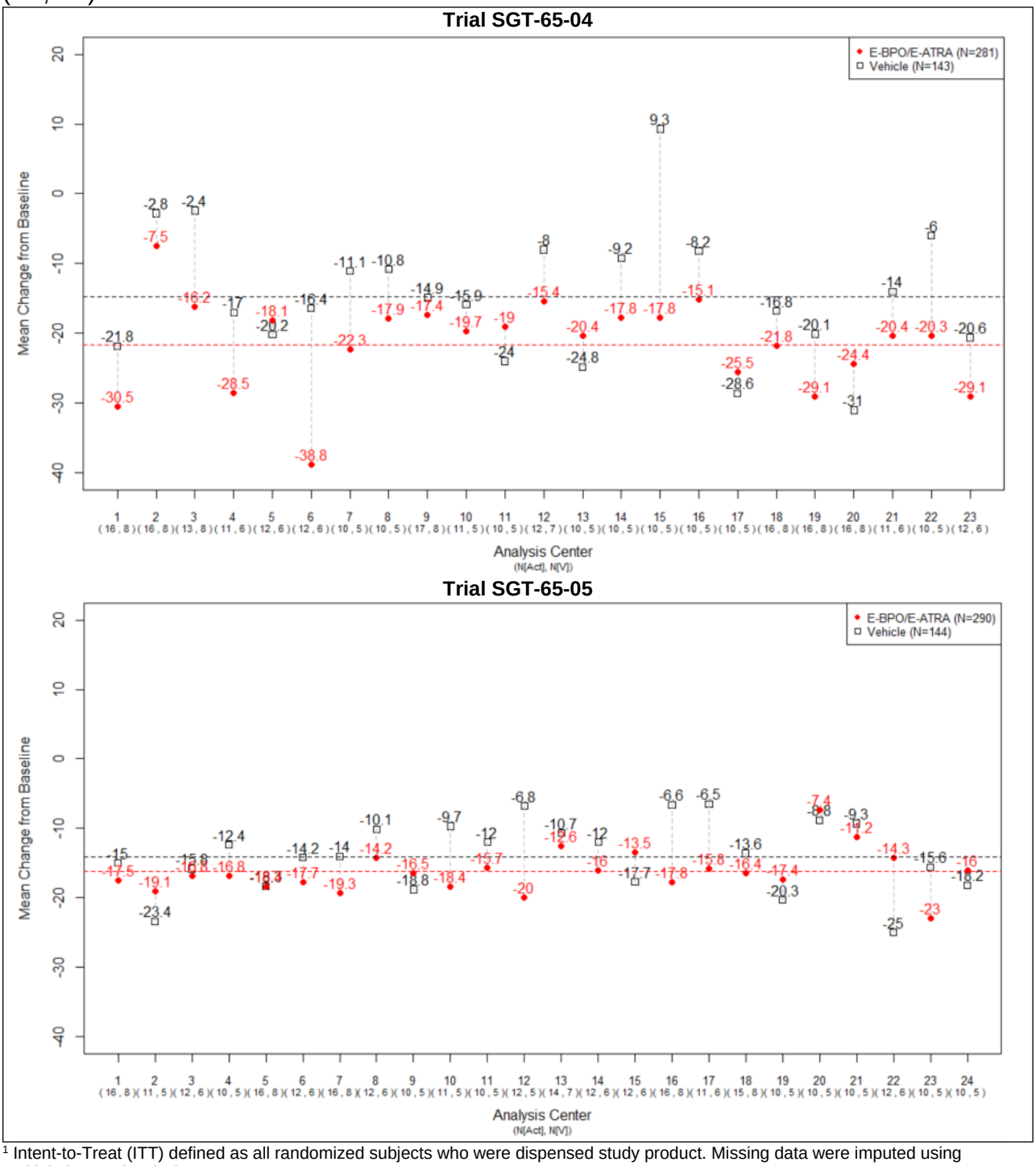
[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
[2] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[3] For IGA success, response is the average over the imputed data sets.
[4] For lesion counts, response is the LS mean. The LS means are based on ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate.

Figure 7: IGA Success at Week 12 by Analysis Center (ITT;MI[1])



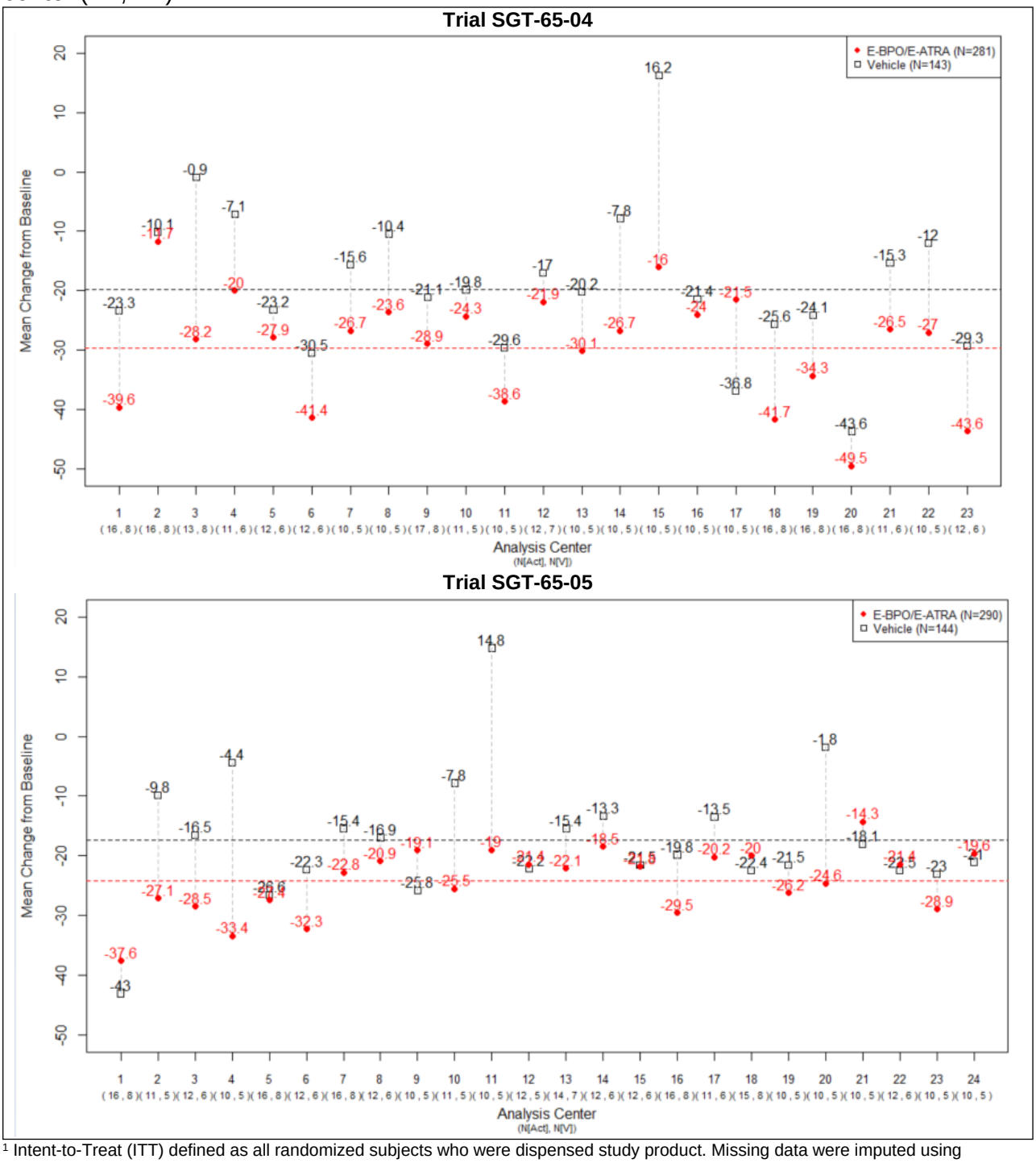
[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
n[Act] = sample size for active (BPO/ATRA) arm, n[V] = sample size for vehicle arm
The dotted horizontal line denotes the overall result for each treatment group (red for BPO/ATRA and black for vehicle).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Figure 8: Absolute Change from Baseline in Inflammatory Lesion Counts by Analysis Center (ITT;MI[1])



[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
n[Act] = sample size for active (BPO/ATRA) arm, n[V] = sample size for vehicle arm
The dotted horizontal line denotes the overall result for each treatment group (red for BPO/ATRA and black for vehicle).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Figure 9: Absolute Change from Baseline in Non-Inflammatory Lesion Counts by Analysis Center (ITT;MI[1])



[1] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
n[Act] = sample size for active (BPO/ATRA) arm, n[V] = sample size for vehicle arm
The dotted horizontal line denotes the overall result for each treatment group (red for BPO/ATRA and black for vehicle).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for Twyneo cream for the treatment of acne vulgaris focuses on pooled data from two phase 3 trials, Study SGT-54-04 and Study SGT-65-05.

Study SGT-65-04 and Study SGT-65-05 were multicenter, randomized, double-blind, parallel-group, vehicle-controlled pivotal studies to evaluate the safety and efficacy of Twyneo cream applied once daily for 12 weeks in subjects with acne vulgaris. These phase 3 studies were of identical design and included a total of 858 subjects (571 Twyneo cream, 287 Vehicle cream) aged 9 years and above with moderate or severe (as defined by IGA score) acne vulgaris who applied the study drug daily for 12 weeks.

The safety population for combined phase 3 trials (ISS) consisted of all subjects in the randomized population who were confirmed to have used the study drug at least once and who provided at least one post-baseline safety evaluation. Overall, 26 subjects were excluded from the safety population because they had no documented use of study drug (14 subjects) or no post-baseline safety assessment (12 subjects). Therefore, the safety population consisted of 832 subjects, 555 in the Twyneo cream group and 277 in the Vehicle cream group. Investigators conducted safety assessments at Baseline, Weeks 2, 4, 8, and 12 visits.

For enrollment, the protocols specified the following key inclusion criteria:

- Male or female, 9 years of age and older
- IGA score of 3 (moderate) or 4 (severe)
- 30 to 150 non-inflammatory lesions (comedones)
- 20 to 100 inflammatory lesions (papules and pustules)
- No more than two facial cysts or nodules (defined as an inflammatory lesion greater than or equal to 5mm in diameter)

The Applicant also submitted supportive safety data from a hase 2 trial (SGT-65-02), a phase 1b PK/Bioavailability maximal use study (SGT-65-03), and 4 dermal safety studies (SGT-65-06, SGT-65-07, SGT-65-08, and SGT-65-09).

To determine the safety profile of Twyneo cream, the review team analyzed the pooled data for exposure, demographics, baseline characteristics, treatment emergent adverse events (TEAEs), SAEs, TEAEs leading to discontinuation, local skin reactions (scaling, erythema, hypopigmentation, and hyperpigmentation), tolerability assessments (itching, burning, and stinging), abbreviated physical examinations, and vital signs.

A TEAE was defined as an AE with an onset on or after the date of the first study product application. All AEs occurring during the pivotal studies were coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology, version 21.0.

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

Because safety data are available for both the LD (Retin-A cream, 0.1%) and benzoyl peroxide, the Applicant requested waivers for the conduct of the following studies to evaluate Twyneo cream:

- Long-term systemic safety study
- Thorough QT Study

During the EOP2 meeting with the Applicant, the Agency agreed that requirements for a long-term safety study for Twyneo cream could be waived if the systemic exposure of tretinoin observed in the maximal use PK study did not exceed that observed for other marketed topical tretinoin products.

During the pre-NDA meeting with the Applicant, the Agency agreed that, based on the MUSE PK study data, the proposal to request a waiver for QT/QTc assessment appeared reasonable but stated that final determination would be made at the time of NDA review. Refer to section 8.2.4 of this review for further details regarding the waiver for the TQT study.

8.2.2. Review of the Safety Database

[Do not insert text here]

Overall Exposure

Overall exposure to Twyneo cream in terms of frequency, duration and target population was adequate for the evaluation of safety. A total of 669 subjects were exposed to the to-be-marketed formulation of Twyneo cream applied once daily for 12 weeks, including 114 subjects in the phase 2 trial (SGT-65-02), and 555 in the combined phase 3 trials. The extent of exposure for the combined phase 3 trials is summarized in the following table:

Table 26: Summary of Extent of Exposure, SGT-65-04 and SGT-65-05 Pooled (Safety Population)

Exposure Parameter	**Twyneo Cream (N=555)**	**Vehicle Cream (N=277)**
Total Number of Days of Exposure		
N	532	269
Mean (SD)	80.2 (15.40)	83.6 (5.71)
Median	84.0	84.0
Minimum to Maximum	5 to 89	27 to 89
Total Number of Applicatons		
N	532	269
Mean (SD)	76.7 (17.53)	71.5 (7.56)
Median	83.0	83.0
Minimum to Maximum	2 to 106	24 to 105

Exposure Parameter	Twyneo Cream (N=555)	Vehicle Cream (N=277)
Total Number of Missed Applications		
N	532	269
Mean (SD)	3.9 (6.92)	2.4 (4.57)
Median	1.0	0.0
Minimum to Maximum	0 to 57	0 to 40
Compliant[a]		
N	532	269
Yes	487 (91.5%)	265 (98.5%)
No	45 (8.5%)	4 (1.5%)

[a] A subject was considered compliant with the dosing regimen if the subjects applied 80-120% of the expected number of applications and did not miss more than 5 consecutive applications while enrolled in the study.
Source: NDA 214902, Adaptped from ISS, Table 14.3.0.1

Adequacy of the safety database:

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

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

Table 27: Demographic Characteristics of Subjects, SGT-65-04 and SGT-65-05 Pooled (Safety Population)

Characteristic	Twyneo Cream (N = 555) n (%)	Vehicle Cream (N = 277) n (%)	Total (N = 832) n (%)
Age			
Median (SD)	20.4 (7.80)	20.8 (7.79)	20.6 (7.79)
Median	18.0	18.0	18.0
Minimum to maximum	10 to 67	9 to 57	9 to 67
< Median (18 years)	260 (46.8)	123 (44.4)	383 (46.0)
≥ Median (18 years)	295 (53.2)	154 (55.6)	449 (54.0)
9-11 years	10 (1.8)	7 (2.5)	17 (2.0)
12-17 years	250 (45.0)	116 (41.9)	366 (44.0)
18-30 years	239 (43.1)	123 (44.4)	362 (43.5)
≥ 31 years	56 (10.1)	31 (11.2)	87 (10.5)
Sex, n (%)			
Male	216 (38.9)	124 (44.8)	340 (40.9)
Female	339 (61.1)	153 (55.2)	492 (59.1)
Ethnicity, n (%)			
Hispanic or Latino	179 (32.3)	96 (34.7)	275 (33.1)
Not Hispanic or Latino	374 (67.4)	179 (64.6)	553 (66.5)
Not Reported/Unknown	2 (0.4)	2 (0.7)	4 (0.5)
Race, n (%)			
American Indian or Alaska Native	3 (0.5)	3 (1.1)	6 (0.7)

Characteristic	Twyneo Cream (N = 555) n (%)	Vehicle Cream (N = 277) n (%)	Total (N = 832) n (%)
Asian	37 (6.7)	16 (5.8)	53 (6.4)
Black or African American	104 (18.7)	37 (13.4)	141 (16.9)
Native Hawaiian/Other Pacific Islander	2 (0.4)	3 (1.1)	5 (0.6)
White	394 (71.0)	210 (75.8)	604 (72.6)
Multiple/Other	15 (2.7)	8 (2.9)	23 (2.8)

Source: Applicant's submission, Section 2.7.4, Table 2.7.4-10 (adapted from ISS, Table 14.1.1.3)

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

[Do not insert text here]

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of Twyneo cream and provides sufficient information to adequately label this product. There were no significant deficiencies discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

The phase 3 trials defined an adverse event (AE) as "any untoward medical occurrence in a subject administered a medicinal product and of which did not necessarily have to have a causal relationship with this treatment. An adverse event could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product."

