CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216632Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA 216632
Cabtreo (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel, 1.2%/0.15%/3.1%

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number(s)	216632
Priority or Standard	Standard
Submit Date(s)	December 22, 2022
Received Date(s)	December 22, 2022
PDUFA Goal Date	October 20, 2023
Division/Office	Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	October 20, 2023
Established/Proper Name	(clindamycin phosphate, adapalene, and benzoyl peroxide) gel
(Proposed) Trade Name	CABTREO
Pharmacologic Class	Combination of clindamycin phosphate (a lincosamide antibacterial), adapalene (a retinoid), and benzoyl peroxide
Code name	IDP-126 gel
Applicant	Bausch Health US, LLC
Dosage form	Topical Gel
Applicant proposed Dosing Regimen	A thin layer to the affected areas once daily
Applicant Proposed Indication(s)/Population(s)	For the treatment of acne vulgaris in patients (b) (4) ears of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of acne vulgaris in patients 12 years of age and older
Recommended Dosing Regimen	A thin layer to the affected areas once daily

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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

NDA 216632
Cabtreo (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel, 1.2%/0.15%/3.1%

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	John P. Dougherty	OII/DPT-II	Sections: 5, 19.3	Select one: _X__ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Barbara Hill	OII/DPT-II	Sections: 5, 19.3	Select one: ___ Authored _X__ Approved
	Signature:			
Clinical Pharmacology Reviewer	Soo Hyeon Shin	OCP/DIIP	Sections: 6, 19.4	Select one: _X_ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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	Signature:			

NDA 216632
Cabtreo (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel, 1.2%/0.15%/3.1%

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

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
AUC	area under the concentration-time curve
BLA	biologics license application
BPO	Benzoyl peroxide
CFR	Code of Federal Regulations
CK	creatine kinase
CSR	clinical study report
CSS	Controlled Substance Staff
DMEPA	Division of Medication Error Prevention and Analysis
DMF	drug master file
EGSS	Evaluator's Global Severity Score
FDA	Food and Drug Administration
GGT	gamma-glutamyltransferase
HD	high dose
IND	Investigational New Drug
ISS	integrated summary of safety
ITT	intent to treat
MCMC	Markov Chain Monte Carlo
MRHD	maximum recommended human dose
NDA	new drug application
NOAEL	no observed adverse effect level
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PDE	permitted daily exposure
PI	prescribing information
PK	pharmacokinetic
PMR	postmarketing requirement
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SLS	sodium lauryl sulfate
TEAE	treatment emergent adverse event
ULN	upper limit of normal

APPEARS THIS WAY ON ORIGINAL

1 Executive Summary

1.1. Product Introduction

CABTREO or IDP-126 (clindamycin phosphate, adapalene, and benzoyl peroxide [BPO]) Gel, 1.2%/0.15%/3.1% is a topical drug product for which the Applicant, Bausch Health US, LLC, seeks approval under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the treatment of acne vulgaris. The drug product will be referred to as IDP-126 gel throughout this review. The listed drug is EPIDUO FORTE [adapalene 0.3%/BPO 2.5%] Gel (new drug application (NDA) 207917). In addition, the Applicant has ownership and right of reference to ACANYA Gel [clindamycin 1.2%/benzoyl peroxide 2.5%] (NDA 050819), ONEXTON Gel [clindamycin 1.2%/benzoyl peroxide 3.75%]) (NDA 050819) and BENZACLIN [clindamycin phosphate 1.2%/BPO 5%] Gel (NDA 050756).

This application is for a new triple fixed combination topical gel containing clindamycin phosphate (a lincosamide antibacterial with anticomedogenic and anti-inflammatory properties), adapalene (a synthetic retinoid with anticomedogenic and anti-inflammatory properties which modulates cellular differentiation, keratinization and inflammatory processes) and benzoyl peroxide (an oxidizing agent with bactericidal, comedolytic, anti-inflammatory and keratolytic properties). The exact mechanism of action of these three active ingredients for the treatment of acne vulgaris is unknown.

The proposed dose is to apply a thin layer to the affected areas once daily. The proposed indication is for the topical treatment of acne vulgaris in patients (b) (4) years of age and older.

The Agency concludes that the proposed proprietary name, CABTREO, is acceptable from both a promotional and safety perspective under NDA 216632 (see Proprietary Name Review by Corwin D. Howard, PharmD, RPh, Division of Medication Error Prevention and Analysis dated March 22, 2023).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials (V01-126A-301 (301) and V01-126A-302 (302) which provided evidence of the effectiveness of IDP-126 gel for

the topical treatment of acne vulgaris. Both trials assessed the changes from Baseline to Week 12 compared to vehicle gel on the co-primary endpoints:

- Absolute change in the inflammatory lesion count from baseline to Week 12
- Absolute change in the noninflammatory lesion count from baseline to Week 12
- Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the Evaluator's Global Severity Score (EGSS) and had an EGSS at Week 12 that equated to "clear" or "almost clear"

IDP-126 gel was statistically superior to Vehicle gel (all p-values ≤ 0.005) on the co-primary endpoints in both trials.

The Applicant also submitted data from a randomized, double-blind trial (V01-126A-201 (201) that compared IDP-126 gel with each dual-component arm (BPO 3.1%/adapalene 0.15% gel, clindamycin phosphate 1.2%/BPO 3.1% gel, clindamycin phosphate 1.2%/adapalene 0.15% gel) and Vehicle gel. This trial evaluated IDP-126 gel versus each of the 4 comparators on the same 3 co-primary endpoints as Trials 301 and 302. IDP-126 gel was statistically superior to each of the 4 comparators for all 3 co-primary endpoints (all p-values ≤0.026), demonstrating that each component makes a contribution to the claimed effects.

The Applicant has demonstrated that IDP-126 gel is effective for its intended use, and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126(a)(b) and 300.50 to support approval for the treatment of acne vulgaris in patients 12 years and older. The Applicant, however, has not demonstrated the safe and effective use of IDP-126 gel for the treatment of acne vulgaris in patients younger than 12 years of age.

Upon review of the benefits and risks, the review team recommends approval of IDP-126 gel for the treatment of acne vulgaris in patients 12 years of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Bausch Health US, LLC submitted a new drug application (NDA) 216632 for CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) Gel, 1.2%/0.15%/3.1%, referred to as IDP-126 gel, for the treatment of acne vulgaris under the 505(b)(2) regulatory pathway. Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. CABTREO topical gel is a new triple fixed combination containing clindamycin phosphate, adapalene and benzoyl peroxide. The safety profile of each moiety (clindamycin phosphate, adapalene, and benzoyl peroxide) is well characterized. The Applicant established a clinical bridge to relied on data from the listed drug, EPIDUO FORTE Gel [adapalene 0.3%/benzoyl peroxide (BPO) 2.5%] (NDA 207917) gel and has ownership and right of reference for ACANYA Gel [clindamycin 1.2%/benzoyl peroxide 2.5%] (NDA 050819), ONEXTON Gel [clindamycin 1.2%/benzoyl peroxide 3.75%] (NDA 050819) and BENZACLIN [clindamycin phosphate 1.2%/BPO 5%] Gel (NDA 050756).

In two, multicenter, randomized, double-blind clinical trials enrolling 363 subjects (242 subjects treated with IDP-126 gel and 121 subjects treated with Vehicle gel) age 10 years and older (inclusion criteria included 9 years and older) with acne vulgaris, IDP-126 gel was statistically superior to Vehicle gel for the treatment of acne vulgaris. The co-primary efficacy endpoints were success on the absolute change in the inflammatory lesion count from baseline to Week 12, absolute change in the noninflammatory lesion count from baseline to Week 12, and percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the Evaluator's Global Severity Score (EGSS) and had an EGSS at Week 12 that equated to "clear" or "almost clear." A randomized, double-blind trial that compared IDP-126 gel with each dual-component arm (BPO 3.1%/adapalene 0.15% gel, clindamycin phosphate 1.2%/BPO 3.1% gel, clindamycin phosphate 1.2%/adapalene 0.15% gel) and Vehicle gel demonstrated that each component makes a contribution to the claimed effects of the fixed combination product.

The safety profile for IDP-126 gel was adequately characterized during the drug development program for patients 12 years and older. Treatment with IDP-126 gel was not associated with an increased risk of mortality or serious adverse events. There were no deaths or drug-related, serious adverse events (SAEs) in the phase 3 trials, Study V01-126A-301 and V01-126A-302 (referred to as Study 301 and Study 302, respectively). Review of the data supports including the potential for skin irritant and allergic contact dermatitis and effects of ultraviolet light in labeling. Active assessment of local tolerability indicated that the percentage of subjects who reported signs and symptoms (scaling, erythema, hyperpigmentation, itching, burning, and stinging) at maximum postbaseline was greater in the IDP-126 gel group than the Vehicle

group. The most common adverse reactions occurred at the application site: pain, erythema, dryness/xerosis, irritation, exfoliation, and dermatitis.

The Applicant seeks an indication for CABTREO (1.2% clindamycin phosphate, 0.15% adapalene, and 3.1% benzoyl peroxide) topical gel for the topical treatment of acne vulgaris in patients (b) (4) years of age and older. However, a limited number of subjects ages 10 to 11 years and 11 months (enrollment permitted down to age 9 years) were treated with IDP-126 gel in the phase 3 trials (5/363 (1.4%) subjects (3/242 (1.2%) in the IDP-126 gel cohort and 2/121 (1.7%) in the Vehicle gel cohort). Additionally, in the phase 1b pharmacokinetic (PK) bridging, maximal use study, systemic exposure was assessed in only 8 subjects ages 9 years to 11 years and 11 months and higher systemic exposures were noted with IDP-126 gel in the 9 to 11 years and 11 months cohort compared to the 12 years and older cohort. The Applicant was able to establish a clinical bridge to Epiduo Forte gel (0.3% adapalene and 2.5% benzoyl peroxide). However, Epiduo Forte gel is approved for 12 years of age and older. Thus, for pediatric patients ages 9 to 11 years and 11 months, additional information is needed about systemic exposure and safety after exposure to IDP-126 gel applied to acne vulgaris. Deferred pediatric studies in pediatric patients ages 9 to 11 years 11 months will be conducted as required by Pediatric Research Equity Act (PREA). The product will be recommended to be approved for the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older.

In summary, acne vulgaris is a chronic disease which may be associated with substantial impairment of quality of life. IDP-126 gel provides an additional treatment option, particularly as a new triple fixed combination therapy. The available evidence of safety and efficacy supports the approval of IDP-126 gel, CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel, 1.2%/0.15%/3.1%, for the treatment of acne vulgaris in the population 12 years of age and older. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. Acne occurs most frequently on the face and is characterized by 2 major types of lesions: noninflammatory (open or closed comedones) and inflammatory lesions (papules, pustules, and nodules). The etiology is multifactorial. Because of the chronic relapsing, and remitting course and potential for scarring after lesions resolve, acne may be associated with substantial impairment of quality of life.	Acne is a common chronic disorder with a range of disease severities which may significantly impact quality of life.
Current Treatment Options	Many topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antibiotics and antimicrobials (e.g., erythromycin, clindamycin, benzoyl peroxide) systemic hormonal therapies (e.g., ethinyl estradiol/norgestimate) and topical retinoids (e.g., tretinoin, tazarotene). Oral formulations of isotretinoin are available for severe, recalcitrant, nodulo-cystic acne. Treatment is individualized according to the types of lesions, severity of disease, and patient preferences. Topical retinoids, topical clindamycin, and topical benzoyl peroxide are generally considered as part of an initial treatment regimen.[1]	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of acne vulgaris in adolescents and adults. However, the response to treatment varies with the lesion type, severity of the disease and compliance with the treatment regimen. There is a need for a new triple fixed combination therapy that promotes compliance by addressing patient preferences.

Benefit	Data from 2 adequate and well controlled trials (Study 301 and 302), provided substantial evidence of the effectiveness of IDP-126 gel for the treatment of acne vulgaris. These trials enrolled 363 subjects (242 subjects treated with IDP-126 gel and 121 subjects treated with Vehicle gel) age 10 years and older with moderate to severe acne vulgaris. IDP-126 gel was superior to vehicle in both trials for the co-primary efficacy endpoints of absolute change in inflammatory lesion count, absolute change in non-inflammatory lesion count and EGSS success.	IDP-126 gel provides an effective treatment option for patients with moderate to severe acne vulgaris.

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

Risk	The primary safety database (Study 301 and 302) included 242 subjects who received IDP-126 gel once daily for 12 weeks. There were no deaths or serious adverse events related to the study product. The most common adverse reactions occurring in ≥1% of subjects and greater than vehicle was localized to the application site: pain, erythema, dryness/xerosis, irritation, exfoliation, and dermatitis. Active assessment of local adverse reactions indicated that some reactions were severe. Review of the safety data from clinical trials identified no new safety signals with this new triple fixed combination of clindamycin phosphate, adapalene, and benzoyl peroxide. IDP-126 gel was well tolerated in all evaluated subgroups. Evaluation of safety and effectiveness of the drug product require further assessment in pediatric subjects 9-11 years and 11 months of age with a post marketing requirement.	The risks associated with the use of IDP-126 gel are similar to other topical clindamycin, adapalene, and benzoyl peroxide products. Local effects such as irritation and pigmentary changes may occur during treatment and may be severe. IDP-126 gel provides a reasonably safe treatment option for patients 12 years of age and older with moderate to severe acne vulgaris. The following postmarketing requirement (PMR) will be recommended: Conduct an open-label study to assess safety, pharmacokinetics, and treatment effect of CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) Topical Gel, 1.2%/0.15%/3.1% in 100 pediatric subjects ages 9 to 11 years 11 months with acne vulgaris.
Risk Management	Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and identified during product development. A risk evaluation and mitigation strategy (REMS) is not recommended.	Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the risks of the product.

1.4. Patient Experience Data

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

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Not applicable. Subjects completed the Acne-Specific Quality of Life Questionnaire at baseline and the end of study visit at Week 12 in Studies 301 and 302. The protocols did not include prespecified endpoints based on this instrument. As the endpoints related to the PRO were not prespecified or controlled for multiplicity, the data will not be included in labeling or discussed in this review.
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1.2
		☐	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

2.1. Analysis of Condition

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

Acne is an inflammatory disease of sebaceous follicles. Factors which contribute to the complex pathophysiology of acne include bacterial colonization of follicles, hypersecretion of the sebaceous glands, and intrafollicular hypercornification. At adrenarche, increased androgen stimulation may result in both abnormal keratinization of the sebaceous follicle and increased sebum production in the sebaceous gland. Obstruction of the follicular orifice of the sebaceous gland by desquamated keratinocytes produces a microcomedone. Prolonged fundibular blockage, proliferation of propionibacterium acnes in the sebaceous follicle, and production of

[2] Bhate K, Williams HC. Epidemiology of acne vulgaris. BJD. 2013 168, pp474–485.

[3] UpToDate. Thiboutot, D et al. Accessed July 4, 2023.

[4] Zaenglein AL et al. Guidelines of care for the management of acne vulgaris. JAAD. 2016 May;74(5):945-73.e33.

multiple chemoattractant and proinflammatory cytokines may trigger the formation of noninflammatory and inflammatory lesions.[5]

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

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

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

The clinical course is characterized by remissions and recurrences. In some individuals, acne may persist for decades and resolve with scarring. The association of acne with depression, anxiety and reduced quality of life is well documented.[7] Successful treatment may produce a significant improvement in self-esteem.[8]

2.2. Analysis of Current Treatment Options

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

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[5] Brown SK, Shalita AR. Acne vulgaris. Lancet. 1998. 351; 9119:1871-1876.

[6] Dawson AL et al. Acne Vulgaris. BMJ 2013;346: 2634.

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

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

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 (b) (4)
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: Table 1, NDA 214902, Clinical Review by Shera Schreiber, 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: headache W&P: flammability, (from oral minocycline): teratogenicity, tooth discoloration, inhibition of bone growth, Clostridium difficile associated diarrhea, hepatotoxicity; azotemia, hyperphosphatemia, and acidosis (w/ renal impairment), 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

			• 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 Active vs. vehicle Trial one: • 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 Active vs. vehicle 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: Table 2, NDA 214902, Clinical Review by Shera Schreiber, MD

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: Table 3, NDA 214902, Clinical Review by Shera Schreiber, MD

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The proposed product, CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) gel, 1.2%/0.15%/3.1%, is not approved in the U.S. or any other jurisdiction. As there is no marketing history, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed IDP-126 gel for the treatment of acne vulgaris under the 505(b)(2) regulatory pathway with reliance on data from the listed drug, EPIDUO FORTE [adapalene 0.3%/BPO 2.5%] Gel (NDA 207917). In addition, the Applicant has ownership and right of reference to ACANYA Gel [clindamycin 1.2%/benzoyl peroxide 2.5%] (NDA 050819), ONEXTON Gel [clindamycin 1.2%/benzoyl peroxide 3.75%]) (NDA 050819) and BENZACLIN [clindamycin phosphate 1.2%/BPO 5%] Gel (NDA 050756).

The Applicant interacted with the Agency during two milestone meetings: End-of-Phase 2 Meeting (EOP2) held on August 28, 2019, and Pre-NDA meeting held on April 27, 2022.

At the EOP2 meeting (under IND 131347, the Agency agreed that conducting two phase 3 studies of IDP-126 gel versus vehicle is acceptable and the design and endpoints proposed in the protocol are appropriate for assessing efficacy (meeting minutes dated September 20, 2019).

At the Pre-NDA meeting, the Agency noted that the bridging strategy to EPIDUO FORTE Gel and the clinical program appeared adequate for filing and that the adequacy of the bridging study and clinical program would be a review issue. The Agency agreed that the Applicant's proposed total subject exposure (925 subjects exposed to at least 1 dose, 646 of whom were subjects with acne treated with the to-be-marketed formulation of IDP-126 gel) appeared reasonable if the Applicant can establish an adequate clinical bridge. The Agency noted (b) (4) The Agency agreed that it was reasonable that a long-term safety study will likely not be needed, however, that the final determination of the issue would be made during the application review of the safety experience and pharmacokinetic (PK) data, (b) (4) . The Agency agreed that the Applicant's plan to request a waiver for conducting a Thorough QT (TQT) study appeared reasonable and a final determination would be made at the time of the NDA review (meeting minutes dated May 27, 2022).

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

4.1. Office of Scientific Investigations

No sites were recommended to OSI for inspections as there were no sites that had disproportionately high enrollment numbers that were driving safety or efficacy results.

Two investigators had >$25,000 payments received from the Applicant reported on their financial disclosure forms. However, the enrollment numbers at each of these sites were not disproportionate to the others (b) (6)

4.2. Product Quality

CABTREO topical gel is opaque, white to off-white gel supplied as 20 and 50 g in tube or pump. The Applicant has referenced to the following drug master files (DMFs) for each drug substance: DMF (b) (4) for adapalene; DMF (b) (4) for clindamycin phosphate; and DMF (b) (4) for benzoyl peroxide. All DMFs are found adequate.

CABTREO Gel, 1.2%/3.1%/0.15% consists of the following ingredients: clindamycin phosphate (active, 1.2%), benzoyl peroxide (active, 3.1%), adapalene (active, 0.15%), propylene glycol, carbomer homopolymer 980, potassium hydroxide, and purified water. All the excipients have a history of safety in topical pharmaceutical products and their corresponding concentrations are within the levels reported in the FDA's Inactive Ingredient Database. There are no excipients of human or animal origin. CABTREO Gel is packaged in 20 g and 50 g fill size (b) (4)

bottles fitted with pumps, 20 g and 50 g fill size laminate tubes with (b) (4) caps, and in 3.5 g (physician sample size) laminate tubes with (b) (4) caps. CABTREO Gel is manufactured at Bausch Health Companies Inc. in Laval, Quebec, Canada. The Applicant provided adequate risk assessments for residual solvents, elemental impurities, and (b) (4) impurities. The proposed shelf-life of IDP-126 drug product in all trade sizes is 21 months at (b) (4) with an in-use stability of 10 weeks at controlled room temperature condition of (b) (4)

Based on OPQ's evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate chemistry, manufacturing, and controls information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. Refer to the original IQA review, dated 08/07/2023 for the details.

Thus, OPQ recommends APPROVAL of NDA 216632 for commercialization of CABTREO (clindamycin phosphate/adapalene/benzoyl peroxide) topical gel, 1.2%/0.15%/3.1%.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(2) application for CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel, 1.2%, 0.15%, and 3.1%, for the treatment of acne vulgaris in patients (b) (4) years of age and older. The active pharmaceutical ingredients are each present at the same or higher strengths in topical drug products approved for the treatment of acne vulgaris in patients 12 years of age and older.

The Applicant is relying on genotoxicity and developmental and reproductive toxicity information from the labeling of topical gel products containing clindamycin phosphate (up to 1.2%) and benzoyl peroxide (up to 5%) and Epiduo Forte (adapalene/benzoyl peroxide) gel, 0.3%/2.5%. The Applicant also submitted the following nonclinical studies to support the NDA: a 13-week dermal repeat dose toxicity study in minipigs; an in vitro hERG assay; an in vitro

phototoxicity assay; an in vitro ocular irritation assay; and in silico assessments of two leachable impurities (b) (4) Under the submitted nonclinical studies, the gel formulation used the code name IDP-126, which contained clindamycin phosphate, adapalene, and benzoyl peroxide at variable concentrations, including sub-clinical (0.24%, 0.03%, and 0.62%, respectively), clinical (1.2%, 0.15%, and 3.1%, respectively), and enriched (2.4%, 0.3%, and 6.2%, respectively) levels; slightly lower concentrations of benzoyl peroxide (2.5%) were used to evaluate phototoxic and ocular irritation potential. For clarity, this review will use the code name IDP-126 in the context of nonclinical studies.