A serious adverse event (SAE) was defined as an adverse event that resulted in any of the following outcomes:

- Death
- Life-threatening event (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It did not include an event that, had it occurred in a more severe form, might have caused death.
- Required in-patient hospitalization or prolongs hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Other AEs that could be considered serious based upon appropriate medical judgment, could jeopardize the subject and could require medical or surgical intervention to prevent one of the outcomes listed above.

An immediately reportable AE (IRAE) was defined as "any SAE or any AE that necessitated discontinuation of study product, including pregnancy." An unexpected AE was defined as "any

adverse drug experience for which the specificity or severity was not consistent with the currently approved product labeling (package insert) for the study product, the Investigator's Brochure, or as described in the clinical protocol and consent materials."

AE reporting began from the date of signing of informed consent/assent. At each study visit, the investigator evaluated subjects for AEs by asking a non-specific question to avoid bias (e.g., "How have you been feeling since your last visit?"), by observation or by documenting spontaneous or directly elicited responses. Investigators recorded the seriousness, expectedness, intensity/severity, and relatedness of the event to the study product or procedure in the case report form (eCRF.)

Investigators categorized the severity of the AE according to the following criteria:

- Mild: AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.
- Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Severe: AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Investigators also assessed the relationship of the AE to the treatment with the study drug using the following criteria:

- Definitely – The AE:
    - follows a reasonable temporal sequence from study product administration.
    - abates upon discontinuation of the study product (de-challenge).
    - is confirmed by reappearance of the reaction on repeat exposure.

- Probably – The AE:
    - follows a reasonable temporal sequence from study product administration.
    - abates upon discontinuation of the study product (de-challenge).
    - cannot be reasonably explained by the known characteristics of the subject's state.

- Possible – The AE:
    - follows a reasonable temporal sequence from study product administration.
    - but that could readily be produced by several other factors.

- Unlikely – The AE:
    - does not follow a reasonable temporal sequence from the time of study drug administration; and
    - was likely produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy but for which relationship could not be definitely ruled out.

- Not related – The AE:
  - does not have a reasonable temporal association with the administration of study product.
  - has some other obvious explanation for the event.

Routine Clinical Tests

Investigators monitored the safety of Twyneo cream by documenting AEs, cutaneous safety assessments (application site dryness and scaling) and local tolerability (application site itching and burning/stinging) at Baseline, Weeks 2, 4, 8 and 12. In addition, investigators recorded findings from brief physical examinations (heart, lungs, abdomen) with vital signs (blood pressure, oral temperature, heart rate and respiratory rate) at Baseline and Week 12 and concomitant medications at all visits. In view of the limited systemic absorption and known safety profile, routine laboratory testing was not included in the protocol. However, investigators performed urine pregnancy testing at Screening, Baseline, Weeks 2, 4, 8 and 12. Systemic adverse events were not anticipated with topical application of Twyneo cream.

8.2.4. Safety Results

[Do not insert text here]

Deaths

Across eight clinical studies, 1 death was reported in the photoallergenicity patch testing Study SGT-65-09.

Subject (b) (6): Myocardial Infarction
This subject was a 62-year-old white female of not Hispanic or Latino ethnicity with a Fitzpatrick Skin Type of II. Her medical history included a total hysterectomy (b) (6) abdominal pain (b) (6), cholecystectomy (b) (6), torn left meniscus (b) (6), left meniscus surgery (b) (6) (b) (6) torn right meniscus (b) (6) and meniscus surgery (b) (6) Subject No. (b) (6) had no prior or concomitant medications. The subject had a heart attack on (b) (6) (Day 2). The SAE was severe and led to the subject's death. The subject's last study visit was (b) (6) (b) (6) (Day 1). Last contact was (b) (6) (Day 4). The event leading to death was a myocardial infarction (severe) and was considered not related to the study drug.

Reviewer's Comment: This reviewer agrees with the assessment that this death does not appear to be related to the investigational product, particularly since the exposure to the investigational product was limited to small patch testing for photoallergy. Fatal outcomes reported for topical acne products, including those with these two active ingredients with a long history of clinical use, are very rare and likely represent random concomitant events.

No additional deaths were reported across the Twyneo cream development program, and no deaths were reported in the pivotal phase 3 studies.

Serious Adverse Events

Combined Trials SGT-65-04 and SGT-65-05 (ISS):
In the pooled phase 3 trials, SGT-65-04 and SGT-65-05, four non-fatal SAEs were reported from 2 subjects (0.2%), one in each treatment group. The investigators assessed all 4 SAEs as not related to the study drug or vehicle. One subject in the Vehicle cream group experienced 3 SAEs, reported as the following: severe bipolar II disorder, depression, and conduct disorder. One subject in the Twyneo cream group experienced the SAE of moderate depression. See tabulation below:

Table 28: Serious Adverse Events in Trials SGT-65-04 and SGT-65-05

		Twyneo Cream (N = 555)		Vehicle Cream (N = 277)		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
Psychiatric disorders	Depression	1	0.2%	1	0.4%	2
	Bipolar II disorder	.	.	1	0.4%	1
	Conduct disorder	.	.	1	0.4%	1

Source: Reviewer's JMP Clinical 7.0 Analysis.

The subject narratives for these SAEs are described below:

- Subject (b) (6) was a 13-year-old White, not Hispanic or Latino female with a primary diagnosis of acne vulgaris since (b) (6) who began topical treatment with Twyneo cream, 3%/0.1% on (b) (6) (Day 1). In addition to acne vulgaris, the subject had a medical history of mild hearing loss (since 2006) and suffered from depression and anxiety since (b) (6) Her depression worsened and was recorded as an SAE of moderate depression on (b) (6) (Day 7). She was hospitalized due to the SAE and treated with bupropion hydrochloride. The event was not considered related to study drug and the outcome of this event was reported as recovered/resolved on (b) (6) (Day 10). No changes were made to the study drug dose and the subject completed the study.

- Subject (b) (6) was a 16-year-old White, Black or African American, not Hispanic or Latino male with a primary diagnosis of acne vulgaris since (b) (6) who began topical treatment with vehicle cream on (b) (6) (Day 1). Since (b) (6) the subject suffered from the psychiatric disorders of anxiety, depression, and insomnia for which he received treatment. On (b) (6) (Day 24) the subject experienced the SAEs of severe bipolar II disorder, depression, and conduct disorder. He was hospitalized due to these events and study drug was interrupted. The events were not considered related to study drug and the outcomes of all 3 events were reported as recovered/resolved on (b) (6)

(b) (6) (Day 32). However, the subject continued to suffer of mild bipolar II disorder and conduct disorder; the study drug dose was not changed, and the subject completed the study on Day 86. The subject had, in addition, a medical history of drug hypersensitivity (since (b) (6)) and allergy to arthropod sting (since (b) (6)). Concomitant medications included epinephrine, trazodone, lamotrigine, mirtazapine, and aripiprazole.

Reviewer's Comment: This reviewer agrees with the investigator's assessments that the SAEs either predated the event or were not related to the study drugs. Plausible explanations for the occurrences are the subjects' psychiatric histories.

Phase 1 and 2 Studies

Across the tolerability studies (SGT-65-06, SGT-65-07, SGT-65-08 and SGT-65-09), 1 non-fatal SAE was reported in SGT-65-07. The event was a lower limb fracture (moderate) that resulted in study discontinuation.

In the MUSE PK study (SGT-65-03), no SAEs were reported.

In the phase 2 study (SGT-65-02), 6 subjects (0.9%) experienced 6 individual, non-fatal SAEs, The events were appendicitis (severe) and seizure (moderate), reported by 2 subjects in the benzoyl peroxide 3% group, brain neoplasm (severe), reported by a subject in the tretinoin 0.05% group, ovarian cyst (moderate), reported by a subject in the tretinoin 0.1% group, abscess (moderate), reported by a subject in the tretinoin/benzoyl peroxide, 0.05%/3% group, and ectopic pregnancy (severe), reported by a subject in the tretinoin/benzoyl peroxide, 0.1%/3% group. The SAEs of seizure, brain neoplasm, and ectopic pregnancy resulted in study discontinuation, and the SAE of ovarian cyst resulted in study drug interruption.

None of the SAEs that occurred in the phase 1 and 2 studies were considered by the investigators to be study drug related.

Dropouts and/or Discontinuations Due to Adverse Effects

Combined Trials SGT-65-04 and SGT-65-05 (ISS):

The disposition of all randomized subjects for the combined phase 3 trials is summarized in the following table:

Table 29: Subject Disposition, SGT-65-04 and SGT-65-05 Pooled (Safety Population)

Disposition	**Twyneo Cream (N=571) n (%)**	**Vehicle Cream (N=287) n (%)**	**Total (N=858) n (%)**
Completed Study			
Yes	491 (86)	263 (91.6)	754 (87.9)
No	80 (14)	24 (8.4)	104 (12.1)
Reason for Discontinuation			
Adverse Event	16 (2.8	0	16 (1.9)
Lost to Follow-Up	25 (4.4)	14 (4.9)	39 (4.5)
Lack of Efficacy	0	0	0
Pregnancy	2 (0.4)	0	2 (0.2)
Protocol Violation	2 (0.4)	0	2 (0.2)
Withdrawal by Parent/Guardian	8 (1.4)	1 (0.3)	9 (1)
Withdrawal by Subjects	23 (4.0)	9 (3.1%	32 (3.7)
Study Terminated by Sponsor	0	0	0
Physician Decision	2 (0.4)	0	2 (0.2)
Worsening of Condition	0	0	0
Other	2 (0.4)	0	2 (0.2)

Source: Applicant's submission, ISS, Table 14.0.1

A greater proportion of subjects withdrew from the trial due to AEs in the Twyneo cream group (2.8%) compared with the vehicle group (0%). The most reported reason in each study drug group for discontinuation was being lost to follow-up or withdrawal by subject (4.4% and 4.0%, respectively, in the Twyneo cream group and 4.9% and 3.1%, respectively, in the Vehicle cream group).

In the safety analysis set (ISS), the TEAEs leading to discontinuation that were more common in the Twyneo cream group than the Vehicle cream group were application site pain (2.7% versus 0), application site exfoliation (0.9% versus 0), application site dryness (0.7% versus 0), application site erythema (0.7% versus 0), and application site pruritis (0.7% versus 0). The TEAEs related to the study drug (ARs) leading to discontinuation are summarized according to the SOC and PT in the following table:

Table 30: Treatment-Emergent Adverse Reactions leading to Discontinuation, SGT-65-04 and SGT-65-05 Pooled (Safety Population)

		Twyneo Cream (N = 555), n (%)		Vehicle Cream (N = 277), n (%)	
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**
General disorders and administration site conditions	Application site pain	15	2.7%	.	.
	Application site exfoliation	5	0.9%	.	.
	Application site dermatitis	3	0.5%	1	0.4%
	Application site	4	0.7%	.	.

		Twyneo Cream (N = 555), n (%)		Vehicle Cream (N = 277), n (%)	
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**
	dryness				
	Application site erythema	4	0.7%	.	.
	Application site pruritus	4	0.7%	.	.
	Application site discolouration	1	0.2%	.	.
	Application site irritation	1	0.2%	.	.

Source: Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Action Takne with Study Treatment = DRUG WITHDRAWN and Causality = PROBABLY, DEFINITELY.

Phase 1 and 2 Studies

In the tolerability studies, between 89.5% and 97.0% of the subjects completed the studies. The most reported reason across studies for discontinuation, if any, was subject request (range = 0.0% and 10.5%).

In the MUSE PK study, 96.8% of the subjects completed the study, including 97.1% of the subjects in the tretinoin/benzoyl peroxide cream group, and 96.3% of the subjects in the Retin-A cream, 0.1% group. Of the 2 subjects who discontinued, 1 subject was lost to follow-up in the tretinoin/benzoyl peroxide cream group, and 1 discontinued due to withdrawal by subject in the Retin-A cream, 0.1% cream group.

In the phase 2 study, 74.6% to 85.7% of the subjects in across study drug groups completed the Study. The most common reasons for subject discontinuation were being lost to follow-up (4.9% to 13.9% across study drug groups), withdrawal by subject (4.2% to 6.6% across study drug groups), and AEs (0.0% to 4.2% across study drug groups).

Significant Adverse Events

Severe TEAEs

In the combined phase 3 trials (ISS), a total of 6 subjects (0.7%), 5 (0.9%) in the Twyneo cream and 1 (0.4%) in the Vehicle cream group, experienced at least 1 severe TEAE. Application site pain occurred in 4 (0.7%) subjects, and application site pruritis occurred in 2 (0.4% subjects); these were the only severe TEAEs in the Twyneo cream group that were deemed related to the study drug by the investigators occurring in > 1 subject. Severe TEAEs deemed related to the study drug are summarized in the table below:

Table 31: Severe Treatment-Emergent Adverse Reactions, SGT-65-04 and SGT-65-05 Pooled (Safety Population)

		Twyneo Cream (N = 555)		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Total**
General disorders and administration site conditions	Application site pain	4	0.7%	4
	Application site pruritus	2	0.4%	2
	Application site dryness	1	0.2%	1
	Application site exfoliation	1	0.2%	1

Source: Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Causality = POSSIBLE, PROBABLY, DEFINITELY and Severity/Intensity = SEVERE.

Human Reproduction and Pregnancy

No pregnancies were reported in the tolerability or MUSE PK studies. In the phase 2 study (SGT-65-02), 1 subject reported a positive urine pregnancy test result after experiencing an SAE of severe ectopic pregnancy on Day 69 of treatment; the SAE was reported as not related to the study drug. Diagnostic laparoscopy with right salpingectomy was peformed. Study medication was withdrawn, and the subject was discontinued from the study on Day 74.

In the pivotal phase 3 studies, 2 subjects (1 in each study) had positive urine pregnancy test results. Both subjects with positive test results were in the Twyneo cream group and both discontinued the respective studies due to their pregnancies. One subject was lost to follow-up in SGT-65-05, and thus the outcome of her pregnancy is unknown. The subject in SGT-65-04 gave birth to a healthy baby following an unremarkable pregnancy; no complications associated with childbirth were reported.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs in the Combined Trials SGT-65-04 and SGT-65-05 (ISS)

In the phase 3 Trials, SGT-65-04 and GT-65-05, a greater proportion of subjects experienced TEAEs in the Twyneo cream group compared with the Vehicle cream group. The incidence of TEAEs in the Twyneo cream group was 137/555 (24.7%), compared to 33/277 (11.9%) in the Vehicle cream group.

Most TEAEs that occurred in ≥ 1% of subjects in the Twyneo cream group were associated with application site reactions (included in the SOC of general disorders and administration site conditions) and occurred at higher frequencies than in the Vehicle cream group. The results are summarized in the following table:

Table 32: Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥ 1% of the Subjects in Either Treatment Group (Safety Population)

System Organ Class Preferred Term	Twyneo Cream (N = 555) n (%)	Vehicle Cream (N = 277) n (%)	P-Value
General disorders and administration site conditions	97 (17.5)	8 (2.9)	<0.001
Application site pain	60 (10.8)	1 (0.4)	<0.001
Application site dryness	27 (4.9)	1 (0.4)	<0.001
Application site exfoliation	23 (4.1)	0	<0.001
Application site erythema	22 (4.0)	0	<0.001
Application site dermatitis	9 (1.6)	1 (0.4)	0.178
Application site pruritis	7 (1.3)	0	0.102
Application site irritation	6 (1.1)	1 (0.4)	0.435
Infections and infestations	28 (5.0)	14 (5.1)	1.000
Upper respiratory tract infection	7 (1.3)	5 (1.8)	0.547
Injury, poisoning and procedural complications	9 (1.6)	3 (1.1)	0.760
Psychiatric disorders	1 (0.2)	3 (1.1)	0.110

Source: Applicant's submission, ISS, Table 14.3.1.2.2.1.1

Adverse Reactions in the Combined Trials SGT-65-04 and SGT-65-05 (ISS)

Adverse Reactions (ARs) occurred at a higher frequency in the Twyneo cream group (16.2%) compared to the vehicle cream group (1.8%). The results are summarized in the following table:

Table 33: Treatment-Emergent Adverse Reactions Occurring in ≥ 1% of the Subjects in Either Treatment Group (Safety Population)

System Organ Class Preferred Term	Twyneo Cream (N = 555) n (%)	Vehicle Cream (N = 277) n (%)
General disorders and administration site conditions	90 (16.2)	5 (1.8)
Application site pain	59 (10.6)	1 (0.4)
Application site dryness	27 (4.9)	1 (0.4)
Application site exfoliation	23 (4.1)	0
Application site erythema	22 (4)	0
Application site dermatitis	7 (1.3)	1 (0.4)
Application site pruritis	7 (1.3)	0
Application site irritation	6 (1.1)	1 (0.4)

Source: Applicant's submission, Section 2.7.4, Table 2.7.4-18, adapted from ISS Table 14.3.1.2.4

Reviewer's comment: The higher incidence of application site-related ARs in subjects treated with Twyneo cream, compared to subjects treated with vehicle cream, is consistent with the known ARs associated with the use of topical retinoid and benzoyl peroxide products. This reviewer agrees with the inclusion of the Table of ARs in Section 6.1 of the Twyneo label.

Laboratory Findings

No clinical laboratory evaluations were conducted in the tolerability and pivotal phase 3 studies; however, clinical laboratory evaluations were conducted in the MUSE PK and phase 2 studies. In both studies, the laboratory parameters included those associated with hematology assays, blood chemistry, and urinalyses. All clinical studies required urine pregnancy testing for all premenarchal females and females of child-bearing potential.

Combined Trials SGT-65-04 and SGT-65-05 (ISS)
Urine pregnancy testing was conducted at Screening, Baseline, Week 2, Week 4, Week 8 and Week 12. In the pivotal phase 3 studies, 2 subjects (1 in each study) had positive urine pregnancy test results. Both subjects with positive test results were in the Twyneo cream group, and both discontinued the respective studies due to their pregnancies. One subject was lost to follow-up in SGT-65-05, and the outcome of her pregnancy is unknown. The subject in SGT-65-04 gave birth to a healthy baby following an unremarkable pregnancy; no complications associated with childbirth were reported.

MUSE PK Study (SGT-65-03)
Specimens for chemistry and hematology laboratory tests were collected at Baseline and Day 17. Overall, no safety signals or trends in clinical laboratory outcomes were observed for any of the study drug groups at the end of the dosing period (Day 17). No pregnancies were reported in this study.

Phase 2 Study (SGT-65-02)
Speciments for chemistry and hematology laboratory tests, as well as urinalyses, were collected at Baseline, Week 8 and Week 12 in this study. No safety signals or trends in clinical laboratory outcomes were observed for any of the study drug groups at Week 8 or Week 12. One subject reported a positive urine pregnancy test result after experiencing an SAE of severe ectopic pregnancy on Day 69 of treatment; the SAE was reported as not related to the study drug. Diagnostic laparoscopy with right salpingectomy was peformed. Study medication was withdrawn, and the subject was discontinued from the study on Day 74.

Tolerabillity Studies
No pregnancies were reported in these studies.

Vital Signs

Combined Trials SGT-65-04 and SGT-65-05 (ISS)
Vital sign measurements (temperature, respiratory rate, heart rate, systolic and diastolic blood pressures) were recorded at Baseline and Week 12. Most subjects had normal vital sign measurements throughout the trial. No meaningful changes were observed in either study drug group, and the mean changes from Baseline at Week 12 were similar between study drug groups.

MUSE PK Study (SGT-65-03)
Vital sign measurements (temperature, respiratory rate, heart rate, systolic and diastolic blood pressures) were recorded at Baseline and Day 17. Overall, no clinically significant abnormal findings were reported, and the mean changes from Baseline at Day 17 were similar between study drug groups.
Phase 2 Study (SGT-65-02)
No clinically significant changes in vital signs were reported in the phase 2 study.

Tolerabillity Studies
Vital signs were not measured in the tolerability studies (SGT-65-06, SGT-65-07, SGT-65-08 and SGT-65-09).

Reviewer's comment: Specific labeling related to laboratory or vital signs assessments is not recommended.

Electrocardiograms (ECGs)

Combined Trials SGT-65-04 and SGT-65-05 (ISS)
ECGs were not performed in either of the pivotal phase 3 trials

MUSE PK Study (SGT-65-03)
ECGs were performed at Baseline and Day 17 following single and multiple topical administration of the Twyneo cream and the RLD, Retin-A cream, 0.1%. Overall, no meaningful changes were observed in either study drug group after 14 days of treatment, and the investigator's and cardiologist's evaluation noted no major shifts in the overall interpretation of the ECG results from baseline (i.e., the last ECG assessment prior to the first application of study drug) to Day 17. Most subjects had normal ECG interpretation at both time points, except for 2 subjects from the Retin-A cream, 0.1% group who had an abnormal but not clinically significant ECG results at Day 17 after a normal screening ECG results were recorded at Baseline. Therefore, following single and repeat applications of Twyneo cream, no adverse safety signals or trends were observed in the ECG results.

Phase 2 Study (SGT-65-02)
In this study, ECGs were performed at Baseline, Week 2, and Week 12. Overall, most subjects had normal ECG results at Baseline and Week 12. No meaningful changes in mean values for ECG parameters were observed from Baseline at Week 2 or Week 12 in either study drug group, and the investigator's and cardiologist's evaluation noted no major shifts in the overall interpretation of the ECG results from Baseline to Week 12.

Two subjects had one or more abnormal ECG findings that were considered clinically significant. One subject in the benzoyl peroxide cream, 3% group had an abnormal ECG at Baseline that was considered to be a Brugada pattern. At Week 2, an ST elevation was reported and premature ventricular complexes were found. The subject discontinued the study due to this AE

of an abnormal ECG. The other subject in the tretinoin/benzoyl peroxide cream, 0.05%/3% group had an ECG finding that was clinically significant at Week 2, but the specific abnormality was not reported. At the other visits, the ECG was normal.

Tolerabillity Studies

ECGs were not performed in the tolerability studies (SGT-65-06, SGT-65-07, SGT-65-08 and SGT-65-09).

QT

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

- Based on the documented clinical history of topical use of both benzoyl peroxide and tretinoin in humans, with no noted cardiovascular safety signals, there is negligible risk of any cardiac adverse events, including QT prolongation, after topical administration of Twyneo cream for the treatment of acne.
- The Applicant conducted a 13-week dermal toxicity study followed by a 4-week recovery period using male and female Göttingen minipigs (n = 6/sex/group) using tretoinoin/benzoyl peroxide cream, 0.1%/6% (Study No. 1256-012). Additional groups included an untreated control, placebo control, tretinoin, 1.0% alone and benzoyl peroxide, 6% alone. The study included a toxicokinetic evaluation that utilized validated bioanalytical methods to detect benzoyl peroxide absorption (measured as benzoic acid) and tretinoin absorption (measured as all-trans 4-keto-retinoic acid, 4-keto-13-cis retinoic acid, 13-cis-retinoic acid and all-trans retinoic acid). The concentrations of benzoic acid, 13-cis-retinoic acid, 4-keto-13-cis-retinoic acid, all-trans retinoic acid and all-trans-4-keto retinoic acid were below the lower limits of quantitation in most samples. There were insufficient measurable concentrations to be able to calculate toxicokinetic parameters. The lower limit of quantitation was 1 ng/mL for each of the retinoic acid congeners and 48.2 ng/mL for benzoic acid (reaction by-product/metabolite of benzoyl peroxide). It was concluded that there was negligible systemic exposure to benzoic acid and retinoic acid congeners after twice daily application of 15 mg/kg benzoyl peroxide/0.25 mg/kg tretinoin in the benzoyl peroxide/tretinoin cream. Due to the lack of systemic exposure, no further pharmacokinetic or metabolism studies were conducted.
- In a 7-day non-GLP dermal tolerability study [MPI Study No. 1161-001 (cross reference is made to NDA (b) (4), Module 4.2.3.2)], one male and one female Gottingen minipig were administered benzoyl peroxide cream once per day on four separate 25 cm^2 sites at concentrations of 0%, 5%, 7% and 10%. No irritation, clinical signs, body weight or gross pathology changes were noted at any concentration.
- The Applicant conduct a GLP-compliant 13-week dermal toxicity study [MPI Study No. 1161-002 (cross reference is made to NDA (b) (4) Module 4.2.3.2)] in Gottingen minipigs (n = 4/sex/group) using four groups: untreated control, Vehicle (placebo), benzoyl peroxide cream, 5% (clinical concentration), and benzoyl peroxide cream, 10%

(maximum feasible concentration). No evidence of systemic toxicity was observed at any dose and mild irritation was reported in some animals treated with the 5% and 10% formulations, which resolved after approximately 5 weeks. No increase in plasma levels of benzoic acid above endogenous or background levels was observed with either the 5% or 10% formulations. The no-observed-adverse-effect-level (NOAEL) was 10%.

- In the MUSE PK Study (SGT-65-03), PK parameters of tretinoin and its metabolites (all-trans 4-keto retinoic acid, 9-cis retinoic acid, 4-keto 13-cis retinoic acid, and 13-cis retinoic acid) were determined after once a day topical application for 14 days Twyneo cream versus the Listed Drug (Retin-A 0.1% cream). In this study, the Day 2 and Day 14 plasma concentrations (trough) of tretinoin and its metabolites were also determined after a once a day application of Twyneo cream. The study results demonstrate that the PK parameters (Cmax and AUC) were not significantly different when comparing Twyneo cream with Retin-A®. Based on the 90% confidence interval (CI) approach, many of the values of the confidence interval for Cmax and AUC of tretinoin and the metabolites in adults and adolescents demonstrated equivalence for E-BPO/E-ATRA cream and Retin-A®, but not all. Overall, in the cases where the bioequivalence criteria were not met, the exposure following the application of Twyneo cream was lower than the exposure following the application of Retin-A®. Furthermore, the study demonstrated that the PK parameters (Cmax and AUC) were not significantly different following Twyneo cream or Retin-A® with the exception for a significant difference observed in exposure between adults and adolescents treated with Retin-A® for 14 days.
- In the phase 2 study (SGT-65-02), blood tests and electrocardiogram (ECG) monitoring were performed. There were no apparent differences in mean changes from Baseline to Week 8 and 12 in any of the hematological and clinical chemistry test results among the six treatment groups. There were no clinically significant abnormalities in ECGs in the study.
- Topical benzoyl peroxide and tretinoin have been marketed for over 50 and 30 years, respectively. There have been no long-term safety issues reported with the use of benzoyl peroxide or tretinoin for the treatment of acne. Benzoyl peroxide at concentrations of 2.5 to 10% is GRASE as an active ingredient in OTC topical products for the treatment of acne. Tretinoin is a naturally occurring metabolite of Vitamin A, and the plasma levels after topical tretinoin are not significantly higher than endogenous levels.

During the pre-NDA meeting held on March 16, 2020, the Agency informed the Applicant that, based on the results of the MUSE PK study, a waiver request for QT/QTc assessments was reasonable. The Agency stated that a final determination regarding the waiver request would be made at the time of NDA review.

Reviewer's Comment: A consultation was requested from the Division of Cardiovascular and Renal Products QT-Interdisciplinary Review Team (QT-IRT) on November 3, 2020 regarding the Applicant's thorough QT (TQT) waiver request for NDA 214902. In a memorandum dated

February 1, 2021, the QT-IRT determined that a TQT study was not required. The following comment was made by the QT-IRT reviewer, Girish K Bende:

"The Sponsor's proposed rationale for not conducting the thorough-QT study appears reasonable. In addition, the submitted safety ECG data do not indicate any unexpected or important effects of Twyneo ream on the QTc interval at the proposed therapeutic dose."

No labeling additions appear warranted for cardiovascular effects.