In vitro, clindamycin phosphate, adapalene, and benzoic acid (the metabolite of benzoyl peroxide) did not produce clinically relevant inhibition of the hERG potassium current.

In a 13-week dermal repeat dose toxicity study in minipigs, IDP-126 (clindamycin phosphate/adapalene/benzoyl peroxide) gel, up to 2.4%/0.3%/6.2%, was applied once daily to 10% body surface area. No IDP-126 gel-related mortality, clinical observations, or microscopic findings were noted. IDP-126 gel-treated groups displayed a generally increased incidence of transient, low severity, non-adverse erythema. The no observed adverse effect level (NOAEL) was the high dose (HD) gel (2.4% clindamycin phosphate, 0.3% adapalene, 6.2% benzoyl peroxide) in both sexes, which corresponds to a Day 91 area under the concentration-time curve $(AUC)_{0\text{-}24}$ and C_{max} of 93.2/158 hr·ng/mL (clindamycin phosphate/adapalene) and 13.9/12.6 ng/mL, respectively, in females, and 66.2/185 hr·ng/mL and 10.7/17.8 ng/mL, respectively, in males.

In vitro, IDP-126 (clindamycin phosphate/adapalene/benzoyl peroxide) gel, 1.2%/0.15%/2.5%, did not display phototoxic potential and was predicted to have minimal to no ocular irritancy potential.

The Applicant proposes to control eight specified impurities (b) (4) at levels requiring qualification; these compounds are qualified at the proposed specification limits.

Four potential leachable impurities, (b) (4) respectively, based on a maximum daily dose of 2.5 g gel. However, these leachable impurities do not present a clinically relevant risk of genotoxicity. Additionally, (b) (4) are well below their permitted daily exposure based on available nonclinical data (b) (4) As such, there are no nonclinical safety concerns regarding the expected levels of leachable impurities.

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

The Applicant owns and has right of reference to the following listed drugs:

- NDA 050819: Acanya (clindamycin phosphate/benzoyl peroxide) gel, 1.2%/2.5%
- NDA 050819: Onexton (clindamycin phosphate/benzoyl peroxide) gel, 1.2%/3.75%
- NDA 050756: Benzaclin (clindamycin phosphate/benzoyl peroxide) gel, 1%/5%

The Applicant generated a clinical bridge to allow for reliance on the nonclinical data from the following listed drug:

- NDA 207917: Epiduo Forte (adapalene/benzoyl peroxide) gel, 0.3%/2.5%

5.3. Pharmacology

Clindamycin is a lincosamide antibacterial.

Adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor protein. Adapalene modulates cellular differentiation, keratinization, and inflammatory processes. However, the mechanism of action is unknown.

Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects, but the mechanism of action is unknown.

Safety Pharmacology

Cardiovascular Effects

In vitro, clindamycin, adapalene, and benzoic acid—individually and all three in combination—did not produce clinically relevant hERG potassium current inhibition.

5.4. ADME/PK

Table 4. Summary of Toxicokinetic Data

Type of Study	Major Findings
TK data from general toxicology studies Three-Month Dermal GLP Repeat Dose Toxicity Study of IDP-126 gel in Minipigs / 0645-17223	Minipig @ HD (2.4% clindamycin phosphate, 6.2% benzoyl peroxide, 0.3% adapalene) on Day 91 Clindamycin: t_{max}: 2 (female) and 1 hr (male) AUC_{0-24}: 93.2 (female) and 66.5 hr·ng/mL (male) C_{max}: 13.9 (female) and 10.7 ng/mL (male) Adapalene: t_{max}: 2 (female) and 2 hr (male) AUC_{0-24}: 158 (female) and 185 hr·ng/mL (male) C_{max}: 12.6 (female) and 17.8 ng/mL (male) Accumulation: Noted between Day 1 and 28, but not thereafter Dose proportionality: Exposure increased approximately dose-proportionally

Source: NDA submission

5.5. Toxicology

5.5.1. General Toxicology

Study Title/ Number: Three-Month Dermal GLP Repeat Dose Toxicity Study of IDP-126 Gel in Minipigs / 0645-17223

- Clindamycin and adapalene exposure increased approximately dose-proportionally, tended to be higher in females, and displayed accumulation between Days 1 and 28, but not thereafter.
- IDP-126 gel was well-tolerated up to the HD in both sexes; no IDP-126 gel-related mortality, clinical observations, or microscopic findings were noted.
- IDP-126 gel-treated groups displayed a generally increased incidence of transient, low severity, non-adverse erythema.
- The NOAEL was the HD gel (2.4% clindamycin phosphate, 0.3% adapalene, 6.2% benzoyl peroxide) in both sexes, which corresponds to a Day 91 AUC0-24 and Cmax of 93.2/158 hr·ng/mL (clindamycin phosphate/adapalene) and 13.9/12.6 ng/mL, respectively, in females, and 66.2/185 hr·ng/mL and 10.7/17.8 ng/mL, respectively, in males.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 5. Methods Table for 3-Month Dermal Minipig Study

Methods	
Dose and frequency of dosing:	Untreated (0% clindamycin phosphate, 0% adapalene, 0% benzoyl peroxide) Vehicle (0%, 0%, 0%) Low dose (0.24%, 0.03%, 0.62%) Mid dose (1.2%, 0.15%, 3.1%) High dose (2.4%, 0.3%, 6.2%) Once daily applied to 10% BSA
Route of administration:	TOPICAL
Formulation/Vehicle:	Clinical vehicle formulation (b) (4) propylene glycol, (b) (4) carbomer 980, (b) (4) potassium hydroxide, (b) (4) (b) (4) water)
Species/Strain:	PIG / (b) (4)
Number/Sex/Group:	2 (untreated) or 4 (vehicle and IDP-126 gel; plus 2/sex vehicle, MD, and HD for 4-week recovery)
Age:	4-5 months old at dosing initiation
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Source: NDA Submission

Table 6. Observations and Results: Changes From Control

Parameters	**Major findings**
Mortality	No IDP-126 gel-related effects.
Clinical Signs	No IDP-126 gel-related effects.
Body Weights	No IDP-126 gel-related effects.
Ophthalmoscopy	No IDP-126 gel-related effects.
ECG	No IDP-126 gel-related effects.
Hematology	No IDP-126 gel-related effects.
Clinical Chemistry	No clear IDP-126 gel-related effects.
Urinalysis	No IDP-126 gel-related effects.
Gross Pathology	No IDP-126 gel-related effects.
Organ Weights	No IDP-126 gel-related effects.
Histopathology Adequate battery: Yes	No IDP-126 gel-related effects.
Dermal Observations	All IDP-126 gel-treated males and MD and HD females displayed non-adverse transient erythema (generally very slight to well-defined). Erythema incidence (but not severity) was generally dose-related in females, but not males.

Source: NDA submission
-: indicates reduction in parameters compared to control.
*: [if the answer is "no" explain why the histopath battery is not adequate]
Abbreviations: LD: low dose; MD: mid dose; HD: high dose.

5.5.2. General Toxicology; Additional Studies

Phototoxicity

EpiDerm tissues were treated with IDP-126 (clindamycin phosphate/adapalene/benzoyl peroxide) gel, 1.2%/0.15%/2.5%, or controls for 24 hours, then rinsed and exposed to UVA (6 J/cm^2) or dark for 1 hour to evaluate phototoxic potential. Negative (IDP-126 vehicle gel), solvent (1% dimethyl sulfoxide in Hanks' Balanced Salt Solution), and positive (0.02% chlorpromazine in Hanks' Balanced Salt Solution) controls yielded expected results. IDP-126 gel was not phototoxic.

Ocular Irritation

EpiOcular cultures were incubated with IDP-126 (clindamycin phosphate/adapalene/benzoyl peroxide) gel, 1.2%/0.15%/2.5%, or controls for 8, 16, or 24 hours and evaluated for ocular irritation potential. Vehicle (IDP-126 vehicle gel), negative (water), and positive (0.3% Triton-X-100 in water) controls yielded expected results. IDP-126 gel was predicted to be non-irritating or minimally irritating.

Impurities

Based on the proposed specifications, two of the drug substances contain impurities above the qualification threshold. Clindamycin phosphate contains (b) (4) As such, the clindamycin impurities are qualified from a nonclinical perspective at the proposed specification limits. The two adapalene impurities above the qualification threshold, (b) (4) However, (b) (4) As such, these drug substance impurities are qualified from a nonclinical perspective.

Four potential leachable impurities of concern were identified in an extractables and leachables assessment for the drug product, including two from (b) (4) with a maximum daily dose of 2.5 g gel. (b) (4) were predicted in silico to be negative for genotoxicity.

The Applicant primarily used (b) (4) to support the safety and permitted daily exposure (PDE) for each. Based on available data from the (b) (4): none are mutagenic in in vitro bacterial reverse mutation assays; erucamide is not clastogenic in an in vitro mammalian chromosome aberration assay; (b) (4)

The Applicant's proposed PDE for each leachable was based on the NOAEL (or lower) dose for (b) (4) in a 90-day repeat dose toxicity study in rats); (b) (4) in a 90-day repeat dose toxicity study in rats); (b) (4) in a reproductive study in which the whole period of organogenesis is covered); and (b) (4) in a 90-day repeat dose toxicity study in rats). The PDE for (b) (4) The Applicant's PDEs for these compounds are acceptable and these leachable compounds do not present safety concerns from a nonclinical perspective.

5.5.3. Genetic Toxicology

Genetic toxicology information contained in the labeling from the listed drugs (Acanya [clindamycin phosphate and benzoyl peroxide] gel, 1.2%/2.5%; Benzaclin [clindamycin phosphate/benzoyl peroxide] gel, 1%/5%; Epiduo Forte [adapalene and benzoyl peroxide] topical gel, 0.3%/2.5%) is provided below.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Clindamycin phosphate was not genotoxic in Salmonella typhimurium or in a rat micronucleus test. (b) (4) was not clastogenic in a mouse micronucleus test.

Adapalene was not mutagenic or genotoxic in vitro (Ames test, Chinese hamster ovary cell assay, or mouse lymphoma toxicokinetic (TK) assay) or in vivo (mouse micronucleus test).

Benzoyl peroxide caused DNA strand breaks and DNA-protein cross-links in mammalian cells, increased sister chromatid exchanges in Chinese hamster ovary cells, and was mutagenic in a few, but not all, in vitro bacterial mutagenicity assays (Ames tests) conducted.

5.5.4. Carcinogenicity

No carcinogenicity studies were conducted with CABTREO gel. However, carcinogenicity information contained in the labeling from two right of reference drugs (Acanya [clindamycin phosphate and benzoyl peroxide] gel, 1.2%/2.5%; Benzaclin [clindamycin phosphate/benzoyl peroxide] gel, 1%/5; and the listed drug Epiduo Forte [adapalene and benzoyl peroxide] topical gel, 0.3%/2.5%) is provided below.

In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 900, 2700, and 15000 mg/kg/day did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. The incidence of keratoacanthoma at the treated site of males treated with 2000 mg/kg/day was statistically significantly higher than that in the sham- and vehicle-controls.

In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900, and 3000 mg/kg/day for up to 97 weeks did not cause any increase in tumors.

Carcinogenicity studies with adapalene were conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m^2/day) and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m^2/day). In the rat study, an increased incidence of benign and malignant pheochromocytomas reported in the adrenal medulla of male rats was observed.

Benzoyl peroxide is a tumor promoter in several animal species. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg/kg benzoyl peroxide. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2-year study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

5.5.5. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Fertility studies have not been performed with CABTREO gel or benzoyl peroxide. Fertility and mating ability have been studied with orally administered clindamycin and adapalene, as described in the labeling from the listed drugs and provided below.

Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin revealed no effects on fertility or mating ability.

In rat oral studies, 20 mg/kg/day adapalene did not affect the reproductive performance and fertility of F_0 males and females, or the growth, development and reproductive function of F_1 offspring.

Embryo-Fetal Development

Embryofetal development studies have been conducted with clindamycin and with Epiduo Forte (adapalene and benzoyl peroxide) topical gel, 0.3%/2.5%, as described in the labeling from the listed drugs and provided below.

Developmental toxicity studies of clindamycin performed in pregnant rats and mice administered during the period of organogenesis at oral doses of up to 600 mg/kg/day or subcutaneous doses of up to 200 mg/kg/day revealed no malformations or embryo-fetal development toxicity.

No malformations were observed in rats treated with oral adapalene doses of 0.15 to 5.0 mg/kg/day. However, malformations were observed in rats and rabbits when treated with oral doses of ≥ 25 mg/kg/day adapalene. Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits.

Dermal adapalene embryofetal development studies in rats and rabbits at doses up to 6.0 mg/kg/day exhibited no fetotoxicity and only minimal increases in skeletal variations (supernumerary ribs in both species and delayed ossification in rabbits).

Prenatal and Postnatal Development

Pre- and postnatal development studies have not been performed with CABTREO gel, clindamycin, benzoyl peroxide, or adapalene.

6 Clinical Pharmacology

IDP-126 gel contains three active ingredients, clindamycin phosphate (1.2%), adapalene (0.15%) and BPO (3.1%). Clindamycin is a lincosamide antibiotic, adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes and benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

The Applicant is pursuing a 505(b)(2) regulatory pathway with EpiDuo Forte Gel, (adapalene/BPO, 0.3%/2.5%) as listed drug.

The proposed dosage regimen is to apply a thin layer of IDP-126 topically to the affected area once daily.

The Clinical Pharmacology program included a maximal use PK bridging study, V01-126A-501, which evaluated the pharmacokinetics of IDP-126 gel in comparison with EpiDuo Forte Gel in subjects with acne vulgaris under maximal use conditions. In Study V01-126A-501, the Applicant compared the PK of adapalene following administration of IDP-126 gel and EpiDuo Forte Gel, in support of clinical bridge establishment in subjects 12 years and older. As the Applicant has the right of reference for Acanya Gel (clindamycin phosphate/BPO, 1.2%/2.5%) and Onexton Gel (clindamycin phosphate/BPO, 1.2%/3.75%), the PK bridging was needed for adapalene only and not for clindamycin. In addition, the Applicant characterized the PK of clindamycin phosphate in the IDP-126 gel treatment group. The PK of BPO was not evaluated due to its rapid and complete conversion to benzoic acid and difficulty analyzing benzoic acid which is an endogenous compound.

The key review findings with specific recommendations and comments are summarized below in Table 7.

Table 7. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or Supportive Evidence of Effectiveness	Efficacy was not evaluated as a part of the Clinical Pharmacology program. See Section 8.1 for efficacy studies and their results.
General Dosing Instruction	The proposed once daily application to the affected areas is acceptable and is supported by efficacy and safety results.
PK	The PK of adapalene and clindamycin phosphate following once daily application of IDP-126 gel was evaluated in subjects 9 years and older. The PK of adapalene was evaluated following once daily application of EpiDuo Forte Gel in subjects 12 years and older.
Clinical Bridge between IDP-126 gel and the Listed Drug(s)	The relative bioavailability (BA) data supports establishment of a clinical bridge between IDP-126 gel and EpiDuo Forte Gel. The PK bridging for clindamycin component was not needed as the Applicant has the right of reference for Acanya Gel and Onexton Gel, both of which contains the same strength (1.2%) of clindamycin phosphate as IDP-126 gel. The PK bridging for benzoyl peroxide is waived due to its rapid and near-complete conversion to benzoic acid and difficulty analyzing benzoic acid which is an endogenous compound.
Formulation used in clinical trial	To-be-marketed formulation of IDP-126 was used in Study V01-126A-501.
Pediatrics	The PK of IDP-126 gel was evaluated in pediatric subjects 9 years and older in Study V01-126A-501. A waiver for conducting a study for subjects 0 to < 9 years of age has been agreed to in the initial Pediatric Study Plan.
Bioanalysis	Validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods were used to quantify adapalene and clindamycin in PK samples obtained from Study V01-126A-501.

Source: Reviewer generated table

6.1. Recommendations

From a clinical pharmacology standpoint, this NDA is approvable.

6.1.1. Post-Marketing Requirement(s) and Commitments(s)

The PK of IDP-126 gel was evaluated in only 8 subjects in the age group 9 to < 12 years in Study V01-126A-501. A postmarketing requirement (PMR) is recommended to obtain additional PK data in this younger pediatric age group along with safety and efficacy data. See Section 13 for details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 8. Summary of Clinical Pharmacology

Mechanism of Action	Clindamycin: a lincosamide antibacterial with anticomedogenic and anti-inflammatory properties Adapalene: a synthetic retinoid with anticomedogenic and anti-inflammatory properties which modulates cellular differentiation, keratinization and inflammatory processes BPO: an oxidizing agent with bactericidal, comedolytic, anti-inflammatory and keratolytic properties The exact mechanism of action of these three active ingredients for the treatment of acne vulgaris is unknown.
PK Parameters	Systemic concentrations of clindamycin and adapalene were at or near steady state by Day 14 following once daily application. The tables below summarize PK parameters of clindamycin and adapalene on Days 28-29 following once daily topical application of IDP-126 gel and/or EpiDuo Forte Gel in subjects with acne vulgaris.
Relative Bioavailability/ PK bridging	In subjects ≥ 12 years of age, the systemic exposure to adapalene in the IDP-126 gel treatment group was lower than that in the EpiDuo Forte Gel treatment group. The ratios of arithmetic mean (IDP-1126/EpiDuo Forte) were

Table 9. PK summary for Clindamycin

Clindamycin[a]			
		IDP-126 9 to < 12 years	**IDP-126** ≥ 12 years
C_{max} (ng/mL)	Mean (SD)[b]	2.71 (2.09)	2.44 (1.95)
	N	8	19
AUC_{0-t} (ng*h/mL)	Mean (SD)[b]	24.5 (19.1)	30.7 (24.5)
	N	8	19

Source: V01-126A-501 CSR Table 14.3.0.1.2.1
[a] Evaluated only in the IDP-126 gel treatment group
[b] Plasma concentrations below the lower limit of quantitation (LLOQ), 0.0500 ng/mL, were set to 0.00 ng/mL.

Table 10. PK summary for Adapalene

Adapalene				
		IDP-126 9 to < 12 years	**IDP-126** ≥ 12 years	**EpiDuo Forte** ≥ 12 years
C_{max} (ng/mL)	Mean (SD)[a]	0.190 (0.155)	0.0966 (0.100)	0.191 (0.139)
	N	8	19	19
AUC_{0-t} (ng*h/mL)	Mean (SD)[a]	3.24 (1.81)	2.40 (1.07)	3.68 (1.85)
	N	6	9	13

Source: V01-126A-501 CSR Table 14.3.0.1.2.2
[a] Plasma concentrations below the LLOQ, 0.100 ng/mL, were set to 0.00 ng/mL.

	0.596 and 0.653 for C_{max} and AUC_{0-t}, respectively on Days 28-29. The results support the establishment of a clinical bridge between the two products in subjects ≥ 12 years of age.
Pharmacodynamics (PD)	PD was not evaluated in this NDA.
Bioanalysis	Validated LC-MS/MS methods were used for quantification of clindamycin and adapalene in plasma samples collected from Study V01-126A-501. The methods were adequately validated and the bioanalysis for sample analysis were acceptable. See Section 14.4 for details.

Source: Reviewer generated table

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is to apply a thin layer of IDP-126 gel topically to the affected areas once daily. This dosing regimen is supported by systemic safety data from the maximal use study (V01-126A-501) and efficacy and safety data from Phase 3 trials, V01-126A-301 and V01-126A-302.

Therapeutic Individualization

Therapeutic individualization was not evaluated in this NDA.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The PK characteristics of clindamycin and adapalene following application of IDP-126 gel and the PK of adapalene following application of EpiDuo Forte were assessed in Study V01-126A-501 under maximal use conditions. V01-126A-501 was a Phase 1b, open-label, randomized study designed to assess the safety and plasma PK of topically applied IDP-126 gel in comparison to EpiDuo Forte in subjects with acne vulgaris.

Eligible subjects for the study were at least 9 years of age and older for the IDP-126 gel group and at least 12 years of age and older for EpiDuo Forte Gel group. Subjects had a clinical diagnosis of moderate to severe acne vulgaris (defined as an EGSS of 3 [moderate] or 4 [severe] and at least 30 inflammatory facial lesions (e.g. papules, pustules, nodules), at least 35 noninflammatory facial lesions (e.g. open and closed comedones), ≤ 2 facial nodules, and acne lesions present in any 1 or more of the truncal areas (i.e., chest, back, and/or shoulder).

Subjects were instructed to apply approximately 2.5 g of the assigned drug to the neck, upper chest, upper back, and shoulders once daily, at approximately the same time each morning, for 28 days.

A total of 61 subjects were randomized, including 38 in the IDP-126 gel group (8 of whom were 9 to 11 years, 11 months of age and 30 of whom were ≥ 12 years of age) and 23 in the EpiDuo Forte Gel group. Of the 61 randomized subjects, 46 (75.4%) subjects completed the study. Of the 15 subjects who discontinued early, 13 were at the Applicant's request due to the randomization system error resulting in no assignment to the EpiDuo Forte Gel group and the other 2 were at the subject's request. A total of 61 subjects were included in the safety population (all enrolled subjects who received at least 1 confirmed application of study drug). A total of 48 subjects were included in the PK population (all enrolled subjects who received at least 1 application of study drug, had at least 1 postbaseline safety assessment, and had any PK data on Days 1, 2, 14, 15, 28, and 29). Demographics and baseline characteristics of the PK population are summarized in Table 11.