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

Cutaneous Safety and Tolerability Assessments

Cutaneous safety evaluations included assessment of erythema, scaling, pigmentation and dryness. Cutaneous tolerability evaluations included assessment of itching, burning and stinging at the drug application site. The following grading scales were used (Refer to Study SGT-65-04 Protocol, Sections 14.1 and 14.2):

Safety:

Erythema:

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

Scaling:

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

Pigmentation:

- 0 – None No disturbance of pigmentation
- 1 – Mild Barely perceptible pigment change
- 2 – Moderate Markedly darker or lighter
- 3 – Severe Complete de-pigmentation or severe hyperpigmentation

Dryness:

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

Local Tolerability:

Itching:

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

Burning:

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

Stinging:

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

The protocol did not categorize application site reactions (erythema, scaling, dryness, pigmentation, itching, burning, and stinging) as adverse events unless they resulted in temporary discontinuation of the study product, discontinuation of the subject from the study, or the use of a new concomitant medication in order to treat the event. These events were distinctly captured and reported separately.

Combined Trials SGT-65-04 and SGT-65-05 (ISS)

Subjects treated with Twyneo cream had transient increases in the severity of local cutaneous signs or symptoms that peaked at Week 2 and decreased thereafter. Overall, the incidence of local cutaneous reactions was higher amongst subjects treated with Twyneo cream compared with subjects treated with Vehicle cream. Most assessments of local tolerability were mild or moderate in severity and improved from Baseline to Week 12. Cutaneous safety and tolerability results for the combined phase 3 trials at Baseline, Week 2, and Week 12 are summarized in the following table:

Table 34: Incidence of Local Mild, Moderate or Severe Cutaneous Irritation at Baseline, Week 2, and Week 12 (Safety Population)

Dermal Reaction	**Twyneo Cream N=555 n (%)**			**Vehicle Cream N=277 n (%)**		
	Baseline (N=555)	Week 2 (N=436)	Week 12 (N=494)	Baseline (N=277)	Week 2 (N=277)	Week 12 (N=264)
Erythema	247 (44.5)	281 (52.3)	198 (40.1)	117 (42.2)	107 (38.6)	92 (34.9)
Scaling	107 (19.3)	219 (40.9)	94 (19)	53 (19.2)	39 (14.1)	36 (13.7)
Pigmentation	223 (40.2)	189 (35.3)	168 (34)	107 (38.6)	87 (31.4)	82 (31)
Dryness	132 (23.8)	274 (51.1)	138 (28)	56 (20.3)	64 (23.1)	50 (19)
Itching	97 (17.5)	114 (21.3)	64 (13)	62 (22.4)	46 (16.6)	30 (11.4)
Burning	34 (6.1)	177 (33.1)	40 (8.1)	20 (7.2)	29 (10.5)	11 (4.2)
Stinging	35 (6.3)	118 (22.1)	27 (5.5)	21 (7.6)	22 (7.9)	8 (3)

Source: Reviewer's table, adapted from ISS Table 14.3.1.1

MUSE PK Study (SGT-65-03)

In the MUSE PK study, cutaneous safety and tolerability assessments included erythema, scaling, pigmentation, dryness, itching, burning and stinging, graded on a 4-oint scale (0 = none, 1 = mild, 3 = moderate, or 3 = severe), assessed daily from Baseline through Day 17. The frequency of most local skin reactions (except for stinging in the Retin-A group and pigmentation in the Twyneo cream group) increased in both Twyneo cream and Retin-A 0.1% cream treatment groups over the 17-day treatment period. A higher proportion of subjects in the Twyneo cream group experienced dermal reactions of erythema, scaling, dryness, burning, and stinging relative to subjects in the Retin-A group. Cutaneous safety and tolerability results for the MUSE PK study at Baseline and Day 17 are summarized in the following table:

Table 35: Incidence of Local Mild, Moderate or Severe Cutaneous Irritation at Baseline and Day 17 (Study SGT-65-03)

Dermal Reaction	**Twyneo Cream N=35 n (%)**		**Retin-A 0.1% Cream N=27 n (%)**	
	Baseline (N=35)	Day 17 (N=34)	Baseline (N=27)	Day 17 (N=26)
Erythema	0	26 (76.5)	0	16 (61.5)
Scaling	1 (2.9)	21 (61.8)	0	10 (38.5)
Pigmentation	4 (11.4)	3 (8.8)	2 (7.4)	2 (7.7)
Dryness	0	25 (73.5)	0	13 (50)
Itching	0	9 (26.5)	0	7 (26.9)
Burning	0	5 (14.7)	0	1 (3.8)
Stinging	0	1 (2.9)	0	0

Source: Reviewer's table, adapted from Clinical Study Report SGT-65-03, Table 14.3.1.2

Phase 2 Study (SGT-65-02)

In the phase 2 study, most subjects across study drug groups had no erythema (range = 58.8% to 69.1%), no scaling (range = 75.7% to 85.1%), no pigmentation (range = 65.0% to 75.3%), no itching (range = 87.4% to 93.0%), no burning (range = 86.5% to 97.0%), and no stinging

(range = 88.1% to 90.2%) at Week 12 (SGT-65-02 Table 14.3.1.1). Overall, the percentages of subjects with scores equating to none for each parameter were similar across study drug groups and generally slightly higher across study drug groups at Week 12 compared with baseline.

Reviewer's comment: The incidence of cutaneous safety/tolerability ARs was higher for Twyneo cream compared to both vehicle control and the listed drug, Retin-A. These results are expected following treatment with a combination of a topical retinoid and benzoyl peroxide product, both of which are known to cause such reactions individually.

Contact Irritation

The potential of Twyneo cream to induce contact skin irritancy under semiocclusion was evaluated in Study SGT-65-06. Subjects underwent repeated patch applications of Twyneo cream, Vehicle cream, saline, 0.9% and sodium lauryl sulfate, 0.5% for 21 days and yielded a mean (standard deviation, SD) irritation score of 1.59 (0.70), 0.11 (0.39), 0.21 (0.57), and 2.87 (0.10), respectively. The mean irritation score of Twyneo cream was statistically different from those of Vehicle cream ($p < 0.0001$) and saline, 0.9% ($p < 0.0001$), where Twyneo cream was significantly more irritating than both Vehicle cream and saline, 0.9%. There was a statistically significant difference between the mean irritation scores of Twyneo cream and sodium lauryl sulfate, 0.5% ($p < 0.0001$), where sodium lauryl sulfate, 0.5% was significantly more irritating than Twyneo cream. Based on the normalized total irritation score, sodium lauryl sulfate, 0.5% was considered highly irritating, Twyneo cream was considered moderately irritating, and saline, 0.9% and Vehicle cream were considered not irritating. Refer to Section 8.2.8 of this review for additional information regarding Study SGT-65-06.

Contact Sensitization

The potential for Twyneo cream to induce sensitization on healthy skin was evaluated in Study SGT-65-07. In this study, 4 subjects (1.8%), who applied Twyneo cream had a cutaneous response score of 3 during the challenge phase, indicating possible sensitization. None of the subjects in the saline, 0.9% and Vehicle cream groups had cutaneous response scores indicating possible sensitization. Of the 4 subjects with a cutaneous response score of 3, 1 subject was thought to be sensitized and was re-challenged to Twyneo cream. The cumulative mean irritation index was 0.61 for subjects who applied Twyneo cream and 0.01 and 0.04 for subjects who applied saline, 0.9% and Vehicle cream, respectively. There were statistically significant differences between the mean cumulative irritation index of Twyneo cream and Vehicle cream ($p < 0.0001$) and Twyneo cream and saline, 0.9% ($p < 0.0001$) with no significant difference between saline, 0.9% and Vehicle cream ($p = 0.330$). The mean total irritation scores showed similar results. Overall, all 3 products were classified as having no significant irritation; although, the observations of the 1 subject at re-challenge was suggestive of the potential for Twyneo cream to cause hypersensitivity due to its component, benzoyl peroxide. Refer to Section 8.2.8 of this review for additional information regarding Study SGT-65-07.

Reviewer's comment: In the literature, there are rare reports of the use of benzoyl peroxide associated with serious hypersensitivity reactions (FDA Safety Announcement dated June 25, 2014). Therefore, the labeling for Twyneo cream should reflect this risk.

Photoxicity

The phototoxic potential of Twyneo cream was evaluated in Study SGT-65-08 using patch testing followed by UV exposure. In this study, 53.1% of subjects in the Twyneo cream group and 46.9% of subjects in the Vehicle cream group had erythema/edema scores of 1 (mild, but definite erythema/edema) at the irradiated sites; none of the subjects had a reaction at the non-irradiated sites. The mean dermal response score was 0.56 in the Twyneo cream group and 0.48 in the Vehicle cream group for irradiated sites, respectively. For non-irradiated sites, the mean dermal response score was 0.25 in the Twyneo cream group and 0.05 in the Vehicle cream group. Overall, no subject met the criterion of having phototoxicity. The dermal response scores of 1 were considered likely related to irritation from the UV light application itself and to the mild inherent irritation of the study drug products rather than phototoxicity. The scores of 1 seen in the non-irradiated sites are most likely related to the inherent irritation of Twyneo cream and Vehicle cream. Refer to Section 8.2.8 of this review for additional information regarding Study SGT-65-08. Labeling based on precedent product labeling for sun protection will still be recommended.

Photoallergy

The photoallergenic potential of Twyneo cream was evaluated in Study SGT-65-09. Sites treated with Twyneo cream had scores of 1 and a few scores of 2 that were attributed mainly to irritation of the product itself (as supported by similar scores in the irradiated and non-irradiated sites). The investigators determined that there was no evidence of photoallergenicity Twyneo cream based on the results of this study. Refer to Section 8.2.8 of this review for additional information regarding Study SGT-65-09. Labeling based on precedent product labeling for sun protection will still be recommended.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The phase 3 protocol included a patient reported outcome (PRO) measure of the tolerability of treatment with Twyneo cream. The Patient Global Impression of Treatment Side Effects (PGI-SE), which was administered at Weeks 2, 4, 8 and 12, was used to assess the impact of the side effects of treatment. It is a single-item questionnaire that asks respondents to describe how bothered they are "right now" with the acne treatment using a 5-point VRS ranging from "I am not bothered" to "I am very bothered." No primary or secondary endpoints were based on this

PRO, and it wasn't included in the multiplicity testing strategy or proposed product labeling. Therefore, data and endpoints based on this PRO are considered exploratory and will not be included in this review, or recommended for product labeling.

8.2.7. Safety Analyses by Demographic Subgroups

The safety population for the combined phase 3 trials (ISS) included 555 subjects in the Twyneo cream groups and 277 subjects in the vehicle cream groups. For subjects included in the combined phase 3 trials, the Applicant conducted safety analyses based on age category, sex, and race (per 21 CFR 314.50 (d)(5)(vi)(a)), and ethnicity. However, because the trials were not powered for these analyses, the data must be interpreted with caution. Treatment-emergent ARs by demographic subgroups are presented in the following tables by age category, sex, race, and ethnicity.

TEAEs and ARs by Age Group:
Subjects ≥ 9 years of age were included in the phase 3 trials. For assessments of age in the pivotal phase 3 studies, AEs were evaluated within two separate age categories. In the first, the analysis considered subjects who were < 18 years of age (the median age of all subjects) relative to subjects who were ≥ 18 years of age. In the second, the analysis compared subjects who were 9 to 11 years of age with subjects who were 12 to 17 years of age, subjects who were 18 to 30 years of age, and subjects who were ≥ 31 years of age. A summary of the numbers of subjects in each age category by study drug group is depicted in the table below:

Table 36: SGT-65-04 and SGT-65-05 Combined numbers of subjects Evaluated in Each Age Category (Safety Population)

	Twyneo Cream N=555 n (%)	**Vehicle Cream N=277 n (%)**
Age Category 1		
< 18 years	260 (46.8)	123 (44.4)
≥ 18 years	295 (53.2)	154 (55.6)
Age Category 2		
9 to 11 years	10 (1.8)	7 (2.5)
12 to 17 years	250 (45)	116 ((41.9)
18 to 30 years	239 (43.1)	123 (44.4)
≥ 30 years	56 (10.1)	31 (11.2)

Source: Applicant's submission, Section 2.7.4, Table 2.7.4-21, adapted from ISS Tables 14.3.1.2.1.2 and 14.3.1.2.1.3

For the combined phase 3 trials, 28.5% of subjects < 18 years of age and 21.4% of subjects ≥ 18 years of age treated with Twyneo cream reported ≥ 1 TEAE. Of subjects < 18 years of age treated with Twyneo cream, 12 (4.6%) discontinued the study drug due to a TEAE, and 10 (3.8%) discontinued from the trial due to a TEAE. Of subjects ≥ 18 years of age treated with Twyneo cream, 10 (3.4%) discontinued the study drug due to a TEAE, and 8 (2.7%) discontinued from the trial due to a TEAE. One subject < 18 years of age in the Twyneo cream group experienced a single SAE that was unrelated to the study drug. A summary of the ARs for subjects in the combined phase 3 trials by age group is presented in the following tables:

Table 37: Treatment-Emergent Adverse Reactions Occurring in ≥ 2 Subjects in Any Subgroup Treated with Twyneo Cream or Vehicle Cream, by Age Category 1 (Safety Population)

	Age < 18 Years		Age ≥ 18 Years	
Dictionary-Derived Term	**Twyneo Cream (N=260) n (%)**	**Vehicle Cream (N=123) n (%)**	**Twyneo Cream (N=295) n (%)**	**Vehicle Cream (N=154) n (%)**
Application site pain	31 (11.9)	1 (0.8)	28 (9.5)	0
Application site erythema	14 (5.4)	0	8 (2.7)	0
Application site dryness	9 (3.5)	0	18 (6.1)	1 (0.6)
Application site exfoliation	8 (3.1)	0	15 (5.1)	0
Application site irritation	5 (1.9)	0	1 (0.3)	1 (0.6)
Application site dermatitis	3 (1.2)	0	4 (1.4)	1 (0.6)
Application site pruritus	3 (1.2)	0	4 (1.4)	0
Application site swelling	3 (1.2)	0	1 (0.3)	0

Source: Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Causality = POSSIBLE, PROBABLY, DEFINITELY and AGE GROUP 2

Table 38: Treatment-Emergent Adverse Reactions Occurring in ≥ 2 Subjects in Any Subgroup Treated with Twyneo Cream or Vehicle Cream, by Age Category 2 (Safety Population)

	Age 9 – 11 Years		Age 12 – 17 Years		Age 18 – 30 Years		Age ≥ 31 Years	
Dictionary-Derived Term	**Twyneo Cream (N=10) n (%)**	**Vehicle Cream (N=7) n (%)**	**Twyneo Cream (N=250) n (%)**	**Vehicle Cream (N=116) n (%)**	**Twyneo Cream (N=239) n (%)**	**Vehicle Cream (N=123) n (%)**	**Twyneo Cream (N=56) n (%)**	**Vehicle Cream (N=31) n (%)**
Application site pain	3 (30)	0	28 (11.2)	1 (0.8)	23 (9.6)	0	5 (8.9)	0
Application site erythema	5 (50)	0	9 (3.6)	0	8 (3.3)	0	0	0
Application site dryness	1 (10)	0	8 (3.2)	0	16 (6.7)	1 (0.8)	2 (3.6)	0
Application site exfoliation	1 (10)	0	7 (2.8)	0	13 (5.4)	0	2 (3.6)	0
Application site irritation	0	0	5 (2)	0	1 (0.4)	1 (0.8)	0	0
Application site dermatitis	0	0	3 (1.2)	0	4 (1.7)	1 (0.8)	0	0
Application site pruritus	0	0	3 (1.2)	0	3 (1.3)	0	1 (1.8)	0
Application site swelling	0	0	3 (1.2)	0	0	0	0	0

Source: Adapted from ISS (Tables 14.3.1.2.1.2 and 14.3.1.2.1.3) and Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent

events. Additional filter to include Causality = POSSIBLE, PROBABLY, DEFINITELY and AGE GROUP 3

Of note, 3 (1.2%) < 18 years of age and 2 (0.7%) subjects ≥ 18 years of age in the Twyneo cream group experienced application site photosensitivity reactions, compared with 1 (0.8%) subject in the Vehicle cream group, aged < 18 years of age. These events were not considered related to the study drug and were therefore classified as TEAEs rather than treatment-emergent adverse reactions.