Table 11. Demographics and Baseline Characteristics of the PK Population in Study V01-126A-501

		IDP-126 9 to < 12 years (n=8)	IDP-126 ≥ 12 years (n=20)	EpiDuo Forte ≥ 12 years (n=20)
Age (years)	Mean (SD)	10.3 (1.04)	19.6 (5.82)	18.6 (4.65)
	Minimum to Maximum	9 to 11	14 to 36	13 to 31
Sex, n (%)	Male	0	9 (45.0)	9 (45.0)
	Female	8 (100.0)	11 (55.0)	11 (55.0)
Race, n (%)	Black or African American	2 (25.0)	3 (15.0)	1 (5.0)
	Native Hawaiian or Other Pacific Islander	0	1 (5.0)	0
	White	6 (75.0)	16 (80.0)	18 (90.0)
Ethnicity, n (%)	Hispanic or Latino	4 (50.0)	9 (45.0)	7 (35.0)
	Not Hispanic or Latin	4 (50.0)	11 (55.0)	13 (65.0)
Inflammatory Lesion Count	Mean (SD)	39.6 (15.85)	44.0 (15.26)	42.1 (6.97)
	Median	33.5	39.0	40.0
	Minimum to Maximum	31 to 78	30 to 80	34 to 63
Noninflammatory Lesion Count	Mean (SD)	43.4 (7.17)	47.6 (17.55)	55.6 (24.10)
	Median	42.0	39.5	52.0
	Minimum to Maximum	36 to 57	35 to 105	35 to 147
Evaluator's Global Severity Score, n (%)	3 – Moderate	8 (100.0)	5 (25.0)	5 (25.0)
	4 – Severe	0	15 (75.0)	15 (75.0)

Source: V01-126A-501 CSR, Table 11-1

The extent of exposure to study drug is summarized in Table 12. The treatment compliance of the PK population was acceptable in all treatment groups. The daily amount of study drug applied is summarized in Table 13.

Table 12. Extent of Exposure to Study Drug (PK Population) in Study V01-126A-501

	IDP-126 (< 12 Years) (N = 8)	IDP-126 (≥ 12 Years) (N = 20)	EpiDuo Forte (≥ 12 Years) (N = 20)
Compliance (%)			
Mean (SD)	99.55 (1.263)	96.87 (5.497)	97.34 (7.521)
Median	100.00	100.00	100.00
Minimum to Maximum	96.4 to 100.0	82.1 to 100.0	68.2 to 103.6
Compliance Categories, n (%)			
≤ 60%	0	0	0
> 60% to 80%	0	0	1 (5.0)
> 80% to 100%	8 (100.0)	20 (100.0)	18 (90.0)
> 100%	0	0	1 (5.0)
Total Amount of Study Drug Used (g)			
Mean (SD)	56.08 (21.386)	57.32 (11.250)	61.37 (20.475)
Median	61.95	57.50	65.40
Minimum to Maximum	29.2 to 92.6	37.4 to 74.7	21.8 to 108.0
Number of Doses			
Mean (SD)	27.9 (0.35)	26.8 (2.81)	27.1 (2.99)
Median	28.0	28.0	28.0
Minimum to Maximum	27 to 28	17 to 29	15 to 29

Source: V01-126A-501 CSR, Table 14.3.0.2.2

Table 13. Daily Amount of Study Drug Applied in Study V01-126A-501

Daily Amount (g)	IDP-126 9 to < 12 years	IDP-126 ≥ 12 years	EpiDuo Forte ≥ 12 years
Mean	2.01	2.16	2.28
SD	0.76	0.43	0.76
Median	2.21	2.10	2.43
Minimum to Maximum	1.04 to 3.31	1.33 to 2.99	0.78 to 4.32
N	8	19	19

Source: Reviewer's analysis

The PK samples were collected to measure plasma concentrations of adapalene and clindamycin from the IDP-126 gel treatment group and adapalene from the EpiDuo Forte Gel group. The sampling timepoints were different in younger subjects (9 to < 12 years) and in older subjects (≥ 12 years) as shown in Table 14 and Table 15, respectively.

Table 14. Schedule of PK Assessments (IDP-126 Gel Group Only) for Subjects 9 to 11 years, 11 Months of Age

Assessment Day	Prior to Application[a]	Postapplication								
		2 hr (± 10 min)	4 hr (± 15 min)	6 hr (± 15 min)	8 hr (± 15 min)	10 hr (± 30 min)	12 hr (± 30 min)	14 hr (± 30 min)	16 hr (± 30 min)	24 hr (± 60 min)
Day 1	X									
Days 14-15	X		X				X			X[b]
Days 28-29	X	X	X	X	X	X	X	X	X	X[c]

a Prior to the morning application of study drug.
b Collected 24 hours after study drug application on Day 1 and Day 14, and prior to the morning application of study drug on Day 2 and Day 15, respectively.
c Collected 24 hours after study drug application on Day 28 (ie, the last study drug application).
Source: V01-126A-501 CSR, Table 9-4

Table 15. Schedule of PK Assessments (IDP-126 Gel and EpiDuo Forte Gel Groups) for Subjects ≥ 12 Years of Age

Assessment Day	Prior to Application[a]	Postapplication								
		2 hr (± 10 min)	4 hr (± 15 min)	6 hr (± 15 min)	8 hr (± 15 min)	10 hr (± 30 min)	12 hr (± 30 min)	14 hr (± 30 min)	16 hr (± 30 min)	24 hr (± 60 min)
Days 1-2	X	X	X	X	X	X	X	X	X	X[b]
Days 14-15	X		X				X			X[b]
Days 28-29	X	X	X	X	X	X	X	X	X	X[c]

a Prior to the morning application of study drug.
b Collected 24 hours after study drug application on Day 1 and Day 14, and prior to the morning application of study drug on Day 2 and Day 15, respectively.
c Collected 24 hours after study drug application on Day 28 (ie, the last study drug application).
Source: V01-126A-501 CSR, Table 9-3

The mean ± SD of clindamycin concentrations following once daily application of IDP-126 gel in subjects 9 to < 12 years of age and ≥ 12 years of age are shown in

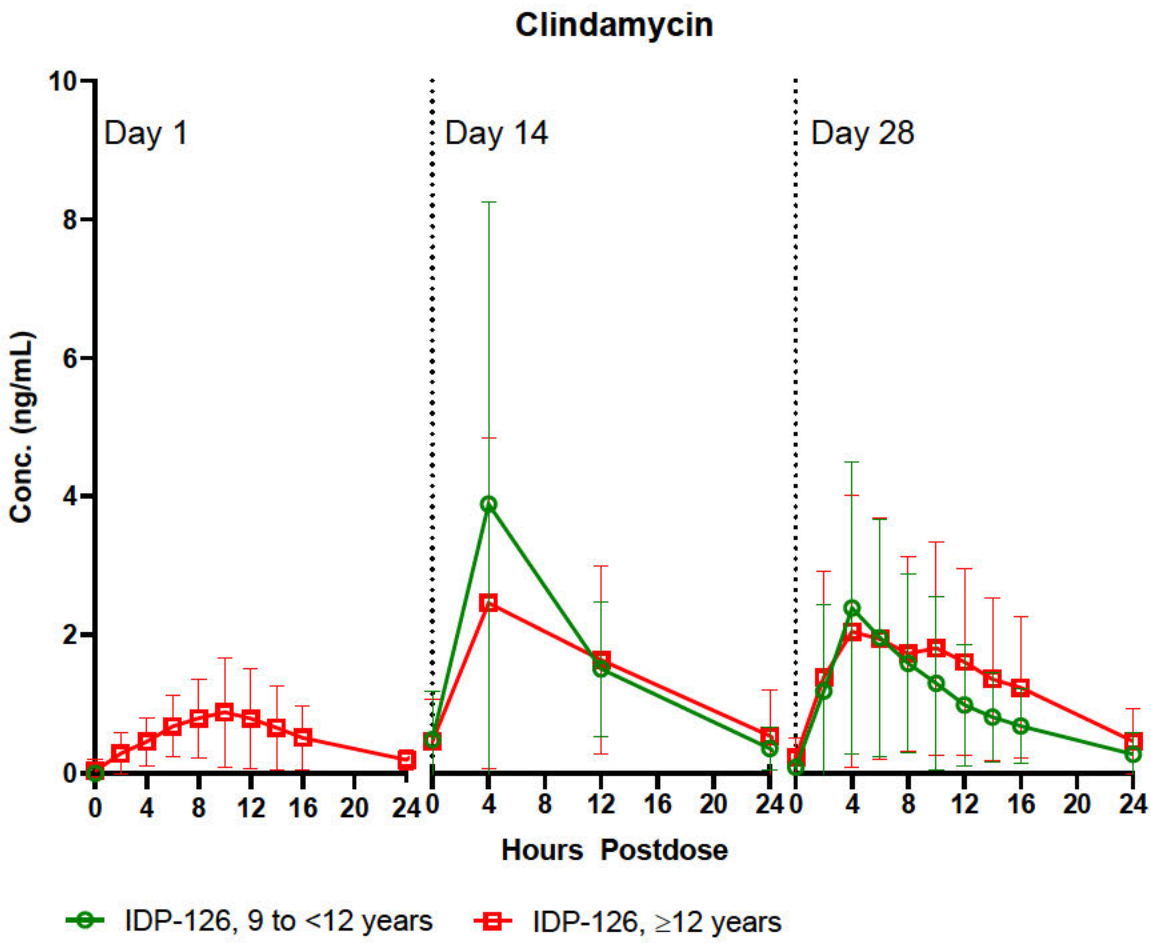
Figure 1.

The PK parameters for clindamycin are summarized in Table 16. The overall systemic exposures in Days 14-15 and Days 28-29 were similar, suggesting that steady state for clindamycin was reached by Day 14.

On Days 14-15, subjects <12 years of age had greater exposure to clindamycin compared with subjects ≥ 12 years of age and the mean C_{max} in younger cohort was 1.54-fold higher. On Days 28-19, the mean C_{max} in younger cohort was 1.11-fold higher compared to the older cohort, but the mean AUC was approximately 80% lower in younger cohort compared to the older cohort.

The accumulation ratios of the PK parameters are summarized in Table 17. Clindamycin accumulated approximately 3-fold between Days 1-2 and Days 28-29 following once daily application of IDP-126 gel.

Figure 1. Plasma Concentrations (Mean ± SD) of Clindamycin Following Once Daily Application of IDP-126 gel



Source: Reviewer's plot
Samples with concentrations below the LLOQ (0.0500 ng/mL) were set to 0.00 ng/mL for calculation.

Table 16. PK Parameters for Clindamycin on Days 1-2, Days 14-15, Days 28-29

		IDP-126 9 to < 12 years	IDP-126 ≥ 12 years
Days 1-2[a]			
C_{max} (ng/mL)	N		20
	Mean (SD)		1.07 (0.839)
	Mean %CV		78.4
	Min, max		0.315, 3.85
T_{max} (h)	N		20
	Mean (SD)		8.33 (2.89)
	Mean %CV		34.7
	Median		8.76
	Min, max		3.82, 14.0

		IDP-126 9 to < 12 years	IDP-126 ≥ 12 years
AUC_{0-t} (ng•h/mL)	N		20
	Mean (SD)		12.0 (8.65)
	Mean %CV		72.1
	Min, max		3.62, 38.8
AUC_{0-24h} (ng•h/mL)	N		17
	Mean (SD)		12.9 (8.99)
	Mean %CV		69.8
	Min, max		5.07, 38.8
$t_{1/2}$ (h)	N		17
	Mean (SD)		6.53 (2.06)
	Mean %CV		31.6
	Median		7.05
	Min, max		3.59, 9.10
Day 14-15[b]			
C_{max} (ng/mL)	N	8	19
	Mean (SD)	3.89 (4.36)	2.53 (2.35)
	Mean %CV	112	93.0
	Min, max	0.413, 13.1	0.0611, 8.42
Day 28-29			
C_{max} (ng/mL)	N	8	19
	Mean (SD)	2.71 (2.09)	2.44 (1.95)
	Mean %CV	77.2	79.8
	Min, max	0.941, 6.62	0.148, 6.14
T_{max} (h)	N	8	19
	Mean (SD)	3.73 (0.739)	7.48 (3.73)
	Mean %CV	19.8	49.9
	Median	4.00	7.88
	Min, max	1.90 to 4.03	2.02 to 13.7
AUC_{0-t} (ng•h/mL)	N	8	19
	Mean (SD)	24.5 (19.1)	30.7 (24.5)
	Mean %CV	78.2	79.7
	Min, max	10.4, 66.4	1.04, 87.4
AUC_{0-24h} (ng•h/mL)	N	8	14
	Mean (SD)	24.5 (19.1)	31.6 (26.6)
	Mean %CV	78.1	84.1
	Min, max	10.5, 66.3	2.92, 87.3
$t_{1/2}$ (h)	N	8	13
	Mean (SD)	6.51 (3.10)	7.11 (2.80)
	Mean %CV	47.7	39.4
	Median	5.36	5.94
	Min, max	3.57, 12.0	4.48, 12.9

Source: V01-126A-501 CSR Table 14.3.0.1.2.1
[a] Since subjects 9 to <12 years of age only provided a pre-application sample on Days 1-2, PK parameters for these subjects were not applicable and thus PK parameters for these subjects could not be determined on Days 1-2.
[b] On Days 14-15, only 4 plasma samples were collected per subject and therefore only Cmax values were reported.

Table 17. Clindamycin Accumulation Ratios Following Once Daily Application of IDP-126 gel in Subjects ≥ 12 Years

Accumulation Ratio[a]	C_{max}	AUC_{0-t}	AUC_{0-24h}
N	19	19	14
Mean (SD)	2.79 (2.79)	3.12 (3.33)	3.35 (3.26)
Mean %CV	100	107	97.3
Min to Max	0.342 to 10.3	0.287 to 12.9	0.320 to 10.1

Source: V01-126A-501 CSR Table 14.3.0.1.3.1.1
[a] The ratio of the PK parameter value at Day 28 divided by the same PK parameter value at Day 1
The mean ± SD of adapalene concentrations following once daily application of IDP-126 gel in subjects 9 to < 12 years of age and ≥ 12 years of age or EpiDuo Forte Gel in subjects ≥ 12 years of age are shown in Figure 2. The PK parameters for adapalene are summarized in
Table 18.

In both treatment groups, the mean adapalene concentration increased through 14 hours post dose on Day 1. The overall systemic exposures in Days 14-15 and Days 28-29 were similar, suggesting that steady-state for adapalene was reached by Day 14.

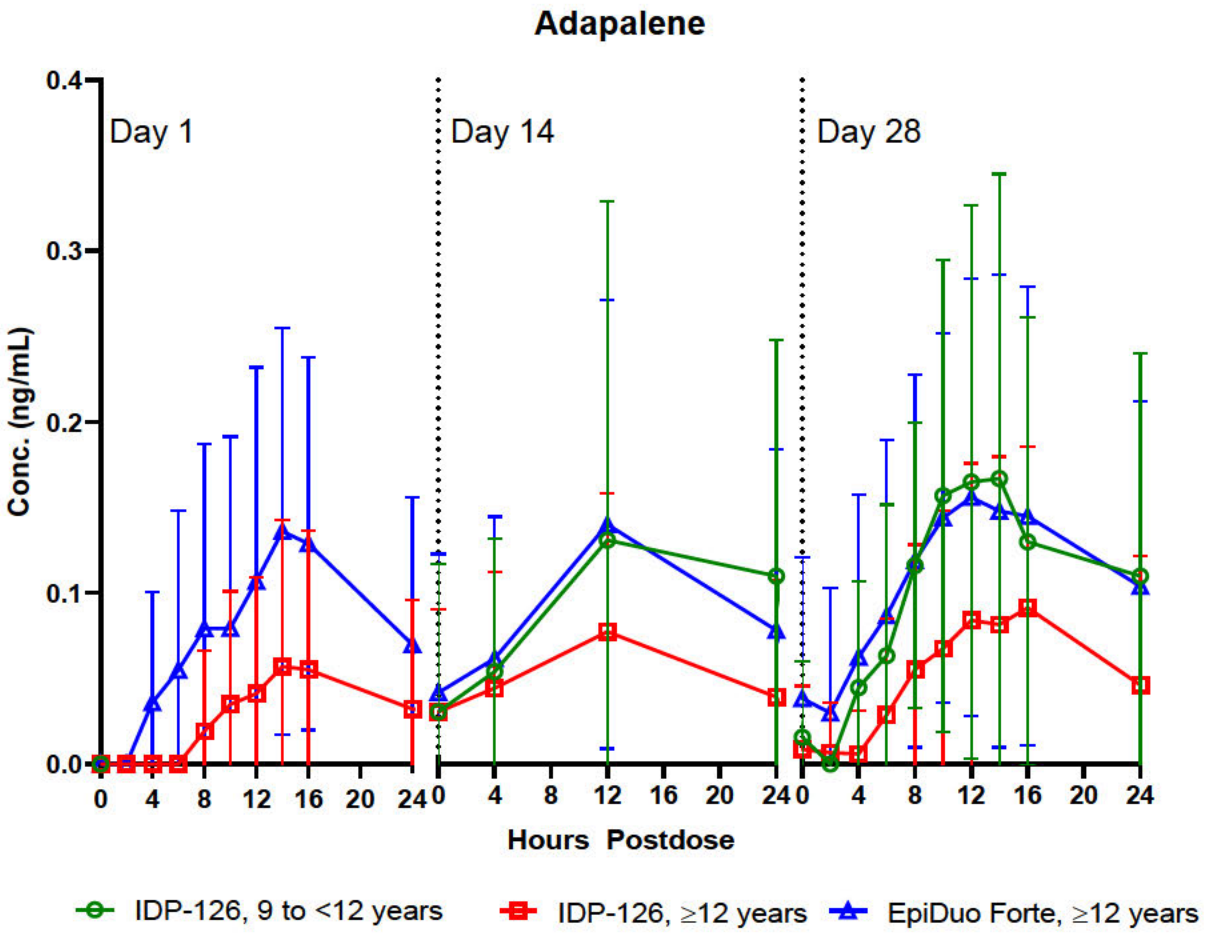
The systemic exposures to adapalene were greater in the younger cohort than in the older cohort in the IDP-126 gel group on both Days 14-15 and Days 28-29; the mean C_{max} in the younger cohort was 1.49-fold and 1.97-fold higher on Days 14-15 and Days 28-29, respectively; the mean AUC_{0-t} on Days 28-29 in the younger cohort was 1.35-fold higher. It was noted that the mean adapalene concentrations in the younger cohort in the IDP-126 gel group were similar to those in subjects ≥ 12 years of age in the EpiDuo Forte Gel group. In subjects ≥ 12 years of age, the mean adapalene concentrations were consistently lower in the IDP-126 gel group than in the EpiDuo Forte Gel group.

The comparisons of the PK parameters by the study drug groups in subjects ≥ 12 years of age are shown in Table 19. The arithmetic mean ratios for adapalene C_{max} and AUC_{0-t} on Days 28-29 in the IDP-126 gel to EpiDuo Forte Gel were 0.505 and 0.653. respectively.

The accumulation ratios of the PK parameters are summarized in Table 20. The mean accumulation ratios for C_{max} were 1.32 and 1.23 for IDP-126 gel and EpiDuo Forte Gel, respectively; the mean AUC_{0-t} ratios were 3.13 and 1.80 for IDP-126 gel and EpiDuo Forte Gel, respectively.

The PK results, which showed lower systemic exposure to adapalene in the IDP-126 gel group compared to the EpiDuo Forte Gel group, support the establishment of a clinical bridge between IDP-126 and EpiDuo Forte Gel in subjects ≥ 12 years of age.

Figure 2. Plasma Concentrations (Mean ± SD) of Adapalene Following Once Daily Application of IDP-126 gel or EpiDuo Forte Gel



Source: Reviewer's plot
Samples with concentrations below the LLOQ (0.0500 ng/mL) were set to 0.00 ng/mL for calculation.