Reviewer's comment: The incidence of application site adverse reactions appears higher in the pediatric age groups, although the analyses are limited due to the small sample sizes, especially in the 9 – 11 year age group. The increased frequency of ARs among younger subjects compared with older subjects could be due to the fact that younger, pre-adolescent patients produce less sebum than older patients, rendering their skin more sensitive. Alternatively, this may reflect increased product usage in this age group.

TEAEs and ARs by Sex:
Subjects treated with Twyneo cream in the combined phase 3 trials reported ≥ 1 TEAE in 34/216 (15.7%) of males and 103/339 (30.4%) of females. Female subjects treated with Twyneo cream reported a higher frequency of application site reactions compared to male subjects as presented in the following table.

Table 39: Treatment-Emergent Adverse Reactions Occurring in ≥ 2 Subjects in Any Subgroup Treated with Twyneo Cream or Vehicle Cream, by Sex (Safety Population)

		F		M	
Body System or Organ Class	**Dictionary-Derived Term**	**Twyneo Cream N= 339 n (%)**	**Vehicle Cream N= 153 n (%)**	**Twyneo Cream N= 216 n (%)**	**Vehicle Cream N= 124 n (%)**
General disorders and administration site conditions	Application site pain	46 (13.6)	0	13 (6)	1 (0.8)
	Application site dryness	23 (6.9)	1 (0.7)	4 (1.9)	0
	Application site exfoliation	15 (4.4)	0	8 (3.7)	0
	Application site erythema	15 (4.4)	0	7 (3.2)	0
	Application site dermatitis	6 (1.8)	1 (0.7)	1 (0.5)	0
	Application site pruritis	5 ((1.5)	0	2 (0.9)	0
	Application site irritation	2 (0.6)	1 (0.7)	4 (1.9)	0
	Application site swelling	3 (0.9)	0	1 (0.5)	0

Source: Adapted from ISS (Table 14.3.1.2.1.4) and Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Causality = POSSIBLE, PROBABLY, DEFINITELY and SEX

Of note, 1 male subject (0.5%) and 4 female subjects (1.2%) the Twyneo cream group experienced application site photosensitivity reactions, compared with 1 (0.7%) female subject and no male subjects in the Vehicle cream group. These events were not considered related to the study drug and were therefore classified as TEAEs rather than treatment-emergent adverse

reactions.

Reviewer's comment: TEAEs and ARs occurred with a higher frequency among female subjects treated with Twyneo cream comapared to male subjects. However, meaningful conclusions related to the observed differences cannot not be made due to an approximately 1.4-fold difference in sample sizes between female and male subjects in each study drug group (Twyneo cream: 339 female and 216 male subjects; Vehicle cream: 153 female and 124 male subjects).

TEAEs and ARs by Race:
Subjects treated with Twyneo cream in the combined phase 3 trials with ≥ 1 TEAE included 102/394 (25.9%) of white subjects and 35/161 (21.7%) non-white subjects. No trends were reported for SAEs, severe TEAEs, TEAEs that led to treatment discontinuation, or ARs between white and non-white subjects. A summary of ARs by race is represented n the following table.

Table 40: Treatment-Emergent Adverse Reactions Occurring in **≥** 2 Subjects in Any Subgroup Treated with Twyneo Cream or Vehicle Cream, by Race (Safety Population)

		White		**Non-White**	
Body System or Organ Class	**Dictionary-Derived Term**	**Twyneo Cream N= 394 n (%)**	**Vehicle Cream N= 210 n (%)**	**Twyneo Cream N= 161 n (%)**	**Vehicle Cream N= 67 n (%)**
General disorders and administration site conditions	Application site pain	43 (10.9)	1 (0.4)	16 (9.9)	0
	Application site dryness	19 (4.8)	1 (0.4)	8 (5)	0
	Application site exfoliation	16 (4.1)	0	7 (4.3)	0
	Application site erythema	19 (4.8)	0	3 (1.9)	0
	Application site dermatitis	6 (1.5)	1 (0.4)	0	0
	Application site pruritis	2 (0.5)	0	5 (3.1)	0
	Application site irritation	5 (1.3)	1 (0.4)	0	0
	Application site swelling	3 (0.8)	0	0	0

Source: Adapted from ISS (Table 14.3.1.2.1.6) and Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Causality = POSSIBLE, PROBABLY, DEFINITELY and RACE GROUP 2

Of note, 4 (1%) white subjects and 1 (0.6%) non-white subject in the Twyneo cream group experienced application site photosensitivity reactions, compared with 1 (0.5%) white subject and 0 non-white subjects in the Vehicle cream group. These events were not considered related to the study drug and were therefore classified as TEAEs rather than treatment-emergent adverse reactions.

Reviewer's comment: The incidence of ARs was generally similar across white and non-white subjects. However, definitive conclusions cannot be drawn due to the differences in sample sizes between white and non-white subjects.

TEAEs and ARs by Ethnicity:
Subjects treated with Twyneo cream in the combined phase 3 trials with ≥ 1 TEAE included 30/179 (16.8%) of Hispanic/Latino and 107/374 (28.6%) of non-Hispanic/non-Latino subjects. Overall, no trends were reported for SAEs, severe TEAEs TEAEs that led to treatment discontinuation, or ARs between Hispanic/Latino and non-Hispanic/non-Latino subjects. A summary of ARs by ethnicity is presented in the following table.

Table 41: Treatment-Emergent Adverse Reactions Occurring in **≥** 2 Subjects in Any Subgroup Treated with Twyneo Cream or Vehicle Cream, by Ethnicity (Safety Population)

		Hispanic/Latino		**Non-Hispanic/Non-Latino**	
Body System or Organ Class	**Dictionary-Derived Term**	**Twyneo Cream N= 179 n (%)**	**Vehicle Cream N= 96 n (%)**	**Twyneo Cream N= 374 n (%)**	**Vehicle Cream N= 179 n (%)**
General disorders and administration site conditions	Application site pain	14 (7.8)	1 (1)	45 (12)	0
	Application site dryness	8 (4.5)	0	19 (5.1)	1 (0.6)
	Application site exfoliation	4 (2.2)	0	19 (5.1)	0
	Application site erythema	4 (2.2)	0	18 (4.8)	0
	Application site dermatitis	2 (1.1)	1 (1)	5 (1.3)	0
	Application site pruritis	0	0	7 (1.9)	0
	Application site irritation	2 (1.1)	0	4 (1.1)	1 (0.6)
	Application site swelling	0	0	3 (0.8)	0

Source: Adapted from ISS (Table 14.3.1.2.1.5) and Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Causality = POSSIBLE, PROBABLY, DEFINITELY and ETHNICITY

Of note, 5 (1.3%) Non-Hispanic/Non-Latino subjects in in the Twyneo cream group and 1 (0.6%) in the Vehicle cream group experienced application site photosensitivity reactions; no Hispanic/Latino subjects experienced application site photosensitivity reactions. These events were not considered related to the study drug and were therefore classified as TEAEs rather than treatment-emergent adverse reactions.

Reviewer's comment: The incidence of ARs was generally similar across Hispanic/Latino and non-Hispanic/non-Latino subjects. However, definitive conclusions cannot be drawn due to the differences in sample sizes between the groups.

8.2.8. Specific Safety Studies/Clinical Trials

Clinical Dermal Safety Studies:

The Applicant conducted four phase 1, provocative dermal safety studies in healthy adult subjects (SGT-65-06, SGT-65-07, SGT-65-08, and SGT-65-09) with the to-be-marketed formulation to support the dermal safety of Twyneo cream. The trials evaluated the potential of Twyneo cream for irritation, sensitization, phototoxicity, and photoallergenicity. The results of these studies are presented below.

Study SGT-65-06 (Cumulative Irritation Patch Test)

This study was a 21-day, randomized, single-center, vehicle-controlled, evaluator-blinded, within-subject study to evaluate the skin irritation potential of Twyneo cream in healthy adult female and male subjects ≥ 18 years of age. Thirty-eight (38) subjects were randomized, and 34 subjects completed the study.

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

- Twyneo cream
- Vehicle cream
- 0.5% sodium lauryl sulfate (positive control)
- 0.9% saline (negative control)

Semi-occlusive patches were applied to randomized assigned, 2 cm x 2 cm adjacent areas on one side of the infrascapular area of each subject once daily for 20 consecutive days and removed after 24 ± 4 hours (21 applications). Each test site was assessed and a fresh patch containing the same study product was re-applied to the same location. Dermal reactions at the application sites were assessed daily by a blinded assessor within 30 minutes following patch removal, using a visual scale for erythema, edema, and other signs of cutaneous irritation. The actual patch test grades were calculated as the sum of numerical grades and letter grades (converted to numerical equivalents), according to the following tables:

Table 42: Response Symbols and Numerical Responses

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

Source: Applicant's submission, protocol DS311318 for Study SGT-65-06, Table 3. Page 32.

Table 43: Effects on Superficial Layers of the Skin

Grade	Score	Definition
A	0	Slightly glazed appearance

C	1	Marked glazing
E	2	Glazing with peeling and cracking
F	3	Glazing with fissures
G	3	Film of dried serous exudate covering all or portion of the patch site
G	3	Small petechial erosions and/or scabs

Source: Applicant's submission, protocol DS311318 for Study SGT-65-06, Table 4. Page 32.4

There were no AEs reported during this study.

Results

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

Table 44: Mean and Total Irritation Scores, Study SGT-65-06 (N=34) (Per-Protocol Population)

Subgroup	Irritation Score, Mean (SD)	Total Irritation Score, Mean (SD)
Twyneo cream	1.59 (0.70)	33.38 (14.79)
Vehicle cream	0.11 (0.39)	2.29 (8.23)
0.9% Saline	0.21 (0.57)	4.41 (12.02)
0.5% SLS	2.87 (0.10)	60.32 (2.00)

Source: Applicant's submission, Clinical Study Report for Study SGT-65-06, Adapted from Table 10. Page 48.
Abbreviations: SD = standard deviation, SLS = sodium lauryl sulfate

Reviewer's comment: The Applicant's proposed label for Twyneo cream appears adequate to convey the risk of potential skin irritation.

Study SGT-65-07 (Repeat Insult Patch Test)

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

Two hundred forty (240) healthy adult subjects were randomized, and 220 subjects completed the study. Two hundred twenty-seven (227) subjects were included in the analysis of cumulative irritancy, and 220 subjects were included in the analysis of sensitization. Seventeen (17) subjects (7.1%) discontinued due to voluntary withdrawal by subject, 2 subjects (0.8%) discontinued due to other reasons (confrontation between the 2 subjects), and 1 subject (0.4%) was discontinued due to a serious AE (lower limb fracture).

Each subject received a total of 10 applications (0.2 mL of each test drug applied to semi-occlusive patches) of each of the following solutions:

- Twyneo cream
- Vehicle cream
- 0.9% Saline (negative control)

During the induction phase of the study, patches were applied to randomly assigned, adjacent sites on the infrascapular area of the back 3 times per week (i.e., Mondays, Wednesdays and Fridays) for 3 consecutive weeks (9 applications). Patches remained in place until removed and the next patch was applied. Dermal reactions were assessed using a visual scale, similar to the scale used for Study SGT-65-06, after each patch removal and prior to application of an identical patch to the same patch site. A 10 to 14-day rest period (with no patch application) followed the completion of the induction phase, prior to the start of the challence phase.

During the challenge phase, a 48-hour application of each test patch was performed at a naïve site on the opposite side of the subjects' infrascapular areas. Test sites were evaluated, using the same dermal irritation scoring used in the induction phase, at 30 minutes, 24 hours, 48 hours, and 72 hours after patch removal.

Results

Twyneo cream yielded a mean (SD) cumulative irritation index of 0.61 (0.62), Vehicle cream yielded a mean (SD) cumulative irritation index of 0.04 (0.16), and the 0.9% Saline yielded a mean (SD) cumulative irritation index of 0.01 (0.08). Twyneo cream yielded a mean (SD) total irritation score of 5.44 (5.62), Vehicle cream yielded a mean (SD) total irritation score of 0.37 (1.41), and 0.9% Saline yielded a mean (SD) total irritation score of 0.07 (0.76). Cumulative and total irritation scores during the induction phase are summarized in the table below.

Table 45: Cumulative Irritation Index and Total Irritation Scores, Study SGT-65-07 (N=227) (Per-Protocol Population)

Subgroup	Cumulative Irritation Index, Mean (SD)	Total Irritation Score, Mean (SD)
Twyneo cream	0.61 (0.62)	5.44 (5.62)
Vehicle cream	0.04 (0.16)	0.37 (1.41)
0.9% Saline	0.01 (0.08)	0.07 (0.76)

Source: Applicant's submission, Clinical Study Report for Study SGT-65-07, Adapted from Table 12. Page 56.
Abbreviations: SD = standard deviation

The investigators concluded that, although Twyneo cream was more irritating that Vehicle cream and 0.9% Saline, all 3 products were classified as having no significant irritation.

There were 4 subjects with a score of 3 or higher during Challenge for Twyneo cream. Of the 4 subjects, 1 subject was thought to be sensitized and was rechallenged to Twyneo cream. Subject No. (b) (6) had a score of 2E (this is equivalent to an analysis score of 3) at 72 hours of Challenge. At Rechallenge the subject had scores of 5, 5, 5, and 4. Therefore the subject was judged by the Investigator to be likely sensitized by the study product. The observation suggested that the test product had the potential to cause hypersensitivity.

Reviewer's comment: This reviewer agrees with the Applicant's conclusion that Twyneo cream has the potential to cause hypersensitivity. This is consistent with known association of benzoyl

peroxide and rare but serious hypersensitivity reactions (FDA Safety Announcement dated 6/25/2014.) Therefore, labeling pertaining to hypersensitivity is recommended.

Study SGT-65-08 (Phototoxicity Patch Test)

This was a single-center, randomized, vehicle-controlled, double-blind, within-subject comparison study to assess the phototoxic potential of Twyneo cream when compared to Vehicle cream and an untreated irradiated site in healthy adult subjects. Thirty-three (33) subjects were randomized, and 32 completed the study.

A total of 4 application sites (2 cm x 2 cm) were marked on the subject's infrascapular region of the back: Twyneo cream was applied to 2 sites and Vehicle cream was applied to 2 sites. An additional untreated irradiated site was marked during challenge. Each study product was applied randomly under semi-occlusive patch conditions once during the study. One application site for each product was irradiated, and one site for each product remained non-irradiated. The irradiated and non-irradiated sites were compared with each other and with a pre-designated untreated irradiated site.

Approximately 24 (±2) hours post study product application, the patches were removed by study staff. The sites were then graded for cutaneous reactions by a trained evaluator and the designated sites, including the untreated site, were exposed to irradiation. One set (Twyneo cream and Vehicle cream patch) on the back was designated for irradiation and the other set remained non-irradiated. An additional site on the back was marked and received no treatment but received irradiation to serve as an untreated irradiated control. The sites were examined at approximately 24 and 48 hours post irradiation and graded for reactions. Cutaneous reactions at the application sites were evaluated using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

Results

On Day 2, all sites were evaluated for dermal response and either no reaction or mild reactions were observed. On Day 3 (24 hours post-irradiation), a maximum dermal response score of 1 (mild, but definite erythema/edema) was observed for 19 (59.4%) subjects at the Twyneo cream irradiated site, 9 (28.1%) subjects at the Twyneo cream non-irradiated site, 16 (50.0%) subjects at the Vehicle cream irradiated site, 3 (9.4%) subjects at the Vehicle cream non-irradiated site, and 19 (59.4%) subjects at the untreated irradiated site. On Day 4 (48 hours post irradiation), a maximum dermal response score of 1 was observed for 17 (53.1%) subjects at the Twyneo cream irradiated site, 7 (21.9%) subjects at the Twyneo cream non-irradiated site, 15 (46.9%) subject at the Vehicle cream irradiated site, and 17 (53.1%) subjects at the untreated irradiated site. The dermal responses on Day 2, Day 3 (24 hours post-irradiation) and Day 4 (48 hours post-irradiation) are summarized in the table below.

Table 46: Summary of Dermal Reponses by Response Scores, Study SGT-65-08 (N=32) (Per-Protocol Population)

	Twyneo Cream		Vehicle Cream		Untreated
Response [1]	**Irradiated**	**Non-Irradiated**	**Irradiated**	**Non-Irradiated**	**Irradiated**
0 hours (Day 2), n (%)					
0	31 (96.9)	31 (96.9)	32 (100)	32 (100)	--
1	1 (3.1)	1 (3.1)	0	0	--
24 hours (Day 3), n (%)					
0	13 (40.6)	23 (71.9)	16 (50)	29 (90.6)	13 (40.6)
1	19 (59.4)	9 (28.1)	16 (50)	3 (9.4)	19 (59.4)
48 hours (Day 4), n (%)					
0	15 (46.9)	25 (78.1)	17 (53.1)	32 (100)	15 (46.9)
1	17 (53.1)	7 (21.9)	15 (46.9)	0	17 (53.1)
Average of days 3-4 Response scores (n=32) Mean (SD)	0.56 (0.44)	0.25 (0.38)	0.48 (0.41)	0.05 (.15)	0.56 (0.42)

[1] Response score is the sum of erythema and edema.
Scores: Erythema: 0 = No reaction; 1 = Mild, but definite erythema; 2 = Moderate erythema; 3 = Marked/severe erythema
Edema: 0 = No reaction; 1 = Mild, but definite edema; 2 = Definite edema with erosion/vesiculation
Source: Applicant's submission, Clinical Study Report for Study SGT-65-08, Adapted from Table 8. Page 50.
Abbreviations: SD = standard deviation

The Twyneo cream irradiated site had a higher mean dermal response score (average of the sum of erythema and edema scores for Day 3 and Day 4) than the Vehicle cream irradiated site: 0.56 and 0.48 respectively and had the same mean dermal response score as the untreated irradiated control site; 0.56. Twyneo cream non-irradiated site had a higher mean dermal response score than Vehicle cream non-irradiated site: 0.25 and 0.05 respectively.

Although some subjects had erythema edema scores of 1 at the irradiated/non-irradiated sites, no one met the criterion of having phototoxicity. The investigators concluded that the dermal response scores of 1 were likely related to irritation due to the light application itself and to the mild inherent irritation of the test and vehicle products rather than phototoxicity. The scores of 1 seen in the non-irradiated sites were most likely related to the inherent irritation of the test and vehicle products. The investigators concluded that there was no indication of phototoxicity present among the subjects in this study.

Reviewer's comment: This reviewer agrees with the Applicant's conclusion that Twyneo cream did not demonstrate phototoxicity in this study, and no labeling pertaining to photoxicity is recommended.

Study SGT-65-09 (Photoallergenicity Patch Test)

This was a single-center, randomized, vehicle-controlled, double-blind, within-subject comparison study to assess the photoallergic potential of Twyneo cream when compared to Vehicle cream and an untreated irradiated site in healthy adult subjects. Sixty-two (62) subjects were randomized, and 57 completed the study.

A total of 8 application sites (2 cm x 2 cm each) were marked on the subject's back and distributed so that 4 sites were on one side of the back for induction, and 4 sites were on the other side for challenge. The investigational prodcts (Twyneo cream and Vehicle cream) were applied in two sets. One set of patches (a defined area of approximately 50 cm^2) on the infrascapular region of each subject's back was designated for irradiation after approximately 24 hours (±5 hours) of study product application, and the other set remained non-irradiated. An additional site was marked on the back during challenge. The site received no treatment but was irradiated at challenge to serve as an untreated irradiated control.

During the 3-week induction phase of the study, 0.2 mL/g of each study product (Twyneo cream and Vehicle cream) was applied to 2 sites twice each week (Monday and Thursday) for approximately 24 hours (±5 hours) under semi-occlusive patch conditions (6 applications). After patch removal, all application sites were evaluated, and one application site of each study product was irradiated with 2 times the subject's minimal erythemal dose (MED) using the full Xenon lamp spectrum. The sites were evaluated by a trained evaluator. All sites were reevaluated post irradiation, at approximately 48 hours later when irradiated on Tuesdays and at approximately 72 hours later when irradiated on Fridays. Dermal reactions at the application sites were evaluated using a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation.

At the end of the induction phase, the subjects entered a rest period of 10-17 days and then a challenge phase. At challenge, each study product was applied in an amount of 0.2 mL/g to 2 naïve sites once for approximately 24 hours (±4 hours) under semi-occlusive patch conditions. After 24 hours (±4 hours) of product application, all sites were evaluated, and one application site of each product and the additional untreated site was irradiated. The sites were examined for dermal reactions at approximately 24 hours (±4 hours), 48 hours (±4 hours), and 72 hours (±4 hours) post-irradiation. A rechallenge was to be performed if a cutaneous response observed during the challenge phase indicated possible photosensitization or at the discretion of the Investigator. A rechallenge was not needed for this study.

Results

There was no dermal response (sum of erythema and edema) observed at 0 hours (pre-patch application) at the Twyneo cream and Vehicle cream irradiated and non-irradiated sites. The

maximum dermal response observed was a score of 1 (mild, but definite erythema and edema) at 0 hours (pre-irradiation/24 hours post-application) at the Twyneo cream irradiated site (7 subjects/12.3%), at the Twyneo cream non-irradiated site (6 subjects/10.5%) and at the Vehicle cream non-irradiated site (1 subject/1.8%). There was no dermal response observed at the Vehicle cream irradiated site and at the untreated irradiated site.

At 24 hours (post-irradiation/48 hours post-application), the maximum dermal response observed was a score of 2 (moderate erythema and definite edema with erosion/vesiculation) at the Twyneo cream irradiated site and non-irradiated sites (1 subject/1.8% each). A score of 1 was observed at the Twyneo cream irradiated site (25 subjects/43.9%), Twyneo cream non-irradiated site (23 subjects/40.4%), Vehicle cream irradiated site (5 subjects/8.8%), and at the untreated irradiated site 6 subjects/10.5%). The Vehicle cream non-irradiated site had a score of 0 (57 subjects/100%).

At 48 hours (post-irradiation/72 hours post-application), the maximum dermal response observed was a score of 2 at the Twyneo cream irradiated and non-irradiated sites (3 subjects/5.3% each). A score of 1 was observed at the Twyneo cream irradiated site (22 subjects/38.6%), Twyneo cream non-irradiated site (20 subjects/35.1), Vehicle cream irradiated site (5 subjects/8.8%), and at the untreated irradiated site (5 subjects/8.8%). The Vehicle cream non-irradiated site had a score of 0 (57 subjects/100%).

At 72 hours (post-irradiation/96 hours post-application), the maximum dermal response observed was a score of 2 at the Twyneo cream irradiated and non-irradiated sites (4 subjects/7.0% each). A score of 1 was observed at the Twyneo cream irradiated site (17 subjects/29.8%), Twyneo cream non-irradiated site (16 subjects/28.1), Vehicle cream irradiated site (1 subject/1.8%), and at the untreated irradiated site (1 subject/1.8%). The Vehicle cream non-irradiated site had a score of 0 (57 subjects/100%). The dermal responses 24, 48, and 72 hours post-irradiation are summarized in the table below.

Table 47: Summary of Dermal Reponses by Response Scores During Challenge, Study SGT-65-09 (N=57) (Per-Protocol Population)

	Twyneo Cream		**Vehicle Cream**		**Untreated**
Response [1]	**Irradiated**	**Non-Irradiated**	**Irradiated**	**Non-Irradiated**	**Irradiated**
0 hrs (pre-patch application, n (%)					
0	57 (100)	57 (100)	57 (100)	57 (100)	0
0 hrs pre-irradation/24 hrs post-application, n (%)					
0	50 (87.7)	51 (89.5)	57 (100)	56 (98.2)	57 (100)
1	7 (12.3)	6 (10.5)	0	1 (1.8)	0
24 hrs post-irradiation/48 hrs					

post-application, n (%)					
0	31 (54.4)	33 (57.9)	52 (91.2)	57 (100)	51 (89.5)
1	25 (43.9)	23 (40.4)	5 (8.8)	0	6 (10.5)
2	1 (1.8)	1 (1.8)	0	0	0
48 hrs post-irradiation/72 hrs post-application, n (%)					
0	32 (56.1)	34 (59.6)	52 (91.2)	57 (100)	52 (91.2)
1	22 (38.6)	20 (35.1)	5 (8.8)	0	5 (8.8)
2	3 (5.3)	3 (5.3)	0	0	0
72 hrs post-irradiation/96 hrs post-application, n (%)					
0	36 (63.2)	37 (64.9)	56 (98.2)	57 (100)	56 (98.2)
1	17 (29.8)	16 (28.1)	1 (1.8)	0	1 (1.8)
2	4 (7)	4 (7)	0	0	0

[1] Response score is the sum of erythema and edema.
Scores: Erythema: 0 = No reaction; 1 = Mild, but definite erythema; 2 = Moderate erythema; 3 = Marked/severe erythema
Edema: 0 = No reaction; 1 = Mild, but definite edema; 2 = Definite edema with erosion/vesiculation
Source: Applicant's submission, Clinical Study Report for Study SGT-65-09, Adapted from Table 8. Page 56.
Abbreviations: SD = standard deviation

The investigators concluded that there was no photosensitization during the challenge phase of the study and that inherent irritation from the product was likely more significant than any minor light-induced irritation, thereby resulting in similar scores between irradiated and non-irradiated test products

Reviewer's comment: This reviewer agrees with the Applicant's conclusion that Twyneo cream did not demonstrate photosensitization in this study. Nonetheless, labeling for sun protection and avoidance of tanning beds and UV A and B treatments should be included based on precedent labeling for these topical products.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a specific clinical trial to evaluate human carcinogenicity or tumor development. During the development of Twyneo cream, the trial designs did not include specific assessments to evaluate for carcinogenicity or screen for safety signals related to malignancy. However, no subjects enrolled in the phase 3 trials reported malignant neoplasms. The Applicant intends to rely on nonclinical information related to carcinogenicity. This information is included in Section 13.1 of labeling. Refer to Section 5.5.3 for this review for

a discussion of the nonclinical data.

Human Reproduction and Pregnancy

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

Pediatrics and Assessment of Effects on Growth

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

The Division agreed with the Applicant's Agreed iPSP on May 27, 2020, following discussion of the Agreed iPSP with the Pediatric Review Committee on May 19, 2020. The Agreed iPSP included a request for partial waiver to conduct clinical studies in subjects less than 9 years of age. The prevalence of moderate to severe acne vulgaris in the pediatric population in this age group is low. Therefore, studies would be impossible or highly impracticable (Section 505B (a)(4)(B)(i) of the Act).
The Applicant did not request a deferral of clinical aassessments in any pediatric age group.
The phase 3 trials (SGT-54-04 and SGT-65-05), the phase 2 study (SGT-65-02) and the MUSE PK Study (SGT-65-03) included subjects in the target pediatric age group (≥ 9 years of age).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
There have been no instances of Twyneo cream overdose in the clinical studies. No unexpected TEAE occurred under maximal use conditions (Study SGT-65-03) in which approximately 2 g of study drug was applied daily for 14 days. However, both tretinoin and benzoyl peroxide have low systemic absorption after topical application; therefore the potential for systemic effects from overdose are limited. The Applicant omitted Section 10 OVERDOSE in labeling for Twyneo cream.