Table 18. PK Parameters for Adapalene on Days 1-2, Days 14-15, Days 28-29

		IDP-126 9 to < 12 years	IDP-126 ≥ 12 years	EpiDuo Forte ≥ 12 years
Days 1-2[a]				
C_{max} (ng/mL)	N		20	20
	Mean (SD)		0.0786 (0.0894)	0.163 (0.119)
	Mean %CV		114	73.4
	Min, max		0, 0.272	0, 0.504
T_{max} (h)	N		10	16
	Mean (SD)		14.6 (3.88)	14.6 (4.35)
	Mean %CV		26.6	29.8
	Median		14.0	14.0
	Min, max		9.77, 23.8	5.77, 23.6

		IDP-126 9 to < 12 years	IDP-126 ≥ 12 years	EpiDuo Forte ≥ 12 years
AUC_{0-t} (ng•h/mL)	N		8	15
	Mean (SD)		1.33 (1.02)	2.25 (1.76)
	Mean %CV		76.8	78.2
	Min, max		0.369, 3.38	0.309, 6.99
AUC_{0-24h} (ng•h/mL)	N		1	3
	Mean (SD)		1.79 (NC)	3.12 (1.32)
	Mean %CV		NC	42.3
	Min, max		1.79, 1.79	1.60, 3.94
$t_{1/2}$ (h)	N		0	2
	Mean (SD)		NC	15.0 (0.424)
	Mean %CV		NC	2.83
	Median		NC	15.0
	Min, max		NC	14.7, 15.3
Day 14-15[b]				
C_{max} (ng/mL)	N	8	19	18
	Mean (SD)	0.139 (0.201)	0.0936 (0.0788)	0.171 (0.123)
	Mean %CV	145	84.2	71.8
	Min, max	0, 0.478	0, 0.232	0, 0.453
Day 28-29				
C_{max} (ng/mL)	N	8	19	19
	Mean (SD)	0.190 (0.155)	0.0966 (0.0995)	0.191 (0.139)
	Mean %CV	81.7	103	72.8
	Min, max	0 to 0.531	0, 0.265	0, 0.488
T_{max} (h)	N	7	9	13
	Mean (SD)	12.1 (2.79)	13.0 (1.95)	11.8 (2.57)
	Mean %CV	23.1	15.0	21.8
	Median	12.1	12.1	11.8
	Min, max	8.08, 16.0	9.70, 15.8	7.87, 15.5
AUC_{0-t} (ng•h/mL)	N	6	9	13
	Mean (SD)	3.24 (1.81)	2.40 (1.07)	3.68 (1.85)
	Mean %CV	55.7	44.4	50.2
	Min, max	0.954 to 6.42	0.557, 3.87	0.749, 6.24
AUC_{0-24h} (ng•h/mL)	N	2	3	6
	Mean (SD)	2.99 (0.368)	3.06 (0.528)	4.04 (0.939)
	Mean %CV	12.3	17.3	23.2
	Min, max	2.73 to 3.25	2.45, 3.38	2.92, 5.08
$t_{1/2}$ (h)	N	1	1	6
	Mean (SD)	10.5 (NC)	9.26 (NC)	11.9 (3.34)
	Mean %CV	NC	NC	28.1
	Median	10.5	9.26	12.0
	Min, max	10.5, 10.5	9.26, 9.26	6.18, 16.3

Source: V01-126A-501 CSR Table 14.3.0.1.2.2
[a] Since subjects 9 to <12 years of age only provided a pre-application sample on Days 1-2, PK parameters for these subjects were not applicable and thus PK parameters for these subjects could not be determined on Days 1-2.
[b] On Days 14-15, only 4 plasma samples were collected per subject and therefore only C_{max} values were reported.
Abbreviations: NC=not calculable due to plasma concentrations below the limit of quantification (BLQ)

Table 19. Comparison of PK Parameters for Adapalene by Study Drug Groups for Subjects ≥ 12 Years

		IDP-126 gel	EpiDuo Forte Gel	IDP-126 gel over EpiDuo Forte Gel
Day 1 C_{max} (ng/mL)	N	20	20	
	Mean (SD)	0.0786 (0.0894)	0.163 (0.119)	0.483[a]
	Geo mean (90% CI)	NC	NC	NC
	Minimum, maximum	0, 0.272	0, 0.504	
Day 28 C_{max} (ng/mL)	N	19	19	
	Mean (SD)	0.0966 (0.0995)	0.191 (0.139)	0.505[a]
	Geo mean (90% CI)	NC	NC	NC
	Minimum, maximum	0, 0.265	0, 0.488	
Day 1 AUC_{0-t} (ng•h/mL)	N	8	15	
	Mean (SD)	1.33 (1.02)	2.25 (1.76)	0.592[a]
	Geo mean (90% CI)	1.03 (0.619, 1.72)	1.59 (1.03, 2.45)	0.650 (0.331, 1.28)[b]
	Minimum, maximum	0.369, 3.38	0.309, 6.99	
Day 28 AUC_{0-t} (ng•h/mL)	N	9	13	
	Mean (SD)	2.40 (1.07)	3.68 (1.85)	0.653[a]
	Geo mean (90% CI)	2.12 (1.46, 3.07)	3.05 (2.13, 4.37)	0.694 (0.418, 1.15)[b]
	Minimum, maximum	0.557, 3.87	0.749, 6.24	
Day 1 AUC_{0-24h} (ng•h/mL)	N	1	3	
	Mean (SD)	1.79 (NC)	3.12 (1.32)	0.573[a]
	Geo mean (90% CI)	1.79 (NC)	2.89 (1.22, 6.86)	0.619 (0.110, 3.48)[b]
	Minimum, maximum	1.79, 1.79	1.60, 3.94	
Day 28 AUC_{0-24h} (ng•h/mL)	N	3	6	
	Mean (SD)	3.06 (0.528)	4.04 (0.939)	0.757[c]
	Geo mean (90% CI)	3.03 (2.22, 4.12)	3.94 (3.23, 4.82)	0.768 (0.565, 1.04)[b]
	Minimum, maximum	2.45, 3.38	2.92, 5.08	

Source: V01-126A-501 CSR Table 14.3.0.1.4.1.1
[a] Ratio of arithmetic means.
[b] Ratio (90% CI) of geometric means, where the CI for the ratio was derived by exponentiating the CI of the difference in log-transformed values.
Abbreviations: NC=not calculable due to plasma concentrations BLQ

Table 20. Adapalene Accumulation Ratios Following Once Daily Application of IDP-126 gel or EpiDuo Forte Gel in Subjects ≥ 12 Years

	Accumulation Ratio[a]	C_{max}	AUC_{0-t}	AUC_{0-24h}
IDP-126 gel	N	8	5	0
	Mean (SD)	1.32 (0.361)	3.13 (1.90)	NC
	Mean %CV	27.3	60.6	NC
	Min to Max	0.701 to 1.70	1.14 to 5.31	NC
EpiDuo Forte Gel	N	13	10	1
	Mean (SD)	1.23 (0.406)	1.80 (0.743)	0.762 (NC)
	Mean %CV	32.9	41.2	0.762
	Min to Max	0.522 to 1.77	0.552 to 2.99	0.762 to 0.762

Source: V01-126A-501 CSR Table 14.3.0.1.3.2.1
[a] The ratio of the PK parameter value at Day 28 divided by the same PK parameter value at Day 1
Abbreviations: NC=not calculable due to plasma concentrations BLQ

The summary of treatment-emergent adverse events is presented in Table 21. Of the 61 subjects in the safety population, 18 (29.5%), including 13 in the IDP-126 gel group (34.2%) and 5 in the EpiDuo Forte Gel group (21.7%), experienced a total 26 treatment emergent adverse event (TEAEs). None of the TEAEs were serious or led to discontinuation. Due to differences in sample sizes between treatment groups and relatively small sample size, no definitive conclusions can be drawn regarding the comparative safety of the treatment groups. The most common TEAEs in the IDP-126 gel (regardless of age) and EpiDuo Forte Gel groups were application site conditions (26.3% and 17.4%, respectively).

Table 21. Summary of Treatment-Emergent Adverse Events (Safety Population in Study V01-126A-501)

	IDP-126 gel (All Ages) (N = 38) n (%)	IDP-126 gel (< 12 Years) (N = 8) n (%)	IDP-126 gel (≥ 12 Years) (N = 30) n (%)	EpiDuo Forte Gel (≥ 12 Years) (N = 23) n (%)
Any TEAE	13 (34.2)	2 (25.0)	11 (36.7)	5 (21.7)
Any SAE	0	0	0	0
Deaths	0	0	0	0
D/C Study Drug Due to TEAE	0	0	0	0
D/C Study Due to TEAE	0	0	0	0
TEAEs Reported	18	2	16	8
Severity				
Mild	8 (21.1)	2 (25.0)	6 (20.0)	2 (8.7)
Moderate	2 (5.3)	0	2 (6.7)	3 (13.0)
Severe	3 (7.9)	0	3 (10.0)	0
Relationship				
Related	10 (26.3)	2 (25.0)	8 (26.7)	4 (17.4)
Not Related	3 (7.9)	0	3 (10.0)	1 (4.3)

Source: V01-126A-501 CSR Table 12-1
Abbreviations: D/C = discontinuation; SAE = serious adverse event; TEAE = treatment-emergent adverse event

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable. The purpose of the clinical pharmacology program in this NDA was to assess PK of IDP-126 gel under maximal use conditions and assess systemic safety and establish a clinical bridge between IDP-126 gel and the listed drug, EpiDuo Forte Gel. The clinical pharmacology study, V01-126A-501, did not directly provide efficacy data.

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

Based on the systemic safety and bridging study results from V01-126A-501 and the efficacy and safety results from Phase 3 trials, the proposed dosing regimen is appropriate.

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

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

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

Food-drug interaction studies are not needed for topical products. Drug-drug interaction assessment was not needed for this product as this is a 505(b)(2) application and the PK bridging for systemic safety was established via Study V01-126A-501.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The development program for IDP-126 gel for the topical treatment of acne vulgaris included 7 clinical studies:

- Phase 1 Tolerability Studies:
  - V01-126A-101: Randomized, evaluator-blind, controlled, within-subject comparison study in healthy volunteers to evaluate the potential of IDP-126 gel to cause skin

irritation using a cumulative irritation patch test design (semi-occlusive patches applied to the back, 21 times over 22 days)
- V01-126A-102: Randomized, evaluator-blind, controlled study in healthy volunteers to evaluate the potential of IDP-126 gel to induce skin sensitization using a repeat insult patch test design (semi-occlusive patch applied to the back, 3 times/week for 3 weeks)

- Phase 1b PK bridging to EpiDuo Forte Gel Study:
  - V01-126A-501: Open-label, randomized (for subjects ≥12 years), study designed to assess the safety and plasma PK of adapalene and clindamycin from IDP-126 gel and to bridge the PK for adapalene between IDP-126 gel and EpiDuo Forte Gel (adapalene 0.3%/BPO 2.5%); enrolled subjects were at least 9 years of age (IDP-126 gel group) or at least 12 years of age (EpiDuo Forte Gel group) with a clinical diagnosis of moderate to severe acne, applied topically once daily for 28 days

- Phase 2 Studies:
  - V01-126A-201: Randomized, double-blind, parallel-group, vehicle-controlled study to evaluate the efficacy and safety of IDP-126 gel, as compared with each dyad (BPO 3.1%/adapalene 0.15% gel, clindamycin phosphate 1.2%/BPO 3.1% gel, clindamycin phosphate 1.2%/adapalene 0.15% gel) and Vehicle gel, applied topically once daily for 12 weeks, 9 years of age and older
  - V01-126A-202: Randomized, double-blind, vehicle-controlled study to compare the efficacy and safety of IDP-126 gel to EpiDuo Forte Gel and combined vehicle gel, applied topically once daily for 12 weeks, 12 years of age and older.

- Phase 3 Pivotal Trials (identically designed):
  - V01-126A-301: Randomized, double-blind, parallel-group, vehicle-controlled, pivotal study to assess the efficacy and safety of IDP-126 gel, applied once daily for 12 weeks, compared with Vehicle gel, 9 years of age and older
    - N = 183 subjects (safety population)
      - IDP-126 gel (clindamycin phosphate, adapalene, and benzoyl peroxide gel, 1.2%/0.15%/3.1%): 122 subjects
      - Vehicle gel: 61 subjects

- V01-126A-302: Randomized, double-blind, parallel-group, vehicle-controlled, pivotal study to assess the efficacy and safety of IDP-126 gel, applied once daily for 12 weeks, compared with Vehicle gel, 9 years of age and older
  - N = 180 (safety population)
    - IDP-126 gel (clindamycin phosphate, adapalene, and benzoyl peroxide gel, 1.2%/0.15%/3.1%): 120 subjects
    - Vehicle gel: 60 subjects

Table 22. Phase 3 Clinical Trials in Support of Efficacy and Safety Determinations

Trial Identity	Trial Design	Regimen (Number Treated)/ schedule/ route / duration	Study Endpoints	No. of patients planned; Actual Randomized	Study Population	No. of Centers and Countries
V01-126A-301	DB, R, VC, PG, MC	IDP-126 (clindamycin phosphate/adapalene/benzoyl peroxide) gel, 1.2%/0.15%/3.1%, (N=122) IDP-126 Vehicle gel (N=61) Applied topically once daily for 12 weeks	Co-primary: • Absolute change in the inflammatory lesion count from baseline to Week 12 • Absolute change in the noninflammatory lesion count from baseline to Week 12 • Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to clear or almost clear (defined as treatment success)	180; 183	Male and female subjects at least 9 years of age with moderate to severe facial acne based on the EGSS score at baseline. The subjects must also have had a minimum of 30 and a maximum of 100 inflammatory lesions and a minimum of 35 and a maximum of 150 noninflammatory lesions, and no more than 2 nodules. Subjects may have had truncal acne and could have chosen to treat their truncal acne (neck, upper chest, upper back, and shoulders).	13 centers in the US; 2 centers in Canada

Trial Identity	Trial Design	Regimen (Number Treated)/ schedule/ route / duration	Study Endpoints	No. of patients planned; Actual Randomized	Study Population	No. of Centers and Countries
V01-126A-302	DB, R, VC, PG, MC	IDP-126 (clindamycin phosphate/adapalene / benzoyl peroxide) gel, 1.2%/0.15%/3.1%, (N=120) IDP-126 Vehicle gel (N=60) Applied topically once daily for 12 weeks	Identical as Study V01-126A-301	180; 180	Identical as Study V01-126A-301	12 centers in the US; 3 centers in Canada

Source: Reviewer's table
Abbreviations: EGSS, Evaluator's Global Severity Score; DB, double-blind; R, randomized; VC, vehicle-controlled; PG, parallel-group; MC, multi-center.

7.2. Review Strategy

The Applicant provided clinical study report (CSR) and datasets (NDA 216632, SDN 0001/eCTD 0001) by electronic submission at the following network path:

\CDSESUB1\evsprod\NDA216632\0001

Data and Analysis Quality

The data submitted by the Applicant to support the efficacy and safety of IDP-126 gel for the topical treatment of acne vulgaris was adequate and the data quality was found to be acceptable by the review team. Appropriate documentation of datasets, variables, and imputation procedures was included in the submission, along with SAS programs of statistical analyses.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial V01-126A-301

Trial Design

Study 301 was a randomized, double-blind, vehicle-controlled, parallel-arm, multicenter trial intended to evaluate the efficacy and safety of IDP-126 gel in subjects with moderate to severe acne vulgaris. Eligible subjects were at least 9 years of age, with a clinical diagnosis of moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the EGSS), presenting with 30-100 inflammatory facial lesions (papules, pustules, and nodules), 35-150 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules.

A total of 183 subjects were randomized at a 2:1 ratio to IDP-126 gel or vehicle gel treatment arms. Study treatment was administered once daily to the face for 12 weeks. Study visits were planned at Screening, Baseline, Weeks 2, 4, 8, and 12.

Study Endpoints

At each study visit, the investigator/evaluator assessed the subject's face, assigning an EGSS and counting all observed inflammatory and noninflammatory lesions. Note that the EGSS was determined prior to lesion counting.

The three coprimary efficacy endpoints were:

- Absolute change in the inflammatory lesion count from baseline to Week 12
- Absolute change in the noninflammatory lesion count from baseline to Week 12
- Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to "clear" or "almost clear" (considered "success" in the dichotomized evaluation)

Negative values for change from baseline to Week 12 endpoints, or a higher percentage of subjects classified as success for the EGSS categorical endpoint, indicate better efficacy.

Statistical Analysis Plan

The intent to treat (ITT) population was defined as all randomized who received at least once dose of study treatment. All subjects did receive study treatment so all randomized were included in the efficacy analyses.

Missing data for lesion counts at Week 12 was imputed by multiple imputation using the Markov Chain Monte Carlo (MCMC) method. Imputation was done independently for each treatment arm to ensure the pattern of missing observations in each treatment group would not influence the missing value estimation in the other arm. A total of 5 imputation datasets were generated for each efficacy endpoint.

The efficacy endpoints derived from inflammatory or noninflammatory lesion counts (absolute change from baseline; percent change from baseline), were analyzed using analysis of covariance (ANCOVA) models with terms for treatment, center, and baseline lesion count. The analyses were conducted on both the count data and on ranked data to determine whether the parametric or nonparametric model approach was appropriate for the between-group comparisons. First the ANCOVA model was tested using actual count data, to enable a test for skewness of the residuals. If the p-value was <0.01 for the skewness test, the results from the non-parametric model (ANCOVA on ranked transformed data) would be used to determine superiority. The skewness test was statistically significant for all the primary efficacy endpoints, so the descriptive statistics on the original scale were reported along with the p-value from the nonparametric model.

Missing data for EGSS at Week 12 was also imputed using the MCMC method for multiple imputation. First the missing values on the 0 to 4 ordinal EGSS scale were imputed, then the EGSS success outcome was classified as success/failure. This was performed independently for the two treatment arms, with five imputed datasets generated for each endpoint.

The percentage of subjects with EGSS success was analyzed using a logistic regression model with factors for treatment group and analysis center. Firth's Penalized Likelihood was applied to allow the model to converge in case of quasi-complete separation of the data.

Four sensitivity analyses were planned to assess the impact of missing data on the efficacy results. The first used model based multiple imputation (rather than the MCMC method primary method). The second used a repeated measures ANCOVA model with all on-treatment postbaseline observed values included with no imputation for missing values. The third was a tipping point analysis using increasing shift values in the imputation to investigate how extreme the imputed values would have to be to change the p-value > 0.05 (i.e., change the conclusion of the comparison). The fourth excluded subjects who had missing data due to interruptions in study participation due to COVID-19.

The analyses provided in the clinical study report followed the planned analyses, methods and models as described in the protocol.

Protocol Amendments

The protocol was amended once (June 17, 2020) to add assessments and analysis plans for truncal acne. These only applied to the subset of patients who had truncal acne at baseline. This amendment did not impact the primary efficacy analyses.

8.1.2. Study Results (Trial 301)

Patient Disposition

Study 301 enrolled and randomized a total of 183 subjects at a 2:1 ratio (122 subjects in the IDP-126 gel arm and 61 subjects in the vehicle gel arm) from 15 centers. All randomized subjects received treatment and were included in the ITT analysis set for efficacy analyses. A total of 21 subjects (15 in IDP-126 gel arm and 6 in the vehicle gel arm) discontinued prior to completing Week 12. The reasons for discontinuation were similar across the two arms, as shown in Table 23 with Withdrew Consent and Lost-to Follow-up as the most common reasons.

Table 23. Subject Disposition – Study 301

Randomized (Intent to Treat [1])	IDP-126 Gel N=122 (100%)	Vehicle Gel N=61 (100%)
Discontinued Study Treatment	**15 (12%)**	**6 (10%)**
Adverse Event	2 (2%)	0
Lack of Efficacy	0	0
Subject Withdrew Consent	7 (6%)	3 (5%)
Parent/Guardian Withdrew Consent	0	1 (2%)
Lost to Follow-up	5 (4%)	1 (2%)
Progressive Disease	0	1 (2%)
Other – due to COVID-19 Disruption	1 (1%)	0
Completed Study	**107 (88%)**	**55 (90%)**

Source: Statistical Reviewer's Analysis; adsl.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects who received at least one dose of study treatment

Table of Demographic Characteristics

As shown in Table 24, approximately half of the enrolled subjects were adolescents (age 10-17 years old) and approximately 58% were females. The majority of the subjects were White (66%) or Black or African American (20%). The majority of the subjects (89%) were from the US.

The two arms were fairly balanced on the demographic and baseline disease characteristics, with the exception of sex. The IDP-126 gel arm had 62% females, while the vehicle gel arm had 51%. An examination of efficacy results by subgroups indicated there was no impact on the results or conclusions due to this imbalance. Subjects were randomized within centers, but no other strata were used.

Table 24. Demographics and Baseline Disease Characteristics – Trial 301 (ITT[1])

	IDP-126 Gel (N=122)	Vehicle Gel (N=61)
Age (years)		
N	122	61
Mean (SD)	20.2 (7.11)	19.8 (6.28)
Median (Min, Max)	17 (10, 42)	18 (12, 44)
Age Group, n (%)		
< 12 years	2 (2)	0
12 to 17 years	63 (52)	28 (46)
≥ 18 years	57 (47)	33 (54)
Sex, n (%)		
Female	75 (62)	31 (51)
Male	47 (39)	30 (49)

	IDP-126 Gel (N=122)	Vehicle Gel (N=61)
Race, n (%)		
White	75 (62)	45 (74)
Black Or African American	28 (23)	9 (15)
American Indian or Alaska Native	0	0
Asian	13 (11)	4 (7)
Native Hawaiian or Other Pacific Islander	1 (1)	1 (2)
Multiple	4 (3)	1 (2)
Not Reported	1 (1)	1 (2)
Ethnicity, n (%)		
Hispanic or Latino	30 (25)	13 (21)
Not Hispanic or Latino	92 (75)	48 (79)
Country, n (%)		
United States	108 (89)	54 (89)
Canada	14 (11)	7 (11)
Inflammatory Lesion Count		
Mean (SD)	36.4 (7.52)	37.1 (9.22)
Median (Min, Max)	34 (30, 78)	34 (30, 82)
Noninflammatory Lesion Count		
Mean (SD)	50.7 (19.38)	45.9 (14.80)
Median (Min, Max)	42 (35, 144)	41 (35, 120)
Evaluator's Global Severity Score n (%)		
0 – Clear	0	0
1 – Almost Clear	0	0
2 – Mild	0	0
3 – Moderate	107 (88)	58 (95)
4 – Severe	15 (12)	3 (5)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects who received study treatment
Abbreviations: Min = Minimum; Max = Maximum; SD = Standard Deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects discontinued all concomitant medication or therapies for acne prior to randomization and were instructed not to use any topical and/or physical treatments other than the study drug for acne. Subjects who used prohibited concomitant medications or therapies during the course of the study were not withdrawn, but were instructed to discontinue the use of the concomitant product. Subjects were to maintain their normal daily cleansing routine and any use of facial makeup and were provided with a list of investigator-approved nonmedicated facial cleansers, moisturizers, and sunscreens.