Drug Abuse Potential/Withdrawal and Rebound
No studies of Twyneo cream have been designed to evaluate drug abuse potential, withdrawal and/or rebound. However, in light of the mechanism of action and low systemic exposure, there is no reason to anticipate any potential for abuse or dependency. There were no data to indicate the occurrence of physical dependency on Twyneo cream during the clinical trials. Therefore, the review team did not consult with the Controlled Substance Staff.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

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

Expectations on Safety in the Postmarket Setting

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

8.2.11. Integrated Assessment of Safety

The safety profile for Twyneo cream was adequately characterized during the drug development program. The primary safety database consisted of 832 subjects from phase 3 trials SGT-65-04 and SGT-65-05 (the pooled safety population, ISS). The phase 3 trials were identical with regard to design, trial population, dosing regimen and key primary and secondary endpoints. Eligible subjects were randomized in a 1:1 ratio to receive either Twyneo cream or Vehicle cream once daily for 12 weeks. All randomized subjects who were included in the safety population used the study drug at least once and provided at least 1 post-baseline evaluation.

Although there were no severe hypersensitivity reactions during the development program for Twyneo cream, literature suggests that rare but severe hypersensitivity reactions may occur following the use of benzoyl peroxide-containing products. Therefore, labeling pertaining to hypersensitivity reaction should be included in Section 4 CONTRAINDICATIONS. Review of the data supports including the potential for skin irritation and increased sun sensitivity in Section 5 WARNINGS AND PRECAUTIONS of labeling. Active assessment of local tolerability indicated that the percentage of subjects who reported signs and symptoms (erythema, scaling, itching, burning, and stinging) at any post-baseline visit was greater in the Twyneo cream group than the Vehicle cream group. Although results of the phototoxicity and photoallergenicity studies (SGT-65-08 and SGT-65-09) support the conclusion that Twyneo cream is neither phototoxic nor photoallergenic, topical tretinoin has been implicated in the development of increased sun sensitivity in some patients.

Treatment with Twyneo cream was not associated with an increased risk of death or serious adverse events. In the pooled phase 3 trials, 2 subjects (0.2%) experienced nonfatal SAEs, one subject in each treatment group. In the Twyneo cream group, 1 subject reported an event of depression (moderate); in the Vehicle cream group, 1 subject reported events of bipolar II disorder (severe), depression (severe), and conduct disorder (severe). Both SAEs resulted in hospitalization without study discontinuation; however, the study drug was interrupted for the subject in the Vehicle cream group. The SAEs were considered to be unrelated to the study product.

The most common adverse reactions which occurred in ≥ 1% of subjects treated with Twyneo cream greater than Vehicle cream were related to the application site, and included pain

(10.6%), dryness (4.9%), exfoliation (4.1%), erythema (4%), dermatitis (1.3%) pruritis (1.3%), and irritation (1.1%).

In the phase 3 trials, 2 subjects had positive urine pregnancy test results. Both subjects were in the Twyneo cream group, and both discontinued the study due to their pregnancies. One subject was lost to follow-up, and the outcome of her pregnancy is unknown. The other subject gave birth to a healthy baby following an unremarkable pregnancy, and no complications associated with childbirth were reported. The data collected in the Twyneo development program is insufficient to ascertain the teratogenicity of Twyneo cream. The Applicant's proposed Section 8 of labeling states that topical administration of tretinoin to pregnant animals (i.e., rats and cynomolgus monkeys) during organogenesis is associated with malformations. Section 8 of labeling also conveys the lack of human data for the use of Twyneo cream during pregnancy and the uncertainty regarding a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Available safety data from the two phase 3 trials demonstrate that Twyneo cream appears safe for the treatment of acne vulgaris in subjects 9 years of age and older. Postmarketing risk management will include professional labeling and routine pharmacovigilance. As both moieties (benzoyl peroxide and tretinoin) are well characterized, the review team recommends no other risk management tools or assessments (REMS or clinical postmarketing studies).

8.3. Statistical Issues

The results for the co-primary efficacy endpoints at Week 12 were higher in Trial SG-65-04 compared to Trial SG-65-05, see Table 15 in Section 8.1.4. The statistical reviewer notes that the higher efficacy results in Trial SGT-65-04 compared to Trial SGT-65-05 appear to be attributed to the active group; results in the vehicle group were consistent across the two trials. Demographics and baseline disease characteristics were generally balanced across the two trials. In addition, both trials were conducted at the same time at similar center locations within the US, with no principal investigator or center being common to both trials. It was observed that the vehicle group had better or similar efficacy results in a larger numbers of analysis centers in Trial SGT-65-05 compared to Trial SGT-65-04 (see discussion in Section 8.1.6.2). A sensitivity analysis identified three analysis centers as extreme results based on the inflammatory lesion counts in Trial SG-65-04. The removal of these extreme analysis centers did not affect the overall conclusions for the co-primary efficacy endpoints; results for all three only slightly decreased in both treatment groups with the treatment effect remaining similar. Other sensitivity analyses assessing robustness of the co-primary endpoints analyses on the methods for handling the missing data and between per protocol and intent-to-treat populations indicated robust results.

8.4. Conclusions and Recommendations

To establish the safety and efficacy of Twyneo cream for the treatment of acne vulgaris, the

Applicant submitted data from two identically designed, randomized, multicenter, double-blind, vehicle-controlled, phase 3 trials (SGT-65-04 and SGT-65-05). Both trials enrolled subjects 9 years of age and older with moderate (3) or severe (4) acne vulgaris on the Investigator Global Assessment (IGA). Enrolled subjects had 20 to 100 inflammatory lesions (papules, pustules, and nodules), 30 to 150 non-inflammatory lesions (open and closed comedones), and two or fewer facial nodules.

In both trials, subjects were randomized in a 1:1 ratio to receive either Twyneo cream or Vehicle cream applied once daily for 12 weeks using a "pea-size" amount for each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead) and avoiding the eyes, lips, inside the nose, mouth and all mucous membranes. The co-primary efficacy endpoints were the absolute change from Baseline in non-inflammatory lesion count on the face at Week 12, absolute change from Baseline in inflammatory lesion count on the face at Week 12, and the the proportion of subjects in active treatment versus vehicle cream with an assessment of clear or almost clear with at least a 2-grade improvement in IGA at Week 12.

Secondary efficacy endpoints included percent change in non-inflammatory lesion counts and percent change in inflammatory lesion counts from Baseline at Weeks 2, 4, 8 and 12, as well as the proportion of subjects with at least a 3-point reduction in average acne sign and symptom domain (ASD) score on the subject-reported evaluation of facial acne (PRE-FACE), and the proportion of subjects with at least a 3-point reduction average acne impact domain (AID) score on the PRE-FACE.

In both pivotal trials, Twyneo cream was statistically superior to vehicle for the co-primary endpoints for subjects 9 years of age and older (p-values <0.025). The results of percent change from baseline in lesion counts at Week 12 (i.e., secondary efficacy endpoints) for both trials are supportive of the results for the absolute change. Refer to Section 8.1.4 for discussion of the results for the co-primary efficacy endpoints and Section 8.1.5 for discussion of the results for the secondary efficacy endpoints.

The Applicant conducted a comprehensive assessment of the safety of Twyneo cream 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, nor do they necessitate any safety mitigation strategies.

Submitted safety and efficacy data support approval of this NDA for Twyneo cream for the topical treatment of acne vulgaris in the patients 9 years of age and older.

9 Advisory Committee Meeting and Other External Consultations

The FDA conducted no advisory committee meeting regarding this application because there were no novel or complex regulatory issues related to efficacy or safety that required discussion with subject-matter experts.

10 Pediatrics

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

The Pediatric Review Committee agreed with the Division that the assessments were adequate (meeting of April 13, 2021). Therefore, no postmarketing requirements or commitments for deferred pediatric studies are needed under the Pediatric Research Equity Act (21 CFR 314.55(b) and 601.27(b)). Refer to Pediatrics and Assessment of Effects on Growth in Section 8.2.9 of this review for a discussion regarding the Pediatric Study Plan.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted proposed Patient Package Insert (PPI), Prescribing Information (PI) and carton/container labels for Twyneo cream. The review team provided recommendations regarding the PI, and these comments are reflected in the final labeling.

Madhuri R. Patel, PharmD, from the Division of Medication Error Prevention and Analysis reviewed the proposed container label, carton labeling, PPI, and PI and provided comments. The Division of Medication Error Prevention and Analysis concluded that the PPI and PI were acceptable from a medicatin error perspective (see review dated March 1, 2021). Dr. Patel reviewed the container labels and carton labeling for Twyneo and recommended improvements to allow for consistent dosing, to facilitate product identification and to prevent drug selection and deteriorated drug errors.

Laurie Buonaccorsi, PharmD, from the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PPI. OPDP had no comments regarding the PI or the carton/container labeling (see review dated May 19, 2021).

Other Prescription Drug Labeling

The Applicant submitted a proposed PPI for Twyneo cream. Jessica Chung, PharmD, MS, from the Division of Medical Policy Programs and Laurie Buonacorsi, PharmD, from OPDP reviewed and provided comments regarding the PPI (see review dated May 25, 2021). The final labeling will reflect their recommendations.

12 Risk Evaluation and Mitigation Strategies (REMS)

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

No postmarketing requirements are recommended.

14 Appendices

14.1. References

- Bhate K, Williams HC. Epidemiology of acne vulgaris. Br J Dermatol. 2013 Mar;168(3):474-85
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14.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant signed the following disclosure statement:

> "As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not

disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

The covered clinical trials, as defined in 21 CFR 54.2(e) were Study SGT-65-04 nd SGT-65-05, w hich provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1 of this review for the trial designs.

The Applicant adequately disclosed financial interests for clinical investigators.

Covered Clinical Study (Name and/or Number): SGT-65-04 and SGT-65-05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Thirty-two (32) investigators for Study SGT-65-04 and 31 investigators for Study SGT-65-05.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: Sol-Gel Technologies		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
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)

		N/A

14.3. Clinical/Biostatistics

Sensitivity analysis for Subject (b) (6) (subject missing baseline IGA score):

Table 48: Results of IGA Success[1] at Week 12 - SGT-65-05 (ITT; MI[2])

	Include Subjects (b) (6)		Exclude Subjects (b) (6)	
	BPO/ATRA Cream (N=290)	**Vehicle Cream (N=144)**	**BPO/ATRA Cream (N=290)**	**Vehicle Cream (N=143)**
IGA Success				
Proportion[3]	26.8%	15.1%	26.8%	15.5%
Difference (95% CI)	11.6% (3.6%, 19.7%)		11.3% (2.8%, 19.8%)	
Adjusted Proportion[4]	25.4%	14.3%	25.4%	14.7%
Difference (95% CI)[4]	11.1% (2.8%, 19.5%)		10.7% (2.0%, 19.5%)	
P-Value[4]	0.009		0.0165	

[1] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline.
[2] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
[3] Average over the five imputed datasets.
[4] Adjusted proportions, difference (95% CI), and p-value are based on logistic regression with factors of treatment group and analysis center. For Trial SGT-54-05, the logistic regression used the Firth's penalized likelihood due to quasi-complete separation of the data.
Note: Subject (b) (6) was excluded from the Applicant's analysis of IGA because the IGA was not performed at baseline.
Source: Statistical Reviewer's Analysis and Applicant's Analysis; ADEFF.xpt

Table 49: Treatment Effect on IGA Success[1] at Week 12 by Analysis Approach (ITT[2]) – Excluding Subject (b) (6)

	Trial SGT-54-04	**Trial SGT-54-05**
Unadjusted[3]		
Difference from Vehicle (95% CI)	25.7% (17.1%, 34.2%)	11.3% (2.8%, 19.8%)
Logistic Regression – Standard[4]		
Difference from Vehicle (95% CI)	26.9% (17.8%, 36.0%)	NA
Logistic Regression – Firth's[5]		
Difference from Vehicle (95% CI)	26.5% (17.4%, 35.7%)	10.7% (2.0%, 19.5%)
CMH (Sensitivity Analysis)[6]		
Difference from Vehicle (95% CI)	25.5% (17.2%, 33.8%)	11.1% (2.8%, 19.4%)

[1] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[3] Average over the five imputed datasets.
[4] Adjusted difference in proportions is based on logistic regression with factors of treatment group and analysis center. For Trial SGT-54-01, the logistic regression did not converge due to quasi-complete separation of the data.
[5] Adjusted difference in proportions is based on logistic regression using the Firth's penalized likelihood with factors of treatment group and analysis center.
[6] Adjusted difference in proportions is the weighted average of the treatment differences across analysis center with the Cochran-Mantel-Haenszel (CMH) weights.
Note: Subject (b) (6) was excluded from the Applicant's analysis of IGA because the IGA was not performed at baseline.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

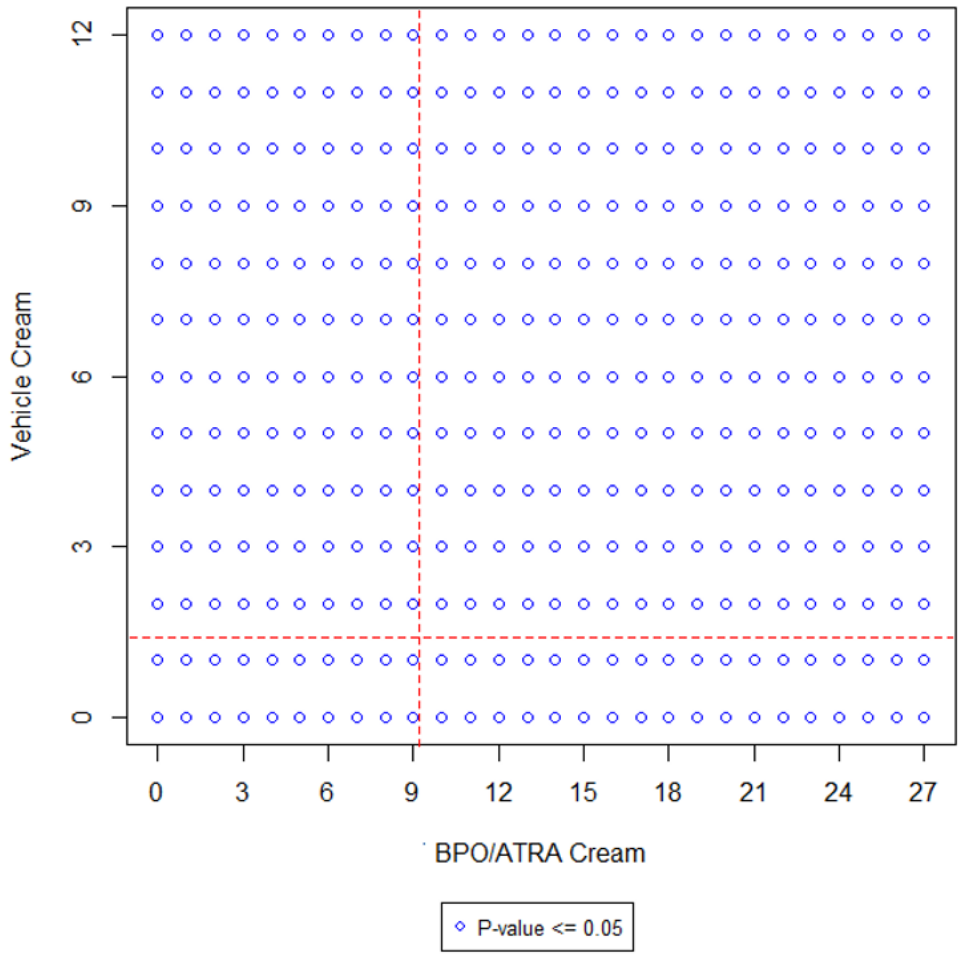
Tipping Point Analysis:

Table 50: Sensitivity Tipping-Point Analysis for Lesion Counts at Week 12 – Trials SG-65-04 and SG-65-05 (ITT; MI[1])

Trial SG-65-04				Trial SG-65-05			
Inflammatory Lesion Count		**Non-Inflammatory Lesion Count**		**Inflammatory Lesion Count**		**Non-Inflammatory Lesion Count**	
Shift Value	P-Value	Shift Value	P-Value	Shift Value	P-Value	Shift Value	P-Value
0	<0.001	0	<0.001	0.00	0.038	0	<0.001
50	0.002	50	<0.001	0.25	0.045	10	<0.001
100	0.004	100	<0.001	0.50	0.045	20	0.03
150	0.004	150	<0.001	0.75	0.045	30	0.010
200	0.004	200	<0.001	1.00	0.054	40	0.015
250	0.004	250	<0.001	1.25	0.064	50	0.018
300	0.004	300	<0.001	1.50	0.064	60	0.021
350	0.004	350	<0.001	1.75	0.064	70	0.024
400	0.004	400	<0.001	2.00	0.076	80	0.027
450	0.004	450	<0.001	2.25	0.089	90	0.031
500	0.004	500	<0.001			100	0.035
550	0.004	550	<0.001			110	0.039
600	0.004	600	<0.001			120	0.044
650	0.004	650	<0.001			130	0.049
700	0.004	700	<0.001			140	0.051
750	0.004	750	<0.001				

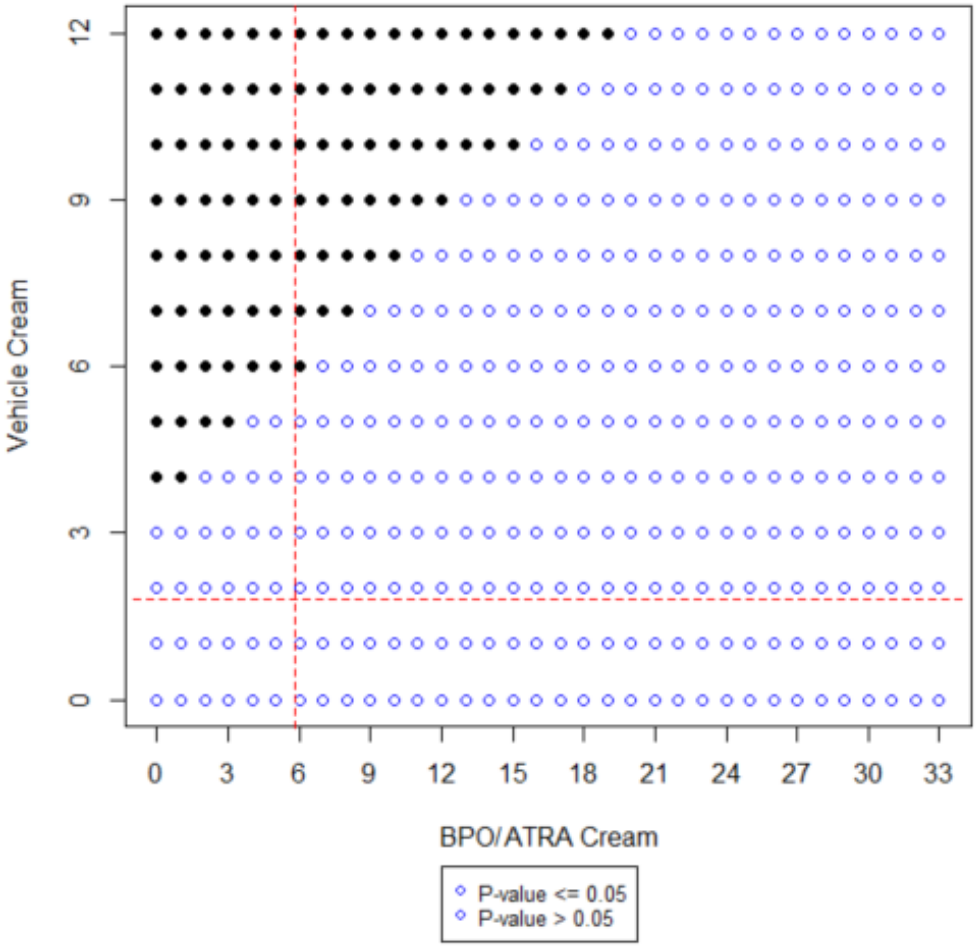
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] P-value from a ranked analysis of covariance with factors of treatment group and analysis center and the respective baseline lesion count as a covariate. For the inflammatory lesion count analysis of covariance in Trial SGT-65-04, the interaction of treatment by analysis center was significant and included in the model.
Note: Multiple imputation (MCMC) used to impute missing values, with shift values applied to the imputed lesion count values from BPO/ATRA 3%/0.1% cream group. Values have been adjusted for multiple imputation.

Figure 10: Sensitivity Tipping-Point Analysis for IGA Success[1] at Week 12 – Trial SG-65-04 (ITT; MI[2])



[1] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline
[2] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Notes: The horizontal and vertical axes indicate the potential number of successes among subjects with missing data in each treatment group. Each plotted point represents the significance of the p-value for every combination of imputed successes in each treatment group. The red lines represent average number of imputed successes from the primary analysis using multiple imputation (MCMC) to impute missing values.
P-value from a logistic regression with a factor of treatment group.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt

Figure 11: Sensitivity Tipping-Point Analysis for IGA Success[1] at Week 12 – Trial SG-65-05 (ITT; MI[2])



[1] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline
[2] Intent-to-Treat (ITT) defined as all randomized subjects who were dispensed study product. Missing data were imputed using multiple imputation (MI).
Notes: The horizontal and vertical axes indicate the potential number of successes among subjects with missing data in each treatment group. Each plotted point represents the significance of the p-value for every combination of imputed successes in each treatment group. The red lines represent average number of imputed successes from the primary analysis using multiple imputation (MCMC) to impute missing values.
P-value from a logistic regression (using Firth's Penalized Likelihood) with a factor of treatment group.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt

14.4. Nonclinical Pharmacology/Toxicology

14.4.1. Multiples of Human Exposure Calculation

The maximum recommended human dose (MRHD) for the product is proposed as 1.5 g of BPO/ATRA cream (containing 0.1% tretinoin) applied daily to a 60-kg person, i.e. 0.03 mg tretinoin/kg body weight. The following table summarizes the multiples of the MRHD and doses from nonclinical studies referenced in the labeling based on body surface area comparisons and assuming 100% absorption.

Table 51: Multiples of the MRHD Adjusted for Total Body Surface Area and Doses from Nonclinical Studies Referenced in Labeling

Study	Species	Dose (mg/kg/day)	HED (mg/kg/day)	Dose Note	Multiples[a]
Embryofetal Development (Topical ATRA)	Rat	1	0.16	NOAEL for Malformation	5
		10	1.61	Malformation	50
	Rabbit	0.2	0.065	NOAEL for Malformation	2.2
		0.5	0.16	Fetotoxicity	5
Embryofetal development (Oral ATRA)	Rat	1	0.16	NOAEL for Malformation	5
		2.5	0.4	Fetotoxicity	13
	Monkey	5	1.61	NOAEL for Malformation	50
		10	3.23	Malformation	100
Fertility (Topical ATRA)	Rat	0.25	0.04	Fertility toxicity	1.3
		0.5	0.08	Fertility toxicity	2.7
Carcinogenicity (ATRA)	Mice	0.025	0.002	NOAEL	0.07
		0.5-1	0.04-0.08	NOAEL	1.3-2.7
Carcinogenicty (BPO)	Rat	15-25%	------	NOAEL	5-8[b]
Carcinogenicty (BPO)	Mice	15-25%	------	NOAEL	5-8[b]

Abbreviations: HED = Human Equivalent Dose; NOAEL = no-observed-adverse-effect-level

[a] Calculated by dividing the nonclinical ATRA HED by the MRHD for ATRA of 0.03mg/kg/day

[b] Calculated by dividing the BPO concentration in nonclinical studies by the clinical concentration of 3%

14.4.2. Nonclinical labeling

Recommended changes to nonclinical information in sections 8.1, 12.1, and 13.1 of the applicant's proposed labeling are provided below.

There is no established pharmacologic class (EPC) for benzoyl peroxide. The EPC for tretinoin is retinoid. The first sentence in the Highlights section of labeling under the Indications and Usage section reflects these information.

(b) (6)

(b) (6) Reviewer recommended deletions and additions are indicated by ~~strikethrough~~ and underlined text, respectively.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

TWYNEO ~~Cream~~ is a combination of ~~encapsulated~~ benzoyl peroxide and ~~encapsulated~~ tretinoin, a retinoid, and is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Available data from published observational studies of topical tretinoin in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Studies conducted with topical benzoyl peroxide have not demonstrated systemic absorption and maternal use is not expected to result in fetal exposure to benzoyl peroxide. There are no data on TWYNEO use in pregnant women.

There are reports of major birth defects reported with maternal use of topical tretinoin similar to those seen in infants exposed to oral retinoids, but these case reports do not establish a pattern or association with tretinoin-related embryopathy (*see Data*).

Animal reproductive studies have not been conducted with TWYNEO or benzoyl peroxide. Topical administration of tretinoin to pregnant rats during organogenesis was associated with malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) at doses greater than 1 mg tretinoin/kg/day, approximately 5 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison and assuming 100% absorption. Oral administration of tretinoin to pregnant cynomolgus monkeys during organogenesis was associated with malformations at 10 mg/kg/day (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption) (*see Data*).

The (b) (4) background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss and other adverse outcomes. The background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from multiple prospective controlled observational studies on the use of topical tretinoin products during pregnancy have not identified an association with topical tretinoin and major birth defects or miscarriage. The available studies have methodologic limitations, including small sample size and in some cases, lack of physical exam by an expert in birth defects. There are

published case reports of infants exposed to topical tretinoin during the first trimester that describe major birth defects similar to those seen in infants exposed to oral retinoids; however, no pattern of malformations has been identified and no causal association has been established in these cases. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Animal Data

For purposes of comparison of the animal exposure to human exposure, the MRHD is defined as 1.5 g of TWYNEO cream (containing 0.1% tretinoin) applied daily to a 60-kg person (0.03 mg tretinoin/kg body weight).

Topical tretinoin embryofetal development studies (b) (4) have generated equivocal results. There is evidence for malformations (b) (4) (shortened or kinked tail) (b) (4) after topical tretinoin administration in Wistar rats at doses greater than 1 mg/kg/day (approximately 5 (b) (4) times the (b) (4) MHRD based on BSA comparison and assuming 100% absorption (b) (4) Anomalies (humerus: short 13%, bent 6%, os parietale incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption) was topically applied to pregnant rats during organogenesis. (b) (4) increased incidence of domed head and hydrocephaly, typical ~~of~~ retinoid-induced fetal malformations- (b) (4) were noted in New Zealand White rabbits administered topical doses greater than 0.2 mg/kg/day (2.2 times the MRHD based on BSA comparison and assuming 100% absorption).

(b) (4)

Oral tretinoin (b) (4) induced malformations (b) (4) in rats, mice, hamsters, and (b) (4) nonhuman primates when administered during the period of organogenesis. Fetal malformations were observed when tretinoin was orally administered to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison and assuming 100% absorption). (b) (4) fetal malformations were reported when an oral (b) (4) doses of 10 mg/kg/day was administered to pregnant monkeys during organogenesis (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption). No fetal malformations were observed at an oral dose of 5 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption). (b) (4) -ncreased skeletal variations were observed at all doses. (b) (4) and a dose-related increase in embryolethality

and abortion was reported in this study. Similar results have also been reported in pigtail macaques.

Oral tretinoin has been shown to be fetotoxic in rats when administered at a dose of 2.5 mg/kg/day (13 times the MRHD based on BSA comparison and assuming 100% absorption). Topical tretinoin has been shown to be fetotoxic in rabbits when administered at a dose of 0.5 mg/kg/day (5 times the MRHD based on BSA comparison and assuming 100% absorption).~~,~~ (b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Benzoyl peroxide is an oxidizing agent with bactericidal~~,~~ and keratolytic (b) (4) effects but the precise mechanism of action is unknown.

Tretinoin is a metabolite of vitamin A that binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus. Tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation. It has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors~~,~~ and/or other mechanisms~~,~~ (b) (4)

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) Carcinogenicity, (b) (4) mutagenicity, and impairment of fertility studies were not conducted with TWYNEO-(b) (4)

Benzoyl peroxide

(b) (4) The role of benzoyl peroxide as a tumor promoter has been well established in several animal species; however, the significance of this finding in humans is unknown.

No significant increase in tumor formation was observed in rats (b) (4) treated topically with 15 to 25% benzoyl peroxide carbopol gel ((b) (4) 5 to 8 times the concentration of benzoyl peroxide in TWYNEO-(b) (4)) for two years. Similar results were obtained in mice (b) (4) treated topically with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment (b) (4) with 15% benzoyl peroxide gel for the rest of the two-year

study period, and in mice (b) (4) treated topically with 5% benzoyl peroxide gel for two years.

(b) (4)

(b) (4)

Bacterial mutagenicity assays (Ames test) conducted with benzoyl peroxide have provided mixed results. (b) (4) Mutagenic potential was observed in a few studies but not in a majority of investigations. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies were not conducted with benzoyl peroxide.

Tretinoin

In a 91-week dermal study, in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are 1.3 and 2.7 times the MRHD based on BSA comparison and assuming 100% absorption (b) (4) The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.07 times the MRHD based on BSA comparison and assuming 100% absorption).

(b) (4)

(b) (4)

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test and an in vivo rat micronucleus assay, both of which were negative.

In dermal (b) (4) fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (approximately 2.7 times the (b) (4) MRHD based on BSA comparison and assuming 100% absorption), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (1.3 times the (b) (4) MRHD based on BSA comparison and assuming 100% absorption) were observed. (b) (4)

14.5. OCP Appendices (Technical documents supporting OCP recommendations)

[Add Text and Figures/Tables Here]

14.6. Additional Clinical Outcome Assessment Analyses

[Add Text and Figures/Tables Here]

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