Efficacy Results – Primary Endpoint

The three coprimary efficacy endpoints were:

- Absolute change in the inflammatory lesion count from baseline to Week 12
- Absolute change in the noninflammatory lesion count from baseline to Week 12
- Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to "clear" or "almost clear" (considered "success" in the dichotomized evaluation)

Negative values for change from baseline to Week 12 endpoints, or a higher percentage of subjects classified as success for the EGSS categorical endpoint, indicate better efficacy.

The overall Type I error was controlled by requiring the three coprimary efficacy endpoints to be statistically significant at an alpha level of 0.05.

As shown in Table 25, IDP-126 gel demonstrated superiority to Vehicle gel for all three coprimary endpoints (all p-values ≤ 0.003). There were four planned sensitivity analyses to assess the impact of missing data or multiple imputation assumptions. The results of all four (CSR Tables 14.2.1.5.1-4) were consistent with the primary results in terms of both estimated treatment effects and model conclusions (all p-values ≤ 0.003).

Table 25. Results for Coprimary Efficacy Endpoints – Study 301 (ITT[1])

	IDP-126 Gel (N=122)	Vehicle Gel (N=61)	Treatment Difference (95% CI)	p-value
Inflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-27.7 (9.55)	-21.7 (8.79)	-5.9 (-8.7, -3.1)	<0.001[3]
Median [4]	-28.9	-22.0		
Range (min, Max) [4]	(-60, -2)	(-49, -3)		
Noninflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-35.4 (15.52)	-23.5 (14.93)	-11.9 (-16.6, -7.1)	<0.001[3]
Median [4]	-35.7	-23.2		
Range (min, Max) [4]	(-101, 16)	(-71, 35)		
EGSS Reduction ≥2 Grades from Baseline and Achieving Clear or Almost Clear at Week 12				
Success (%)	49.6	24.9	24.7 (10.7, 38.7) [5]	0.003[6]

	IDP-126 Gel (N=122)	Vehicle Gel (N=61)	Treatment Difference (95% CI)	p-value
Failure (%)	50.4	75.1		

Source: Study 301 Applicant's analysis CSR Table 9 confirmed by statistical reviewer
[1] Intent-to-Treat (ITT) population: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.
[2] Least squares means, standard deviations, differences in LS means, and associated 95% CIs were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation. Negative LS mean values represent decreases from baseline.
[3] P-values were obtained from a ranked analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the ranked analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation.
[4] Median, minimum, and maximum values were obtained by averaging the summary statistics generated from each imputed dataset. Negative median values represent decreases from baseline.
[5] Treatment difference and corresponding 95% confidence interval based on the reported percentages of success.
[6] P-value was obtained from a logistic regression (using Firth's penalized likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; LS=Least Squares; SD=Standard Deviation

Data Quality and Integrity

There were no known data quality or integrity issues for the statistical analysis of efficacy for Study 301. The data were submitted in an appropriate format with sufficient documentation to conduct all necessary analyses. The derived endpoints provided by the Applicant were pre-specified in the protocol. The plans for imputation of missing data and the analyses of efficacy endpoints were provided in the protocols and conducted as planned.

Efficacy Results – Secondary and Other Relevant Endpoints

The Applicant predefined the following secondary endpoints, to be tested in this order:

- Percent change in the noninflammatory lesion count from baseline to Week 12
- Percent change in the inflammatory lesion count from baseline to Week 12
- Percentage of subjects who had at least a 2-grade reduction from baseline in the EGSS at Week 12
- Percent change in the noninflammatory lesion count from baseline to Week 8
- Percent change in the inflammatory lesion count from baseline to Week 8
- Percent change in the noninflammatory lesion count from baseline to Week 4
- Percent change in the inflammatory lesion count from baseline to Week 4

The hierarchical testing order was used to control the overall Type I error for multiplicity. Each test was conducted at alpha = 0.05. Results for the first three secondary endpoints were considered for inclusion in Section 14 of the label. Additional secondary endpoints at visits prior

to Week 12 (Weeks 8 and 4) were also included in the testing order but are not intended for inclusion in the label and are not reproduced here. As shown in Table 26, IDP-126 gel demonstrated superiority to vehicle gel on all the secondary endpoints at Week 12.

Table 26. Results for Secondary Efficacy Endpoints – Study 301 (ITT[1])

	IDP-126 Gel (N=122)	Vehicle Gel (N=61)	Treatment Difference (95% CI)	p-value
Noninflammatory Lesion Count Percent Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-72.7 (32.36)	-47.6 (31.07)	-25.1 (-35.0, -15.2)	<0.001[3]
Median [4]	-77.1	-57.9		
Range (min, Max) [4]	(-100, 33)	(-97, 76)		
Inflammatory Lesion Count Percent Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-75.7 (26.66)	-59.6 (24.35)	-16.1 (-23.7, -8.4)	<0.001[3]
Median [4]	-84.01	-66.7		
Range (min, Max) [4]	(-100, -5)	(-100, -9)		
EGSS Reduction ≥2 Grades from Baseline at Week 12				
Success (%)	57.2	24.8	32.4 (18.5, 46.4)[5]	<0.001[6]
Failure (%)	42.8	75.2		

Source: Study 301 Applicant's analysis CSR Table 10 confirmed by statistical reviewer
[1] Intent-to-Treat (ITT) population: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.
[2] Least squares means, standard deviations, differences in LS means, and associated 95% CIs were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. Values have been adjusted for multiple imputation. Negative LS mean values represent decreases from baseline.
[3] P-values were obtained from a ranked analysis of covariance with factors of treatment group, analysis center, and the respective baseline lesion count as a covariate. Values have been adjusted for multiple imputation.
[4] Median, minimum, and maximum values were obtained by averaging the summary statistics generated from each imputed dataset. Negative median values represent decreases from baseline.
[5] Treatment difference and corresponding 95% confidence interval based on the reported percentages of success.
[6] P-value was obtained from a logistic regression (using Firth's penalized likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; LS=Least Squares; SD=Standard Deviation

Additional Analyses Conducted on the Individual Trial

The eligibility criteria for this trial included ages 9 and above. However, this is a combination product of three components for this indication. Safety for the adapalene 0.15% component was based on a bridging study to a product (Epiduo Forte) which contains adapalene 0.3% but is only approved for ages 12 and older. There were 2 subjects, both in the IDP-126 gel arm, who were under age 12 (Subject # (b) (6) age 11 Female; Subject # (b) (6) age 10 Female). As shown in Table 27, the reanalysis without those two subjects did not change the results or conclusions, with IDP-126 gel demonstrating superiority versus Vehicle gel on all three coprimary endpoints.

Table 27. Coprimary Efficacy Endpoints: Ages 12 and Above [1] – Study 301

	IDP-126 Gel (N=120)	Vehicle Gel (N=61)	Treatment Difference (95% CI)	p-value
Inflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-27.6 (9.65)	-21.8 (8.82)	-5.8 (-8.7, -3.0)	<0.001[3]
Median [4]	-28.9	-22.0		
Range (min, Max) [4]	(-60, -2)	(-49, -3)		
Noninflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-35.3 (15.68)	-23.6 (15.02)	-11.7 (-16.5, -7.0)	<0.001[3]
Median [4]	-35.7	-23.2		
Range (min, Max) [4]	(-101, 16)	(-71, 35)		
EGSS Reduction ≥2 Grades from Baseline and Achieving Clear or Almost Clear at Week 12				
Success (%)	48.7	24.9	23.8 (9.7, 37.8) [5]	0.005[6]
Failure (%)	51.3	75.1		

Source: Statistical Reviewer adsl.xpt, admiinf.xpt, admininf.xpt, admiegss.xpt
[1] Intent-to-Treat (ITT) population with two subjects age less than 12 removed: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.
[2] Least squares means, standard deviations, differences in LS means, and associated 95% CIs were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation. Negative LS mean values represent decreases from baseline.
[3] P-values were obtained from a ranked analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the ranked analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation.
[4] Median, minimum, and maximum values were obtained by averaging the summary statistics generated from each imputed dataset. Negative median values represent decreases from baseline.
[5] Treatment difference and corresponding 95% confidence interval based on the reported percentages of success.
[6] P-value was obtained from a logistic regression (using Firth's penalized likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; LS=Least Squares; SD=Standard Deviation

Table 28 presents the results for the coprimary efficacy endpoints by demographic and baseline characteristic subgroups. The results in the IDP-126 gel arm were consistent across all the subgroups in the direction representing better efficacy. These are descriptive statistics only and are not intended to support conclusions or between group comparisons.

Table 28. Results by Subgroups: Coprimary Efficacy Endpoints – Study 301 (ITT; MI[1])

	IDP-126 Gel (N=122)		Vehicle Gel (N=61)	
Inflammatory Lesion Count Absolute Change from Baseline to Week 12	**n**	**Mean**	**n**	**Mean**
Age (years)				
<18	65	-28.4	28	-20.4
≥18	57	-27.0	33	-22.8
Sex				
Female	75	-27.1	31	-21.1
Male	47	-28.7	30	-22.3
Race				
White	75	-28.1	45	-22.6
POC	47	-27.8	16	-19.0
Ethnicity				
Hispanic or Latino	30	-29.7	13	-21.5
Not Hispanic or Latino	92	-27.1	48	-21.8
Baseline EGSS				
3 (Moderate)	107	-26.2	58	-21.6
4 (Severe)	15	-38.3	3	-23.3
Noninflammatory Lesion Count Absolute Change from Baseline to Week 12	**n**	**Mean**	**n**	**Mean**
Age (years)				
<18	65	-38.7	28	-20.8
≥18	57	-33.1	33	-22.0
Sex				
Female	75	-35.9	31	-21.6
Male	47	-36.5	30	-21.3
Race				
White	75	-36.9	45	-21.1
POC	47	-34.8	16	-22.5
Ethnicity				
Hispanic or Latino	30	-40.1	13	-15.5
Not Hispanic or Latino	92	-34.8	48	-23.1
Baseline EGSS				
3 (Moderate)	107	-35.0	58	-21.9
4 (Severe)	15	-44.1	3	-12.8

	IDP-126 Gel (N=122)		Vehicle Gel (N=61)	
EGSS Reduction ≥2 Grades from Baseline and Achieving Clear or Almost Clear at Week 12	**n**	**% Success**	**n**	**% Success**
Age (years)				
<18	65	53%	28	33%
≥18	57	46%	33	19%
Sex				
Female	75	50%	31	31%
Male	47	49%	30	20%
Race				
White	75	49%	45	25%
POC	47	50%	16	28%
Ethnicity				
Hispanic or Latino	30	57%	13	23%
Not Hispanic or Latino	92	47%	48	26%
Baseline EGSS				
3 (Moderate)	107	52%	58	27%
4 (Severe)	15	33%	3	0%

Source: Statistical Reviewer adsl.xpt, admiinf.xpt, admininf.xpt, admiegss.xpt
[1] Intent-to-Treat (ITT) population: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data. Summary statistics represent average values, obtained from averaging the summary statistics generated from each imputed dataset. Negative absolute change values represent decrease from baseline.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; POC=People of Color

8.1.3. Trial V01-126A-302

Trial Design

The design of Study 302 was identical to Study 301. It was a randomized, double-blind, vehicle-controlled, parallel-arm, multicenter trial intended to evaluate the efficacy and safety of IDP-126 gel in subjects with moderate to severe acne vulgaris. Eligible subjects were at least 9 years of age, with a clinical diagnosis of moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the EGSS), presenting with 30-100 inflammatory facial lesions (papules, pustules, and nodules), 35-150 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules.

A total of 180 subjects were randomized at a 2:1 ratio to IDP-126 gel or Vehicle gel treatment arms. Study treatment was administered once daily to the face for 12 weeks. Study visits were planned at Screening, Baseline, Weeks 2, 4, 8, and 12.

Study Endpoints

At each study visit, the investigator/evaluator assessed the subject's face, assigning an EGSS and counting all observed inflammatory and noninflammatory lesions. Note that the EGSS was determined prior to lesion counting.

The three coprimary efficacy endpoints were:

- Absolute change in the inflammatory lesion count from baseline to Week 12
- Absolute change in the noninflammatory lesion count from baseline to Week 12
- Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to "clear" or "almost clear" (considered "success" in the dichotomized evaluation)

Negative values for change from baseline to Week 12 endpoints, or a higher percentage of subjects classified as success for the EGSS categorical endpoint, indicate better efficacy.

Statistical Analysis Plan

The ITT population was defined as all randomized who received at least once dose of study treatment. All subjects did receive study treatment so all randomized were included in the efficacy analyses.

Missing data for lesion counts at Week 12 was imputed by multiple imputation using the Markov Chain Monte Carlo (MCMC) method. Imputation was done independently for each treatment arm to ensure the pattern of missing observations in each treatment group would not influence the missing value estimation in the other arm. A total of 5 imputation datasets were generated for each efficacy endpoint.

The efficacy endpoints derived from inflammatory or noninflammatory lesion counts (absolute change from baseline; percent change from baseline), were analyzed using ANCOVA models with terms for treatment, center, and baseline lesion count. The analyses were conducted on both the count data and on ranked data to determine whether the parametric or nonparametric model approach was appropriate for the between-group comparisons. First the ANCOVA model was tested using actual count data, to enable a test for skewness of the residuals. If the p-value was <0.01 for the skewness test, the results from the non-parametric model (ANCOVA on ranked transformed data) would be used to determine superiority. The skewness test was statistically significant for all the primary efficacy endpoints, so the descriptive statistics on the original scale were reported along with the p-value from the nonparametric model.

Missing data for EGSS at Week 12 was also imputed using the MCMC method for multiple imputation. First the missing values on the 0 to 4 ordinal EGSS scale were imputed, then the EGSS success outcome was classified as success/failure. This was performed independently for the two treatment arms, with five imputed datasets generated for each endpoint.

The percentage of subjects with EGSS success was analyzed using a logistic regression model with factors for treatment group and analysis center. Firth's Penalized Likelihood was applied to allow the model to converge in case of quasi-complete separation of the data.

Four sensitivity analyses were planned to assess the impact of missing data on the efficacy results. The first used model based multiple imputation (rather than the MCMC method primary method). The second used a repeated measures ANCOVA model with all on-treatment postbaseline observed values included with no imputation for missing values. The third was a tipping point analysis using increasing shift values in the imputation to investigate how extreme the imputed values would have to be to change the p-value > 0.05 (i.e., change the conclusion of the comparison). The fourth excluded subjects who had missing data due to interruptions in study participation due to COVID-19.

The analyses provided in the clinical study report followed the planned analyses, methods and models as described in the protocol.

Protocol Amendments

The protocol was amended once (June 17, 2020) to add assessments and analysis plans for truncal acne. These only applied to the subset of patients who had truncal acne at baseline. This amendment did not impact the primary efficacy analyses.

8.1.4. Study Results (Trial 302)

Patient Disposition

Study 302 enrolled and randomized a total of 180 subjects at a 2:1 ratio (120 subjects in the IDP-126 gel arm and 60 subjects in the vehicle gel arm) from 15 centers. All randomized subjects received treatment and were included in the ITT analysis set for efficacy analyses.

A total of 17 subjects (13 in IDP-126 gel arm and 4 in the vehicle gel arm) discontinued prior to completing Week 12. The reasons for discontinuation were similar across the two arms, as shown in Table 29, with Lost-to Follow-up as the most common reason.

Table 29. Subject Disposition – Study 302

Randomized (Intent to Treat [1])	IDP-126 gel N=120 (100%)	Vehicle Gel N=60 (100%)
Discontinued Study Treatment	**13 (11%)**	**4 (7%)**
Adverse Event	3 (3%)	0
Lack of Efficacy	0	1 (2%)
Subject Withdrew Consent	1 (1%)	1 (2%)
Lost to Follow-up	6 (5%)	2 (3%)
Other – due to COVID-19 Disruption	3 (3%)	0
Completed Study	**107 (89%)**	**56 (93%)**

Source: Statistical Reviewer's Analysis; adsl.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects who received at least one dose of study treatment

Table of Demographic Characteristics

As shown in Table 30, 47% of the enrolled subjects were adolescents (age 10-17 years old) and approximately 59% were females. The majority of the subjects were White (82%) or Black or African American (9%). The majority of the subjects (77%) were from the United States (US).

The two arms were fairly balanced on the demographic and baseline disease characteristics, with the exception of age group. The IDP-126 gel arm had 51% pediatric subjects, while the Vehicle gel arm had 40%. An examination of efficacy results by subgroups indicated there was no impact on the results or conclusions due to this imbalance. Subjects were randomized within centers, but no other strata were used.

Table 30. Demographics and Baseline Disease Characteristics – Trial 302 (ITT[1])

	IDP-126 Gel (N=120)	Vehicle Gel (N=60)
Age (years)		
N	120	60
Mean (SD)	20.2 (7.50)	21.4 (7.49)
Median (Min, Max)	17 (10, 48)	19.5 (11, 43)
Age Group, n (%)		
< 12 years	1 (1)	2 (3)
12 to 17 years	60 (50)	22 (37)
≥ 18 years	59 (49)	36 (60)
Sex, n (%)		
Female	69 (58)	37 (62)
Male	51 (43)	23 (38)
Race, n (%)		
White	94 (78)	53 (88)
Black Or African American	12 (10)	5 (8)
American Indian or Alaska Native	0	0
Asian	8 (7)	1 (2)
Native Hawaiian or Other Pacific Islander	0	0
Multiple	5 (4)	0
Not Reported	1 (1)	1 (2)

	IDP-126 Gel (N=120)	Vehicle Gel (N=60)
Ethnicity, n (%)		
Hispanic or Latino	27 (23)	10 (17)
Not Hispanic or Latino	93 (78)	50 (83)
Country, n (%)		
United States	92 (77)	46 (77)
Canada	28 (23)	14 (23)
Inflammatory Lesion Count		
Mean (SD)	37.4 (7.94)	37.7 (9.43)
Median (Min, Max)	34.5 (30, 77)	34 (30, 79)
Noninflammatory Lesion Count		
Mean (SD)	48.2 (14.92)	49.3 (15.94)
Median (Min, Max)	42 (35, 108)	42 (35, 107)
Evaluator's Global Severity Score n (%)		
0 – Clear	0	0
1 – Almost Clear	0	0
2 – Mild	0	0
3 – Moderate	109 (91)	57 (95)
4 – Severe	11 (9)	3 (5)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects who received study treatment
Abbreviations: Min = Minimum; Max = Maximum; SD = Standard Deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects discontinued all concomitant medication or therapies for acne prior to randomization and were instructed not to use any topical and/or physical treatments other than the study drug for acne. Subjects who used prohibited concomitant medications or therapies during the course of the study were not withdrawn but were instructed to discontinue the use of the concomitant product. Subjects were to maintain their normal daily cleansing routine and any use of facial makeup and were provided with a list of investigator-approved nonmedicated facial cleansers, moisturizers, and sunscreens.

Efficacy Results – Primary Endpoints

The three coprimary efficacy endpoints were:

- Absolute change in the inflammatory lesion count from baseline to Week 12
- Absolute change in the noninflammatory lesion count from baseline to Week 12
- Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to "clear" or "almost clear" (considered "success" in the dichotomized evaluation)

Negative values for change from baseline to Week 12 endpoints, or a higher percentage of subjects classified as success for the EGSS categorical endpoint, indicate better efficacy.

The overall Type I error was controlled by requiring the three coprimary efficacy endpoints to be statistically significant at an alpha level of 0.05.

As shown in Table 31, IDP-126 gel demonstrated superiority to vehicle gel for all three coprimary endpoints (all p-values ≤ 0.001). There were four planned sensitivity analyses to assess the impact of missing data or multiple imputation assumptions. The results of all four (CSR Tables 14.2.1.5.1-4) were consistent with the primary results in terms of both estimated treatment effects and model conclusions (all p-values ≤ 0.001).

Table 31. Results for Coprimary Efficacy Endpoints – Study 302 (ITT[1])

	IDP-126 gel (N=120)	Vehicle Gel (N=60)	Treatment Difference (95% CI)	p-value
Inflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-30.1 (9.64)	-20.8 (9.90)	-9.3 (-12.4, -6.2)	<0.001[3]
Median [4]	-29.1	-21.1		
Range (min, Max) [4]	(-69, -1)	(-43, 22)		
Noninflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-35.2 (14.48)	-22.0 (14.27)	-13.3 (-17.7, -8.8)	<0.001[3]
Median [4]	-33.1	-24.7		
Range (min, Max) [4]	(-95, 8)	(-60, 23)		
EGSS Reduction ≥2 Grades from Baseline and Achieving Clear or Almost Clear at Week 12				
Success (%)	50.5	20.5	30.0 (16.4, 43.6)[5]	0.001[6]
Failure (%)	49.5	79.5		

Source: Study 301 Applicant's analysis CSR Table 9 confirmed by statistical reviewer
[1] Intent-to-Treat (ITT) population: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.
[2] Least squares means, standard deviations, differences in LS means, and associated 95% CIs were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation. Negative LS mean values represent decreases from baseline.
[3] P-values were obtained from a ranked analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the ranked analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation.
[4] Median, minimum, and maximum values were obtained by averaging the summary statistics generated from each imputed dataset. Negative median values represent decreases from baseline.
[5] Treatment difference and corresponding 95% confidence interval based on the reported percentages of success.
[6] P-value was obtained from a logistic regression (using Firth's penalized likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; LS=Least Squares; SD=Standard Deviation

Data Quality and Integrity

The data for Study 302 were submitted in an appropriate format with sufficient documentation to conduct all necessary analyses. The derived endpoints provided by the Applicant were pre-specified in the protocol. The plan for imputation of missing data was provided in the protocols and conducted as planned. There are no known data quality or integrity concerns for the statistical review.

Efficacy Results – Secondary and Other Relevant Endpoints

The Applicant predefined the following secondary endpoints, to be tested in this order:

- Percent change in the noninflammatory lesion count from baseline to Week 12
- Percent change in the inflammatory lesion count from baseline to Week 12
- Percentage of subjects who had at least a 2-grade reduction from baseline in the EGSS at Week 12
- Percent change in the noninflammatory lesion count from baseline to Week 8
- Percent change in the inflammatory lesion count from baseline to Week 8
- Percent change in the noninflammatory lesion count from baseline to Week 4
- Percent change in the inflammatory lesion count from baseline to Week 4

The hierarchical testing order was used to control the overall Type I error for multiplicity. Each test was conducted at alpha = 0.05. Results for the first three secondary endpoints were considered for inclusion in Section 14 of the label. Additional secondary endpoints at visits prior to Week 12 (Weeks 8 and 4) were also included in the testing order but are not intended for inclusion in the label and are not reproduced here. As shown in Table 32, IDP-126 gel demonstrated superiority to vehicle gel on all the secondary endpoints at Week 12.

Table 32. Results for Secondary Efficacy Endpoints – Study 302 (ITT[1])

	IDP-126 gel (N=120)	Vehicle Gel (N=60)	Treatment Difference (95% CI)	p-value
Noninflammatory Lesion Count Percent Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-73.3 (27.64)	-49.0 (27.35)	-24.3 (-32.9, -15.7)	<0.001[3]
Median [4]	-76.9	-47.6		
Range (min, Max) [4]	(-100, 19)	(-100, 40)		
Inflammatory Lesion Count Percent Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-80.1 (25.27)	-56.2 (25.15)	-24.0 (-31.7, -16.2)	<0.001[3]

	IDP-126 gel (N=120)	Vehicle Gel (N=60)	Treatment Difference (95% CI)	p-value
Median [4]	-85.8	-57.3		
Range (min, Max) [4]	(-100, -3)	(-100, 50)		
EGSS Reduction ≥2 Grades from Baseline at Week 12				
Success (%)	55.2	23.1	32.1 (18.3, 46.0) [5]	<0.001 [6]
Failure (%)	44.8	76.9		

Source: Study 301 Applicant's analysis CSR Table 10 confirmed by statistical reviewer
[1] Intent-to-Treat (ITT) population: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.
[2] Least squares means, standard deviations, differences in LS means, and associated 95% CIs were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. Values have been adjusted for multiple imputation. Negative LS mean values represent decreases from baseline.
[3] P-values were obtained from a ranked analysis of covariance with factors of treatment group, analysis center, and the respective baseline lesion count as a covariate. Values have been adjusted for multiple imputation.
[4] Median, minimum, and maximum values were obtained by averaging the summary statistics generated from each imputed dataset. Negative median values represent decreases from baseline.
[5] Treatment difference and corresponding 95% confidence interval based on the reported percentages of success.
[6] P-value was obtained from a logistic regression (using Firth's penalized likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; LS=Least Squares; SD=Standard Deviation

Additional Analyses Conducted on the Individual Trial

The eligibility criteria for this trial included ages 9 and above. However, this is a combination product of three components for this indication. Safety for the adapalene 0.15% component was based on a bridging study to a product (Epiduo Forte) which contains adapalene 0.3% but is only approved for ages 12 and older. There were 3 subjects, one in the IDP-126 gel arm, (Subject # (b) (6) age 10 Female) and two in the vehicle gel arm (Subject # (b) (6) age 11 Female; Subject # (b) (6) age 11 Female) who were under age 12. As shown in Table 33, the reanalysis without those 3 subjects did not change the results or conclusions, with IDP-126 gel demonstrating superiority versus vehicle gel on all three coprimary endpoints.

Table 33. Coprimary Efficacy Endpoints: Ages 12 and Above [1] – Study 302

	IDP-126 gel (N=119)	Vehicle Gel (N=58)	Treatment Difference (95% CI)	p-value
Inflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-29.9 (9.66)	-20.7 (9.84)	-9.1 (-12.2, -6.0)	<0.001 [3]
Median [4]	-29.0	-21.1		
Range (min, Max) [4]	(-69, -1)	(-40, 22)		
Noninflammatory Lesion Count Absolute Change from Baseline to Week 12				
LS Mean (LS SD) [2]	-35.0 (13.76)	-23.2 (13.53)	-11.8 (-16.1, -7.5)	<0.001 [3]
Median [4]	-33.2	-25.4		
Range (min, Max) [4]	(-95, 8)	(-60, 23)		

	IDP-126 gel (N=119)	Vehicle Gel (N=58)	Treatment Difference (95% CI)	p-value
EGSS Reduction ≥2 Grades from Baseline and Achieving Clear or Almost Clear at Week 12				
Success (%)	49.9	21.0	28.9 (15.1, 42.7)[5]	0.001[6]
Failure (%)	50.1	79.0		

Source: Statistical Reviewer adsl.xpt, admiinf.xpt, admininf.xpt, admiegss.xpt
[1] Intent-to-Treat (ITT) population with three subjects age less than 12 removed: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.
[2] Least squares means, standard deviations, differences in LS means, and associated 95% CIs were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation. Negative LS mean values represent decreases from baseline.
[3] P-values were obtained from a ranked analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the ranked analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation.
[4] Median, minimum, and maximum values were obtained by averaging the summary statistics generated from each imputed dataset. Negative median values represent decreases from baseline.
[5] Treatment difference and corresponding 95% confidence interval based on the reported percentages of success.
[6] P-value was obtained from a logistic regression (using Firth's penalized likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; LS=Least Squares; SD=Standard Deviation

Table 34 presents the results for the coprimary efficacy endpoints by demographic and baseline characteristic subgroups. The results in the IDP-126 gel arm were consistent across all the subgroups in the direction representing better efficacy. These are descriptive statistics only and are not intended to support conclusions or between group comparisons.

Table 34. Results by Subgroups: Coprimary Efficacy Endpoints – Study 302 (ITT; MI[1])

	IDP-126 gel (N=120)		Vehicle Gel (N=60)	
Inflammatory Lesion Count Absolute Change from Baseline to Week 12	**n**	**Mean**	**n**	**Mean**
Age (years)				
<18	61	-30.3	24	-18.0
≥18	59	-29.3	36	-21.8
Sex				
Female	69	-28.7	37	-19.9
Male	51	-31.2	23	-21.0
Race				
White	94	-30.2	53	-19.7
POC	26	-28.4	7	-25.0
Ethnicity				
Hispanic or Latino	27	-33.3	10	-19.2
Not Hispanic or Latino	93	-28.8	50	-20.5
Baseline EGSS				
3 (Moderate)	109	-28.5	57	-20.0

	IDP-126 gel (N=120)		Vehicle Gel (N=60)	
4 (Severe)	11	-42.9	3	-25.7
Noninflammatory Lesion Count Absolute Change from Baseline to Week 12	**n**	**Mean**	**n**	**Mean**
Age (years)				
<18	61	-36.1	24	-17.0
≥18	59	-33.1	36	-25.0
Sex				
Female	69	-36.1	37	-20.5
Male	51	-32.8	23	-23.8
Race				
White	94	-36.4	53	-21.3
POC	26	-28.6	7	-25.6
Ethnicity				
Hispanic or Latino	27	-36.8	10	-21.0
Not Hispanic or Latino	93	-34.0	50	-22.0
Baseline EGSS				
3 (Moderate)	109	-34.7	57	-22.6
4 (Severe)	11	-34.8	3	-6.7
EGSS Reduction ≥2 Grades from Baseline and Achieving Clear or Almost Clear at Week 12	**n**	**% Success**	**n**	**% Success**
Age (years)				
<18	61	52%	24	13%
≥18	59	46%	36	27%
Sex				
Female	69	58%	37	16%
Male	51	37%	23	30%
Race				
White	94	50%	53	19%
POC	26	45%	7	37%
Ethnicity				
Hispanic or Latino	27	62%	10	10%
Not Hispanic or Latino	93	45%	50	23%
Baseline EGSS				
3 (Moderate)	109	51%	57	22%
4 (Severe)	11	33%	3	0%

Source: Statistical Reviewer adsl.xpt, admiinf.xpt, admininf.xpt, admiegss.xpt
[1] Intent-to-Treat (ITT) population: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data. Summary statistics represent average values, obtained from averaging the summary statistics generated from each imputed dataset. Negative absolute change values represent decrease from baseline.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; POC=People of Color

8.1.5. Trial V01-126A-201

Trial Design

This was a multicenter, randomized, double-blind, vehicle controlled, parallel group, 12-week study designed to assess the safety, tolerability, and efficacy of IDP-126 Gel in comparison with

its combination component gel products and vehicle to establish the contribution of each single component versus the remaining pair components. The five arms were as follows:

- IDP-126 Gel (clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel)
- IDP-126 Component A (BPO 3.1%/adapalene 0.15% gel)
- IDP-126 Component B (clindamycin phosphate 1.2%/BPO 3.1% gel)
- IDP-126 Component C (clindamycin phosphate 1.2%/adapalene 0.15% gel)
- IDP-126 vehicle gel

The study design, patient population, treatment plan, and study visits were the same as Studies 301 and 302.

The coprimary efficacy endpoints were the same as in Studies 301 and 302.

Study Endpoints

At each study visit, the investigator/evaluator assessed the subject's face, assigning an EGSS and counting all observed inflammatory and noninflammatory lesions. Note that the EGSS was determined prior to lesion counting.

The three coprimary efficacy endpoints were:

- Absolute change in the inflammatory lesion count from baseline to Week 12
- Absolute change in the noninflammatory lesion count from baseline to Week 12
- Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to "clear" or "almost clear" (considered "success" in the dichotomized evaluation)

Negative values for change from baseline to Week 12 endpoints, or a higher percentage of subjects classified as success for the EGSS categorical endpoint, indicate better efficacy.

Statistical Analysis Plan

The ITT population was defined as all randomized who received at least once dose of study treatment.

Missing data for lesion counts at Week 12 was imputed by multiple imputation using the MCMC method. Imputation was done independently for each treatment arm to ensure the pattern of missing observations in each treatment group would not influence the missing value estimation in the other arm. A total of 5 imputation datasets were generated for each efficacy endpoint.

The efficacy endpoints derived from inflammatory or noninflammatory lesion counts (absolute change from baseline; percent change from baseline), were analyzed using ANCOVA models with terms for treatment, center, and baseline lesion count. The analyses were conducted on both the count data and on ranked data to determine whether the parametric or nonparametric model approach was appropriate for the between-group comparisons. First the ANCOVA model was tested using actual count data, to enable a test for skewness of the residuals. If the p-value was <0.01 for the skewness test, the results from the non-parametric model (ANCOVA on ranked transformed data) would be used to determine superiority. The skewness test was statistically significant for all the primary efficacy endpoints, so the descriptive statistics on the original scale were reported along with the p-value from the nonparametric model.

Missing data for EGSS at Week 12 was also imputed using the MCMC method for multiple imputation. First the missing values on the 0 to 4 ordinal EGSS scale were imputed, then the EGSS success outcome was classified as success/failure. This was performed independently for the two treatment arms, with five imputed datasets generated for each endpoint.

The percentage of subjects with EGSS success was analyzed using a logistic regression model with factors for treatment group and analysis center. Firth's Penalized Likelihood was applied to allow the model to converge in case of quasi-complete separation of the data.

Because IDP-126 gel is a 3-part combination, the objective of this trial was to confirm that each component of the combination product contributes to the efficacy versus the other two components combined. IDP-126 gel was compared to each of the four comparator arms for all three co-primary endpoints at α=0.05. Success on all 12 comparisons was planned to demonstrate superiority of IDP-126 gel.

The analyses provided in the clinical study report followed the planned analyses, methods and models as described in the protocol.

8.1.6. Study Results (Trial 201)

Patient Disposition

Study 201 randomized a total of 741 subjects at an equal ratio to the five treatment arms. One subject in the IDP-126 gel arm did not receive treatment and was excluded from the ITT analysis set, defined as all randomized subjects who received treatment. A total of 92 subjects discontinued prior to completing Week 12. As shown in Table 35, the reasons for discontinuation were similar across the five arms, with Withdrew Consent and Lost-to Follow-up as the most common reasons. The five arms were fairly balanced across reasons for discontinuation.

Table 35. Subject Disposition – Study 201

	IDP-126 Gel n (%)	IDP-126 Component A n (%)	IDP-126 Component B n (%)	IDP-126 Component C n (%)	Vehicle Gel n (%)
Randomized	**147 (100)**	**150 (100)**	**146 (100)**	**150 (100)**	**148 (100)**
Intent to Treat [1] (ITT)	**146 (99)**	**150 (100)**	**146 (100)**	**150 (100)**	**148 (100)**
Discontinued Study Treatment	**22 (15)**	**18 (12)**	**13 (9)**	**18 (12)**	**21 (14)**
Adverse Event	4 (3)	8 (5)	0	3 (2)	1 (1)
Lack of Efficacy	0	0	1 (1)	0	0
Subject Withdrew Consent	5 (3)	1 (1)	4 (3)	7 (5)	9 (6)
Parent Withdrew Consent [2]	1 (1)	2 (1)	3 (2)	1 (1)	1 (1)
Lost to Follow-up	9 (6)	7 (5)	5 (3)	6 (4)	7 (5)
Worsening Condition	0	0	0	0	1 (1)
Other	3 (2)	0	0	1 (1)	2 (1)
Completed Study	**125 (85)**	**132 (88)**	**133 (91)**	**132 (88)**	**127 (86)**

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt and CSR Table 10-1
[1] Intent-to-Treat (ITT) population: all randomized subjects who received treatment (one subject in IDP-126 gel arm did not receive study treatment)
[2] Refers to the parent or legal guardian.
Abbreviations: IDP-126 Component A = benzoyl peroxide/adapalene; IDP-126 Component B = clindamycin phosphate/benzoyl peroxide; IDP-126 Component C = clindamycin phosphate/adapalene

Table of Demographic Characteristics

As shown in Table 36, just over half the subjects were adolescents (age 10-17) and approximately 61% were female. The majority were White (69%) or Black or African American (17%). The majority were from the United States (83%). The five arms were fairly balanced for the demographic and baseline characteristics.

Table 36. Demographics and Baseline Disease Characteristics – Trial 201 (ITT[1])

	IDP-126 gel (N=146)	IDP-126 Component A (N=150)	IDP-126 Component B (N=146)	IDP-126 Component C (N=150)	Vehicle Gel (N=148)
Age (years)					
N	146	150	146	150	148
Mean (SD)	19.9 (7.0)	19.2 (8.0)	19.6 (6.9)	19.4 (6.5)	19.6 (7.1)
Median (Min, Max)	17 (11, 46)	17 (10, 60)	17 (10, 45)	17 (11, 50)	17 (11, 47)
Age Group, n (%)					
< 12 years	2 (1)	2 (1)	6 (4)	4 (3)	2 (1)
12 to 17 years	74 (51)	85 (57)	71 (49)	74 (49)	74 (50)
≥ 18 years	70 (48)	63 (42)	69 (47)	72 (48)	72 (49)
Sex, n (%)					
Female	94 (64)	86 (57)	91 (62)	93 (62)	89 (60)
Male	52 (36)	64 (43)	55 (38)	57 (38)	59 (40)

	IDP-126 gel (N=146)	IDP-126 Component A (N=150)	IDP-126 Component B (N=146)	IDP-126 Component C (N=150)	Vehicle Gel (N=148)
Race, n (%)					
White	98 (67)	109 (73)	101 (69)	109 (73)	95 (64)
Black Or African American	24 (16)	26 (17)	30 (21)	20 (13)	26 (18)
American Indian or Alaska Native	1 (1)	1 (1)	1 (1)	1 (1)	2 (1)
Asian	10 (7)	6 (4)	8 (6)	9 (6)	17 (12)
Native Hawaiian or Other Pacific Islander	2 (1)	4 (3)	0	1 (1)	0
Other/Multiple	11 (8)	4 (3)	6 (4)	10 (7)	8 (5)
Ethnicity, n (%)					
Hispanic or Latino	33 (23)	30 (20)	29 (20)	27 (18)	34 (23)
Not Hispanic or Latino	113 (77)	120 (80)	117 (80)	123 (82)	114 (77)
Country, n (%)					
United States	122 (84)	125 (83)	121 (83)	126 (84)	123 (83)
Rest of World	24 (16)	25 (17)	25 (17)	24 (16)	25 (17)
Inflammatory Lesion Count					
Mean (SD)	39.0 (11.8)	39.0 (10.2)	40.0 (12.8)	38.2 (7.9)	38.2 (9.2)
Median (Min, Max)	35 (30, 89)	36 (30, 79)	35.5 (30, 94)	36 (30, 81)	35 (30, 74)
Noninflammatory Lesion Count					
Mean (SD)	51.8 (20.3)	48.0 (14.7)	49.2 (17.6)	51.1 (18.4)	50.7 (18.7)
Median (Min, Max)	43 (35, 150)	43 (35, 132)	42 (35, 144)	44 (35, 136)	42.5 (35, 126)
Evaluator's Global Severity Score n (%)					
0 – Clear	0	0	0	0	0
1 – Almost Clear	0	0	0	0	0
2 – Mild	0	0	0	0	0
3 – Moderate	124 (85)	119 (79)	124 (85)	129 (86)	127 (86)
4 – Severe	22 (15)	31 (21)	22 (15)	21 (14)	21 (14)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects who received study treatment
Abbreviations: Min = Minimum; Max = Maximum; SD = Standard Deviation

Efficacy Results – Primary Endpoint

The three coprimary efficacy endpoints were:

- Absolute change in the inflammatory lesion count from baseline to Week 12
- Absolute change in the noninflammatory lesion count from baseline to Week 12
- Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to "clear" or "almost clear" (considered "success" in the dichotomized evaluation)

Negative values for change from baseline to Week 12 endpoints, or a higher percentage of subjects classified as success for the EGSS categorical endpoint, indicate better efficacy.

The overall Type I error was controlled by requiring the three coprimary efficacy endpoints to be statistically significant at an alpha level of 0.05 for all comparisons to the four control arms, for a total of 12 tests. The objective was to meet the combination product requirement. As shown in Table 37, IDP-126 gel demonstrated superiority to each of the two-component treatment arms as well as to the vehicle gel arm, on all three coprimary endpoints. These results support the contribution of each of the three components to the efficacy of the combination drug.

Table 37. Results for Coprimary Efficacy Endpoints – Study 201 (ITT[1])

	IDP-126 Gel (N=146)	IDP-126 Component A (N=150)	IDP-126 Component B (N=146)	IDP-126 Component C (N=150)	Vehicle Gel (N=148)
Inflammatory Lesion Count Absolute Change from Baseline to Week 12					
LS Mean (LS SD) [2]	-29.9 (11.9)	-26.7 (11.7)	-24.8 (11.7)	-26.8 (11.7)	-19.6 (12.1)
Median [3]	-29.5	-27.2	-27.0	-26.8	-19.8
Contrast p-value [4]		0.013	0.003	0.026	<0.001
Noninflammatory Lesion Count Absolute Change from Baseline to Week 12					
LS Mean (LS SD) [2]	-35.5 (16.3)	-29.9 (16.4)	-27.8 (16.0)	-30.0 (16.4)	-21.8 (16.6)
Median [3]	-33.6	-30.1	-29.8	-31.4	-23.5
Contrast p-value [4]		0.004	<0.001	0.005	<0.001
EGSS Reduction ≥2 Grades from Baseline and Achieving Clear or Almost Clear at Week 12					
Success (%)	52.5%	27.8%	30.5%	30.3%	8.1%
Failure (%)	47.5%	72.2%	69.5%	69.7%	91.9%
Contrast p-value [5]		<0.001	0.001	0.001	<0.001

Source: Study 201 Applicant's analysis CSR Table 11-3
[1] Intent-to-Treat (ITT) population: Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.
[2] Least squares means and standard deviations, were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. Values have been adjusted for multiple imputation. Negative LS mean values represent decreases from baseline.
[3] Median values were obtained by averaging the summary statistics generated from each imputed dataset. Negative median values represent decreases from baseline.
[4] P-values were obtained from a ranked analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. Values have been adjusted for multiple imputation.
[5] P-value was obtained from a logistic regression with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.
Abbreviations: CI:=Confidence Interval; EGSS=Evaluator's Global Severity Score; ITT=Intent-to-Treat; LS=Least Squares; SD=Standard Deviation

Integrated Review of Effectiveness

8.1.7. Assessment of Efficacy Across Trials

No additional analyses of efficacy across the three efficacy trials were reviewed.

8.1.8. Integrated Assessment of Effectiveness

The Applicant provided results from two randomized, double-blind, vehicle-control, parallel-arm pivotal phase 3 trials, V01-126A-301 (301) and V01-126A-302 (302), to support the efficacy and safety of IDP-126 gel for the treatment of acne vulgaris. Three co-primary endpoints were: treatment success, defined as at least a 2-grade improvement from Baseline in EGSS and an EGSS score of clear (0) or almost clear (1); and absolute change from baseline to Week 12 in noninflammatory lesion counts and inflammatory lesion counts separately. In both trials IDP-126 demonstrated statistical significance versus vehicle gel (all p-values ≤ 0.003) on all three co-primary endpoints. Additional secondary efficacy endpoints, tested in hierarchical order, included percent change from baseline to Week 12 in noninflammatory lesion counts and inflammatory lesion counts, and improvement by at least 2 grades in the EGSS scale by Week 12. IDP-126 gel was statistically significant versus vehicle gel on these endpoints in both trials as well.

The Applicant also conducted a phase 2 randomized, double-blind, dual-component and vehicle-control trial, V01-126A-201 (201), to provide evidence that each of the 3 separate components in the IDP-126 gel combination contributed to efficacy over that of the other two combined. The three coprimary endpoints were the same as in the phase 3 trials. IDP-126 gel demonstrated superiority for all three efficacy endpoints versus each of the dual-component arms as well as the vehicle gel arm.

From a statistical perspective, the phase 2 combination drug trial and the two phase 3 trials in this application provide sufficient evidence of efficacy to support the indication of treatment of moderate to severe acne vulgaris.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for IDP-126 gel for the treatment of acne vulgaris derives from pooled data from two identically designed phase 3 trials, V01-126A-301 (301) and V01-126A-302 (302).

Study 301and Study 302 were multicenter, randomized, double-blind, parallel-group studies to evaluate the efficacy and safety of IDP-126 gel applied topically once daily for 12 weeks in subjects 9 years of age and older with acne vulgaris. These phase 3 studies were of identical design and included a total of 363 subjects (242 subjects treated with IDP-126 gel and 121 subjects treated with vehicle gel) with moderate to severe acne vulgaris defined by the EGSS score.

The safety population for the combined phase 3 trials consisted of all subjects in the randomized population who were confirmed to have used the study drug at least once. Subjects in the safety population were analyzed according to the study drug they received.

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

Subjects who met all of the following criteria were eligible for participation in the study:

- Male or female, at least 9 years of age
- Subjects must have had an EGSS for facial acne of 3 (moderate) or 4 (severe) at the
- baseline visit
- Subjects must have had a facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 30 but no more than 100
- Subjects must have had a facial acne noninflammatory lesion (open and closed comedones) count no less than 35 but no more than 150
- Subjects with 2 or fewer facial nodules

To determine the safety profile of IDP-126 gel, the review team analyzed the pooled data from the two phase 3 studies for exposure, demographics, baseline characteristics, TEAEs, serious adverse events (SAEs), TEAEs leading to discontinuation, tolerability assessments (scaling, erythema, itching, burning, stinging), physical examinations, and vital signs. Treatment-emergent adverse events are those with an onset on or after the date of first application of study drug. Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 22.0.

The Applicant also submitted supportive safety data from two phase 1 tolerability studies (V01-126A-101 and V01-126A-102), a phase 1b PK bridging to EpiDuo Forte Gel study (V01-126A-501), and two phase 2 studies (V01-126A-201 and V01-126A-202), summarized below.

- Phase 1 Tolerability Studies:
  - V01-126A-101: Randomized, evaluator-blind, controlled, within-subject comparison study in healthy volunteers to evaluate the potential of IDP-126 gel to cause skin irritation using a cumulative irritation patch test design (semi-occlusive patches applied to the back, 21 times over 22 days)
  - V01-126A-102: Randomized, evaluator-blind, controlled study in healthy volunteers to evaluate the potential of IDP-126 gel to induce skin sensitization using a repeat insult patch test design (semi-occlusive patch applied to the back, 3 times/week for 3 weeks)

- Phase 1b PK bridging to EpiDuo Forte Gel Study:
  - V01-126A-501: Open-label, randomized (for subjects ≥12 years), study designed to assess the safety and plasma PK of adapalene and clindamycin from IDP-126 gel and to bridge the PK for adapalene between IDP-126 gel and EpiDuo Forte Gel (adapalene 0.3%/BPO 2.5%); enrolled subjects were at least 9 years of age (IDP-126 gel group) or at least 12 years of age (EpiDuo Forte Gel group) with a clinical diagnosis of moderate to severe acne, applied topically once daily for 28 days

- Phase 2 Studies:
  - V01-126A-201: Randomized, double-blind, parallel-group, vehicle-controlled study to evaluate the efficacy and safety of IDP-126 gel, as compared with its active components and vehicle gel, applied topically once daily for 12 weeks, 9 years of age and older
  - V01-126A-202: Randomized, double-blind, vehicle-controlled study to compare the efficacy and safety of IDP-126 gel to EpiDuo Forte Gel and combined vehicle gel, applied topically once daily for 12 weeks, 12 years of age and older.

Safety data from subjects enrolled in the phase 1 and 2 trials were not pooled with data from the phase 3 trials due to differences in the study designs.

There were no ongoing trials for IDP-126 gel at the time of the NDA submission and the 120-day safety update. There was no new safety information at the time of the 120-day safety update.

The Applicant requested waivers for the following studies to evaluate IDP-126 gel:

- Long-term systemic safety study
- Thorough QT study

During the pre-NDA meeting, the Agency noted that the preliminary data indicated that the systemic exposure may initially be higher in subjects under 12 years of age (b) (4) . The Agency agreed that it was reasonable that a long-term safety study will likely not be needed, however, that the final determination of the issue would be made during the application review of the safety experience and PK data, (b) (4) The Agency agreed that the Applicant's plan to request a waiver for conducting a Thorough QT (TQT) study appeared reasonable and a final determination would be made at the time of the NDA review. Refer to Section 8.2.4, subsection QT of this review for further details regarding the waiver for the TQT study.

8.2.2. Review of the Safety Database

Overall Exposure

All subjects in the clinical development plan who received IDP-126 gel applied the to-be-marketed formulation of the product. The safety population consisted of 2114 subjects of which 930 received at least 1 application of IDP-126 gel either on the face or under semi-occluded patch conditions; in some studies, subjects with truncal acne were permitted to also apply study drug to the trunk. In total, 279 subjects received IDP-126 gel as a topical patch for assessments of cumulative irritation or dermal sensitization; 38 subjects in the maximal use PK study applied IDP-126 gel to the face and trunk, once daily, for up to 28 days; and 613 subjects in the phase 2 and pivotal phase 3 studies combined applied IDP-126 gel topically to the face, once daily, for up to 12 weeks (this includes 118 subjects in the phase 2 clinical bridging study and both pivotal phase 3 studies combined who also chose to also apply IDP-126 gel topically to their trunks).

The primary safety pool includes 363 subjects from two identical phase 3 studies. This safety pool includes 242 subjects treated with IDP-126 gel and 121 subjects treated with vehicle gel. Given the two phase 3 studies were identically designed, the pooling strategy is appropriate.

In the pooled phase 3 trials, the Applicant evaluated the extent of exposure by documenting the weight of the containers before and after product distribution and the number of applications per diary. In the IDP-126 gel group, the mean amount of study drug applied was 47 grams (g) or 79 applications. In the vehicle Gel group, the mean amount of study drug applied was 49 g or 81 applications. More than 90% of subjects in each treatment arm were compliant with the dosing regimen. Compliance was defined by the Applicant as applying 80-120% of expected applications and not missing more than 5 consecutive days dosing. The Applicant proposes to supply IDP-126 gel commercially in 20-gram and 50-gram tubes and 20-gram and 50-gram pumps which is reasonable based on the total amount of study drug used in the phase 3 trials. Additionally, the exposure and total amount of study drug used in the phase 3 trials are reasonable to inform safety for the proposed 20-gram and 50-gram tubes and pumps.

Table 38. Integrated Summary of Studies V01-126A-301 and V01-126A-302: Summary of Extent of Exposure (Safety Population)

	IDP-126 Gel (N = 242)	IDP-126 Vehicle Gel (N = 121)	Total (N = 363)
Total amount of study drug used (g)			
N	222	115	337
Mean (SD)	47.41 (25.664)	49.05 (25.274)	47.97 (25.506)
Median	43.40	48.10	44.80
Minimum to maximum	1.8 to 148.2	2.8 to 168.2	1.8 to 168.2
Total number of days of exposure			
N	230	116	346
Mean (SD)	81.6 (14.54)	83.2 (10.56)	82.1 (13.34)
Median	84.0	84.0	84.0
Minimum to maximum	6 to 123	17 to 109	6 to 123
Total number of applications			
N	230	116	346
Mean (SD)	79.1 (14.88)	81.3 (10.95)	79.8 (13.71)
Median	83.0	84.0	84.0
Minimum to maximum	6 to 122	14 to 104	6 to 122

SD = standard deviation
Source: ISS Table 14.3.0.1

Phase 3 trial – 301:
Mean total amount of study drug used = 50.12 g
Mean total number of days of exposure = 81.1 days

Mean daily dose for trial 301 = 50.12/81.1 = 0.6180 g/day

Phase 3 trial – 302
Mean total amount of study drug used = 44.60 g
Mean total number of days of exposure = 82 days

Mean daily dose for trial 302 = 44.6/82 = 0.5439 g/day

The max daily dose will the mean of mean daily dose for trial 301 and 302

0.6180 + 0.5439 / 2 = 0.5809 g = 0.58 g

The maximum daily dose would be 0.58 g of the formulation applied once daily.

Relevant Characteristics of the Safety Population

In the pooled phase 3 trials, the majority of subjects were female (58%), not Hispanic/Latino (78%), and white (74%). The mean age was 20.3 years (range: 10 to 48 years). Five of 363 (1.4%) subjects (3/242 (1.2%) in the IDP-126 gel cohort and 2/121 (1.7%) in the vehicle gel cohort) were ages 10 to <12 years (enrollment allowed down to 9 years of age). The demographic characteristics of both treatment groups were comparable. Across the two phase 3 trials, no subjects were 65 years of age or older. Most of the subjects enrolled in the phase 3 trials resided in the United States. At baseline, most subjects (91%) had EGSS scores that equated to moderate acne.

Table 39. Demographic Characteristics of Subjects From Studies V01-126A-301 and V01-126A-302 Pooled (Safety Population)

Subgroup	IDP-126 gel (N = 242) n (%)	IDP-126 Vehicle Gel (N = 121) n (%)	Total (N = 363) n (%)
Sex			
Female	144 (59.5)	68 (56.2)	212 (58.4)
Male	98 (40.5)	53 (43.8)	151 (41.6)
Age			
Mean	20.18	20.59	20.31
Standard Deviation	7.29	6.93	7.17
Minimum	10	11	10
Median	17	19	18
Maximum	48	44	48
Age Group			
10-11 years	3 (1.2)	2 (1.7)	5 (1.4)
12-17 years	123 (50.8)	50 (41.3)	173 (47.7)
18+ years	116 (47.9)	69 (57.0)	185 (51.0)
Race			
Asian	21 (8.7)	5 (4.1)	26 (7.2)
Black or African American	40 (16.5)	14 (11.6)	54 (14.9)
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.8)	2 (0.6)
Other	11 (4.5)	3 (2.5)	14 (3.9)
White	169 (69.8)	98 (81.0)	267 (73.6)
Ethnicity			
Hispanic or Latino	57 (23.6)	23 (19.0)	80 (22.0)
Not Hispanic or Latino	185 (76.4)	98 (81.0)	283 (78.0)

Source: Reviewer created table with MAED and DM tool based on Applicant submitted ISS ADSL dataset

Adequacy of the Safety Database:

The safety database presented by the Applicant is adequate to characterize the safety profile of IDP-126 gel for the treatment of acne vulgaris in subjects 12 years of age and older:

- The size of the safety database is adequate.
- The total subject exposure to IDP-126 gel, applied once daily for 12 weeks, provides adequate data for the evaluation of safety.
- The demographics of the study population are representative of the target population and the racial representation of the study population is representative of the United States population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of data submitted is adequate to assess the safety of IDP-126 gel and inform labeling. There were no significant deficiencies discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An adverse event (AE) was defined by the Applicant as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product that did not necessarily have a causal relationship with the study drug. Adverse events included any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that appeared or worsened during the course of the clinical study, regardless of causal relationship to the study drug(s) under study.

Events that occurred on or after the date of the first application of study drug were considered TEAEs. Clinical laboratory findings and any vital sign abnormalities were recorded as AEs only if they were considered by the investigator to be clinically significant (e.g., were symptomatic, required corrective treatment, led to discontinuation, or were serious). Any AEs/SAEs considered by the investigator to be study drug related that were reported or observed at the final study visit were to be followed until stabilization or resolution.

In the phase 3 study protocols, cutaneous safety and tolerability assessments were to be reported as AEs only if they resulted in the need for concomitant therapy, interruption of study drug administration, or subject discontinuation. The Applicant excluded all AEs related to cutaneous safety and tolerability assessments per protocol in their safety analysis.. The review team disagrees with the Applicant's exclusion of these reported AEs and have included all

reported AEs related to cutaneous safety and tolerability assessments in the Agency's analysis.

Routine Clinical Tests

In trials, 301and 302 (the pooled safety analysis set), safety monitoring was conducted during clinic visits at Screening, at Baseline prior to randomization, Weeks 2, 4, 8 and 12. The evaluation of safety included abbreviated physical examinations, vital signs, clinical laboratory tests, pregnancy testing, concomitant medications, active local cutaneous safety assessments and adverse events.

An abbreviated physical examination and vital sign measurements will be performed at Baseline and Week 12 (end of study).

The protocols included clinical laboratory testing at Baseline and Week 12. The assessments included hematology (complete blood count with differential) and serum chemistry.

Urine pregnancy testing was performed at Screening, prior to randomization at Baseline, and at Weeks 2, 4, 8 and 12. Serum pregnancy testing was performed at the Baseline and Week 12 study visits.

8.2.4. Safety Results

Deaths

No subjects died in the phase 3 trials, 301 and 302.

Across the 5 earlier phase clinical studies, 1 death was reported in V01-126A-102 in the setting of hospitalization for suspected COVID-19 infection, considered not related to the study drug.

Serious Adverse Events

No SAEs were reported in the phase 3 trials, 301 and 302.

Across the 5 earlier phase clinical studies, 1 fatal SAE (suspected COVID-19 infection) and 6 non-fatal SAEs (enteritis, pelvic fracture, road traffic accident, sickle cell anemia with crisis, hyperbilirubinemia, and abortion-induced (elective pregnancy termination (see narrative below under the subheading for Pregnancies) were reported.

Other than enteritis, these SAEs are not considered related to the study drug. Enteritis occurred in a subject who received IDP-126 Component C (1.2% clindamycin phosphate/0.15% adapalene) gel in study 201, was reported as severe and resulted in study discontinuation. Enteritis is included in the proposed prescribing information (PI) in contraindications as labeled for Acanya and Benzaclin for the clindamycin component. Colitis is included in the proposed PI

in contraindications and warnings and precautions as labeled for Acanya and Benzaclin for the clindamycin component (see Section 11).

Dropouts and/or Discontinuations Due to Adverse Effects

A total of 7 subjects (2.9%) in the IDP-126 gel group and 0 subjects in the placebo group discontinued the study drug due to TEAEs in the phase 3 trials, 301 and 302. Discontinued subjects by trial are described below:

- V01-126A-301:
  - 3 subjects IDP-126 gel discontinued study drug due to TEAEs of mild erythema (1 subject), severe application site burn (1 subject), and moderate swelling face, moderate application site pain, moderate erythema, and mild application site exfoliation (all reported in a single subject).
  - Of the TEAEs leading to discontinuation, all were considered drug related and the only event that occurred in more than 1 subject in the treatment group was erythema (in 2 subjects)
- V01-126A-302:
  - 4 subjects IDP-126 gel discontinued the study drug due to TEAEs of application site dermatitis, application site irritation, application site pain, and influenza like illness (1 subject each).
  - All TEAEs were non-serious and all considered drug related (except for influenza like illness).

While the majority of TEAEs leading to discontinuation were related to application site reactions, data from the phase 2 trial, 202 (clinical bridging study), demonstrated that the rate of discontinuations due to TEAEs for IDP-126 gel was comparable to Epiduo Forte Gel. Application site reactions will be described in labeling.

Significant Adverse Events

In the phase 3 trials, a total of 3/242 subjects (1.2%) in the IDP-126 gel group and no subjects in the vehicle group, experienced at least 1 severe TEAE. Application site pain occurred in 2 subjects (0.8%), application site dryness occurred in 1 subject (0.4%) (this subject also had application site pain), and application site burn occurred in 1 subject (0.4%).

Severe application site reactions were infrequent and labeling will include a warning and strategies to mitigate such reactions.

Treatment Emergent Adverse Events and Adverse Reactions

Table 40. Treatment Emergent Adverse Event (TEAE) reported in Trials 301 and 302

	V01-126A-301				V01-126A-302			
	IDP-126 gel (N=122)		Vehicle gel (N=61)		IDP-126 gel (N=120)		Vehicle gel (N=60)	
	N	%	N	%	N	%	N	%
Subjects with any TEAE	30	24.6	5	8.2	36	30	5	8.3
Subjects with severe TEAE	1	0.8	0	0	2	1.7	0	0
Subjects with any treatment emergent SAE	0	0	0	0	0	0	0	0
Subjects with any Treatment Emergent Adverse Events leading to death	0	0	0	0	0	0	0	0
Subjects with any Treatment Emergent Adverse Events leading to permanent treatment discontinuation	3	2.5	0	0	4	3.3	0	0

Source: JMP Clinical derived table based on Applicant provided ADAE datasets
Abbreviations: TEAE: Treatment emergent adverse event, SAE: Serious adverse event; N (%): Number and percentage of subjects with at least one TEAE

Common Adverse Events

In the phase 3 study protocols, cutaneous safety and tolerability assessments were to be reported as AEs only if they resulted in the need for concomitant therapy, interruption of study drug administration, or subject discontinuation. The Applicant excluded all AEs related to cutaneous safety and tolerability assessments per protocol in their analysis.. The review team disagrees with the Applicant's exclusion of these reported AEs and have included all reported cutaneous AEs in the Agency's analysis.

In the pivotal phase 3 studies, 76 subjects (20.9%) reported 133 individual TEAEs. Most subjects experienced TEAEs that were mild or moderate in severity. A higher percentage of subjects in the IDP-126 gel group experienced TEAEs compared with the Vehicle Gel group (33.6% vs 3.9%, respectively).

The majority of the TEAEs were related to application site reactions. Based on the well-characterized safety of the individual components, TEAEs for cutaneous reactions are expected. There was one TEAE of sunburn reported in the IDP-126 gel cohort compared to 0 TEAE of sunburn reported in the vehicle gel (Table 41). During the phase 3 studies, subjects were instructed to avoid exposure to direct sunlight to prevent sunburn. Use of sunscreens with a sun protection factor of at least 15 and protective clothing (e.g., a hat) were recommended

when exposure could not be avoided. During the phase 3 studies, each subject was permitted to use only approved nonmedicated cleansers, moisturizers, and sunscreens. Thus, the low number of TEAE of sunburn reported in the IDP-126 gel cohort in the phase 3 studies is likely artificially low. The risk of photosensitivity for topical retinoids is a known potential class effect and adverse reaction and will be reflected in labeling. A pooled analysis of reported TEAEs is shown in the tables below.

Table 41. Pooled TEAEs Reported in Trials 301 and 302

		Description of Actual Arm				
		IDP-126 gel (N = 242)		IDP-126 Vehicle Gel (N = 121)		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
General disorders and administration site conditions	Application site pain	33	13.6%	1	0.8%	34
	Application site dryness	7	2.9%	.	.	7
	Application site irritation	5	2.1%	.	.	5
	Application site exfoliation	4	1.7%	.	.	4
	Xerosis	3	1.2%	1	0.8%	4
	Application site dermatitis	3	1.2%	.	.	3
	Application site erythema	3	1.2%	.	.	3
	Application site pruritus	2	0.8%	.	.	2
	Application site burn	1	0.4%	.	.	1
	Application site paraesthesia	1	0.4%	.	.	1
	Influenza like illness	1	0.4%	.	.	1
Skin and subcutaneous tissue disorders	Erythema	8	3.3%	.	.	8
	Dermatitis contact	2	0.8%	.	.	2
	Acne	.	.	1	0.8%	1
	Dry skin	1	0.4%	.	.	1
	Swelling face	1	0.4%	.	.	1
	Urticaria	1	0.4%	.	.	1
Investigations	Coronavirus test positive	3	1.2%	.	.	3
	Blood pressure increased	.	.	2	1.7%	2
	Blood glucose increased	1	0.4%	.	.	1
	Blood potassium increased	1	0.4%	.	.	1
	Gamma-glutamyltransferase increased	1	0.4%	.	.	1
Infections and infestations	Folliculitis	.	.	1	0.8%	1
	Herpes simplex	1	0.4%	.	.	1
	Influenza	1	0.4%	.	.	1
	Nasopharyngitis	1	0.4%	.	.	1
	Pharyngitis	1	0.4%	.	.	1
	Pharyngitis streptococcal	.	.	1	0.8%	1
	Urinary tract infection	1	0.4%	.	.	1

		Description of Actual Arm				
		IDP-126 gel (N = 242)		IDP-126 Vehicle Gel (N = 121)		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
Injury, poisoning and procedural complications	Animal scratch	1	0.4%	.	.	1
	Ligament sprain	.	.	1	0.8%	1
	Sunburn	1	0.4%	.	.	1
Nervous system disorders	Paraesthesia	2	0.8%	.	.	2
	Headache	.	.	1	0.8%	1
Gastrointestinal disorders	Abdominal pain	1	0.4%	.	.	1
	Hematochezia	1	0.4%	.	.	1
Psychiatric disorders	Depression	2	0.8%	.	.	2
Blood and lymphatic system disorders	Neutropenia	1	0.4%	.	.	1
Hepatobiliary disorders	Hepatic steatosis	.	.	1	0.8%	1
Musculoskeletal and connective tissue disorders	Scoliosis	1	0.4%	.	.	1
Respiratory, thoracic and mediastinal disorders	Sinus congestion	1	0.4%	.	.	1

Source: JMP Clinical derived table based on Applicant provided ISS ADAE dataset

To inform labeling, related adverse events reported within 12 weeks of treatment in at least 1% of subjects treated with IDP gel and more frequently than subjects treated with the vehicle gel are presented in Table 42.

Table 42. Adverse Reactions Reported in >1% of the IDP-126 Gel Group and More Frequently Than the Vehicle Group in Pooled Data From Trials 301 and 302

		Description of Actual Arm				
		IDP-126 gel (N = 242)		IDP-126 Vehicle Gel (N = 121)		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
General disorders and administration site conditions	Application site pain	33	13.6%	1	0.8%	34
	Application site erythema and erythema	11	4.5%	.	.	11
	Application site dryness and xerosis	10	4.1%	1	0.8%	11
	Application site irritation	5	2.1%	.	.	5
	Application site exfoliation	4	1.7%	.	.	4
	Application site dermatitis	3	1.2%	.	.	3

Source: JMP Clinical derived table based on Applicant provided ISS 301 and 302 ADAE dataset (Reviewer edited)

Most of the adverse reactions reported in >1% of the IDP-126 gel Group and more frequently than the vehicle group in the integrated summary of safety (ISS) 301 and 302 were related to application site reactions. Table 42 will be reflected in labeling. Of the adverse reactions reported in >1% of the IDP-126 gel Group and more frequently than the vehicle group in ISS 301 and 302, 39/66 (59%) were mild, 24/66 (36.4%) were moderate, and 3/66 (4.5%) were severe.

Safety data from Trial 202 is supportive of a comparable safety profile between IDP-126 gel and EPIDUO FORTE Gel based on comparable TEAEs and adverse reactions (

Table 43).

Table 43. Adverse Reactions Reported in >1% of the IDP-126 gel Group and More Frequently Than the Vehicle Group, Trial 202

		Description of Actual Arm								
		IDP-126 gel		Epiduo Forte Gel		IDP-126 Vehicle Gel (stored at CRT)		IDP-126 Vehicle Gel (stored at 2-8°C)		
		(N = 230)		(N = 226)		(N = 115)		(N = 113)		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Total**
General disorders and administration site conditions	Application site pain	23	10.0%	16	7.1%	.	.	.	.	39
	Application site dryness	9	3.9%	11	4.9%	1	0.9%	1	0.9%	22
	Application site dermatitis	3	1.3%	8	3.5%	.	.	.	.	11
	Application site irritation	3	1.3%	6	2.7%	1	0.9%	1	0.9%	11
	Application site erythema	4	1.7%	4	1.8%	.	.	1	0.9%	9
	Application site exfoliation	4	1.7%	4	1.8%	.	.	.	.	8
Skin and subcutaneous tissue disorders	Rash	3	1.3%	4	1.8%	1	0.9%	.	.	8
Injury, poisoning and procedural complications	Sunburn	4	1.7%	3	1.3%	.	.	.	.	7

Source: JMP Clinical derived table based on Applicant provided 202 ADAE dataset (Reviewer edited)

Laboratory Findings

While there were several subjects with missing laboratory values in the pooled phase 3 trials, there was an adequate number of subjects with assessable laboratory evaluations.

In the pooled phase 3 trials, a total of 4 subjects (4/209; 2% in the IDP-126 gel group and 1/108; 0.9% in the vehicle group) had elevated liver enzymes, both aspartate transaminase and alanine transaminase (AST and ALT), at Week 12. Of the 4 subjects in the IDP-126 gel group, 3 subjects had normal AST and ALT at Baseline and elevated levels at Week 12 and 1 subject had an unknown shift of AST and ALT (no baseline levels recorded). The 1 subject in the vehicle group had normal AST and ALT at Baseline and elevated levels at Week 12.

In the pooled phase 3 trials, a total of 4 subjects (3/209; 1.4% in the IDP-126 gel group and 1/108; 0.9% in the vehicle group) had elevated AST at Week 12. All 3 subjects in the IDP-126 gel group had normal AST at Baseline and elevated levels at Week 12.

In the pooled phase 3 trials, a total of 7 subjects (4/209; 1.9% in the IDP-126 gel group and 2/108; 1.9% in the vehicle group) had elevated ALT at Week 12. Of the 4 subjects in the IDP-126 gel group, 1 subject had normal ALT at Baseline and elevated levels at Week 12; 1 subject had elevated ALT at Baseline which became more elevated at Week 12 (ALT: 37 to 38 U/L, normal reference range: 6-34 U/L); 1 subject had elevated levels at Baseline which decreased at Week 12; 1 subject unknown (no baseline ALT recorded). Of the 2 subjects in the vehicle group, both subjects had elevated ALT at Baseline which decreased at Week 12.

Among subjects with normal or elevated hepatic enzymes at Baseline, none had levels that became more than 3 times the upper limit of normal in either the IDP-126 gel or vehicle group. Given the low number of subjects with elevated AST and ALT, AST, and ALT at Week 12, conclusions regarding study drug relatedness cannot be made. Nevertheless, differences noted between IDP-126 gel cohort and vehicle gel cohort regarding AST and ALT elevation at Week 12 were minimal and more likely due to normal variations in the population. Furthermore, no related TEAEs were reported in subjects with elevated liver enzymes at Week 12 and the differences are not likely clinically meaningful.

In the pooled phase 3 trials, a total of 31 subjects [22/212 subjects (10%) in the IDP-126 gel group and 9/108 (8%) in the vehicle group] had elevated creatine kinase (CK) levels at Week 12. Of the 22 subjects in the IDP-126 gel group, 8/212 (3.8%) subjects with normal CK at Baseline developed elevated CK up to 2.5x upper limit of normal (ULN)), 3/212 (1.4%) subjects developed elevated CK >2.5xULN to 5x/ULN, and 2/212 (0.9%) subjects developed elevated CK >5xULN to 10xULN at Week 12. Of the 9 subjects in the vehicle group, 4/108 (3.7%) subjects with normal CK at Baseline developed up to 2.5xULN, 0 subjects developed elevated CK >2.5xULN to 5x/ULN, and 1/108 (0.9%) subjects developed elevated CK >5xULN to 10xULN at Week 12. The difference for the proportion of subjects with elevated CK levels at Week 12 between the IDP-126 gel cohort and vehicle gel cohort was marginal. In addition, among the subjects with elevated CK at Week 12, 4/22 (18%) subjects had elevated AST and/ or ALT in the IDP-126 gel group and 1/9 (11%) subjects had elevated AST and/ or ALT in the vehicle group. The literature supports the finding that the CK elevation alone may result in liver enzyme

elevation.[9] In one study of patients with creatine phosphokinase > 1000 units/L 93.1% had elevated AST and 75% had elevated ALT.[10] Furthermore, elevated serum creatine phosphokinase levels may occur in healthy teen-aged boys.[11]

In the pooled phase 3 trials, a total of 44 subjects (34/212; 16% in the IDP-126 gel group and 10/108; 9% in the vehicle group) had elevated triglycerides at Week 12. Of the 34 subjects in the IDP-126 gel group, 17 subjects had normal triglycerides at Baseline and elevated levels (16 subjects with elevated triglycerides up to 3.42 mmol/L and 1 subject with elevated triglycerides up to 5.7 mmol/L) at Week 12; 4 subjects had elevated levels at Baseline which became more elevated (up to 3.42 mmol/L) at Week 12; 13 subject had elevated levels at Baseline which decreased at Week 12. In the vehicle group, 4 subjects had normal triglycerides at Baseline and elevated levels (up to 3.42 mmol/L) at Week 12; 1 subject had elevated levels at Baseline which became more elevated (up to 3.42 mmol/L) at Week 12; 5 subjects had elevated levels at Baseline which decreased at Week 12. Therefore, a total of 21/212 (10%) of subjects in the IDP-126 gel group and 5/108 (5%) in the vehicle group had triglycerides that became elevated or more elevated from Baseline to Week 12. No related TEAEs were reported in subjects with elevated triglycerides at Week 12. While a difference was noted between the IDP-126 gel and vehicle gel cohorts for elevated triglycerides at Week 12, the differences were not clinically meaningful, and all elevations were grade 1 (triglycerides up to 3.42 mmol/L) with the exception of 1 subject who had a grade 2 (triglycerides up to 5.7 mmol/L) elevation.

In the IDP-126 gel group, 1 subject each experienced AEs of blood glucose increased, blood potassium increased, gamma-glutamyltransferase (GGT) (subject (b) (6)) increased, and neutropenia (ISS Table 14.3.1.2.3.1.1.x). The subject ((b) (6)) with the reported AE of GGT increased had a decrease GGT from baseline to Week 12 (361 U/L to 214 U/L) (baseline levels were elevated) and normal AST and ALT from baseline to Week 12. In the IDP-126 vehicle gel group, 1 subject experienced an event of hepatic steatosis. All these AEs were mild or moderate in intensity (ISS Table 14.3.1.2.5.x), none were serious (ISS Table 14.3.1.3.3.x), none were considered by the investigator to be study drug related (ISS Table 14.3.1.2.6.x), and none resulted in discontinuation (ISS Table 14.3.1.2.2.x).

The AEs of blood glucose increased, blood potassium increased, gamma-glutamyltransferase increased, and neutropenia are unlikely to be study drug related.

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[9] Miller ML. Clinical manifestations and diagnosis of rhabdomyolysis. UpToDate. Updated Feb 08, 2018. Accessed June 28, 2018

[10] Nathwani RA, Pais S, Reynolds TB, Kaplowitz N. Serum alanine aminotransferase in skeletal muscle diseases. Hepatology. 2005;41(2):380

[11] Hunter A. Elevated Serum Creatine Phosphokinase Levels in Healthy Teen-aged Boys. Arch Neurol. 1975;32(8):576. doi:10.1001/archneur.1975.00490500096016

Vital Signs

No meaningful changes were observed in vital signs (oral temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and heart rate) for either study drug group, and the mean changes from baseline at Week 12 were similar between study drug groups.

Electrocardiograms

Electrocardiograms were not obtained.

QT

Per the review by the Interdisciplinary Review Team for Cardiac Safety Studies (Eliford N Kitabi and Dr. Christine E Garnett) dated April 21, 2023, findings from the maximal use study indicates that systemic exposure to adapalene and clindamycin after topical application of IDP-126 gel are in the sub nanomolar range, has similar (or lower exposures) to the exposures with other marketed acne vulgaris products containing adapalene and clindamycin, and therefore, meet the criteria for waiving the TQT study.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Cutaneous Tolerability In the phase 3 studies, cutaneous safety and tolerability (scaling, erythema, hypopigmentation, hyperpigmentation, itching, burning, and stinging) were assessed at baseline, Weeks 2, 4, 8, and 12 using 4-point scales (0=none, 1=mild, 2=moderate, or 3=severe).

In the pooled phase 3 studies, most subjects in the safety population reported no signs and symptoms at Baseline although approximately 40% and 30% of subjects had erythema and hyperpigmentation, respectively, at Baseline in both the IDP-126 gel and vehicle gel treatment groups.

In the IDP-126 gel group, based on all parameters with the exception of erythema, the majority of subjects tolerated cutaneous application on the face. When maximum, post-baseline signs and symptoms occurred, they were mostly mild to moderate in severity. It should be noted that more than 1% of subjects in the IDP-126 gel group had erythema, hyperpigmentation, burning, and stinging graded as severe. The results of the tolerability assessments at Baseline, Week 12, and maximum postbaseline are summarized in Table 44.

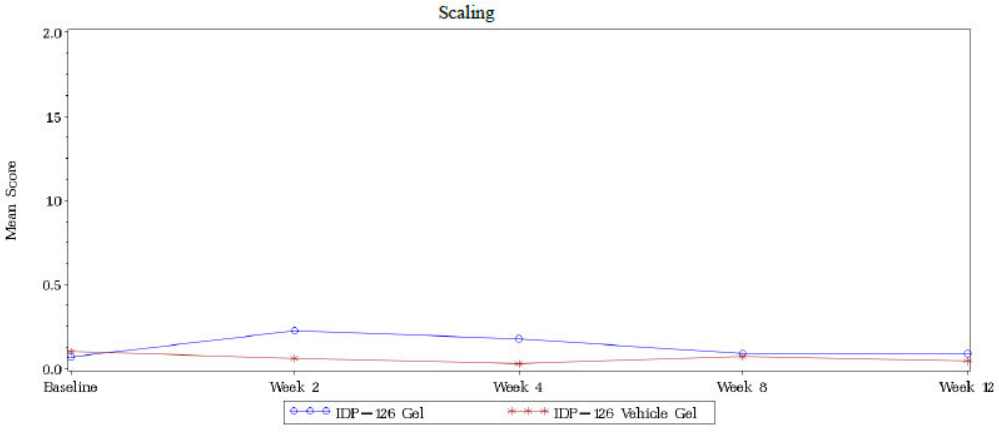
Table 44. Facial Cutaneous Tolerability Results by Assessment Parameter and Study Period (Trials 301 and 302 Safety Population)

	Baseline (Prior to Treatment)				Week 12 (End of Treatment)				Maximum Postbaseline			
	None n (%)	Mild n (%)	Mod n (%)	Severe n (%)	None n (%)	Mild n (%)	Mod n (%)	Severe n (%)	None n (%)	Mild n (%)	Mod n (%)	Severe n (%)
IDP-126 Gel (N = 242)												
Scaling	226 (93.4)	16 (6.6)	0	0	197 (92.1)	15 (7.0)	2 (0.9)	0	162 (69.8)	62 (26.7)	8 (3.4)	0
Erythema	151 (62.4)	47 (19.4)	40 (16.5)	4 (1.7)	151 (70.6)	48 (22.4)	14 (6.5)	1 (0.5)	103 (44.0)	80 (34.2)	46 (19.7)	5 (2.1)
Hypo	236 (97.5)	5 (2.1)	1 (0.4)	0	213 (99.5)	1 (0.5)	0	0	227 (97.0)	7 (3.0)	0	0
Hyper	160 (66.1)	63 (26.0)	15 (6.2)	4 (1.7)	161 (75.2)	39 (18.2)	11 (5.1)	3 (1.4)	147 (62.8)	63 (26.9)	19 (8.1)	5 (2.1)
Itching	230 (95.0)	7 (2.9)	4 (1.7)	1 (0.4)	200 (93.0)	13 (6.0)	2 (0.9)	0	169 (71.9)	57 (24.3)	8 (3.4)	1 (0.4)
Burning	238 (98.3)	2 (0.8)	1 (0.4)	1 (0.4)	201 (93.5)	9 (4.2)	3 (1.4)	2 (0.9)	132 (56.7)	69 (29.6)	25 (10.7)	7 (3.0)
Stinging	237 (97.9)	5 (2.1)	0	0	207 (96.3)	5 (2.3)	2 (0.9)	1 (0.5)	168 (71.8)	48 (20.5)	12 (5.1)	6 (2.6)
IDP-126 Vehicle Gel (N = 121)												
Scaling	111 (91.7)	8 (6.6)	2 (1.7)	0	105 (95.5)	5 (4.5)	0	0	105 (87.5)	15 (12.5)	0	0
Erythema	72 (59.5)	29 (24.0)	20 (16.5)	0	76 (69.1)	28 (25.5)	6 (5.5)	0	65 (54.2)	27 (22.5)	26 (21.7)	2 (1.7)
Hypo	118 (97.5)	2 (1.7)	0	1 (0.8)	110 (100.0)	0	0	0	116 (95.9)	5 (4.1)	0	0
Hyper	83 (68.6)	29 (24.0)	8 (6.6)	1 (0.8)	85 (77.3)	17 (15.5)	6 (5.5)	2 (1.8)	83 (68.6)	24 (19.8)	12 (9.9)	2 (1.7)
Itching	113 (93.4)	6 (5.0)	2 (1.7)	0	109 (98.2)	2 (1.8)	0	0	106 (87.6)	14 (11.6)	1 (0.8)	0
Burning	120 (99.2)	0	1 (0.8)	0	110 (99.1)	1 (0.9)	0	0	116 (95.9)	3 (2.5)	1 (0.8)	1 (0.8)
Stinging	120 (99.2)	0	1 (0.8)	0	109 (98.2)	2 (1.8)	0	0	116 (95.9)	4 (3.3)	1 (0.8)	0

Hyper = hyperpigmentation; Hypo = hypopigmentation; Mod = moderate
Source: ISS Table 14.3.1.1.1.1

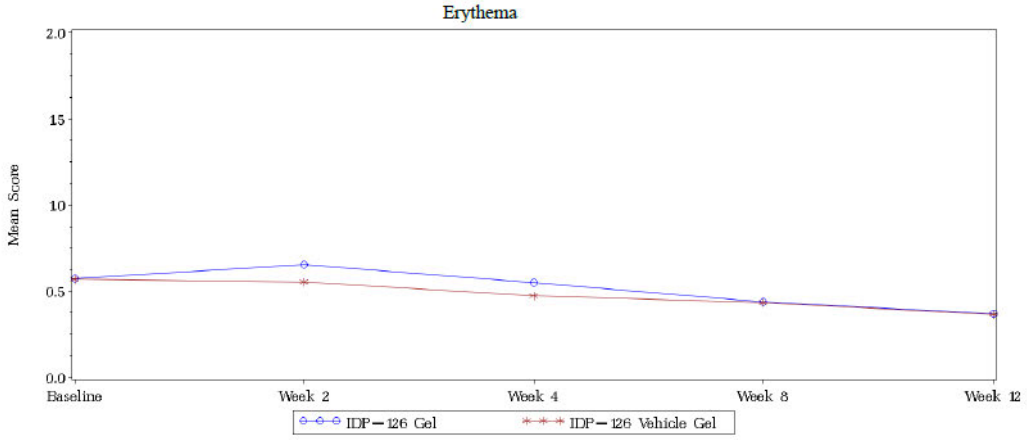
Of the subjects experiencing cutaneous irritation, the greatest proportion was reported to occur between Weeks 2 and 4. By Week 12, the percentage of subjects reporting signs and symptoms associated with IDP-126 gel administration declined toward Baseline levels or lower.

Figure 3. Mean Local and Cutaneous Safety and Tolerability Scores by Visit (Studies 301 and 302 Combined)



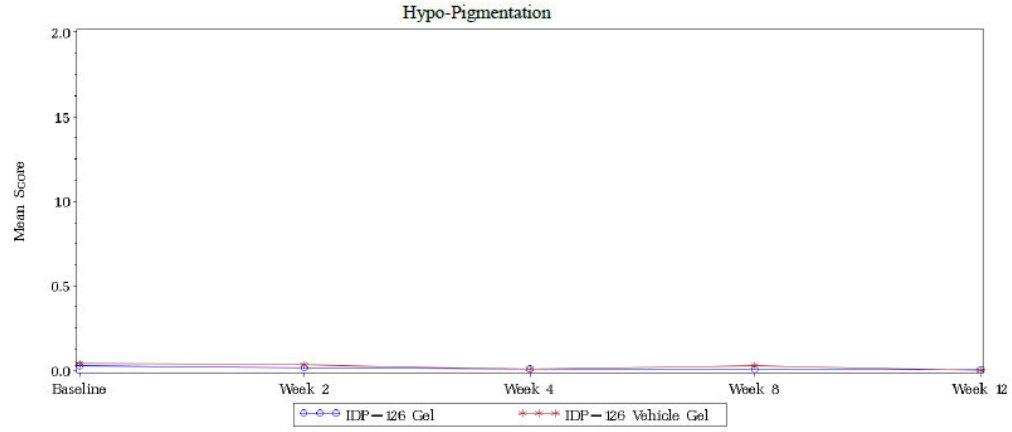
	Baseline			Week 2			Week 4			Week 8			Week 12		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
IDP-126 Gel (N=242)	242	0.07	0.25	228	0.22	0.48	217	0.18	0.40	213	0.09	0.30	214	0.09	0.32
IDP-126 Vehicle Gel (N=121)	121	0.10	0.35	119	0.06	0.24	112	0.03	0.16	111	0.07	0.26	110	0.05	0.21

SOURCE: AMOORE\BauschHealth\V01_126A_ISS\Stats\Outputs\Production\Tables\fscsaf (Jul 12, 2022 11:41)



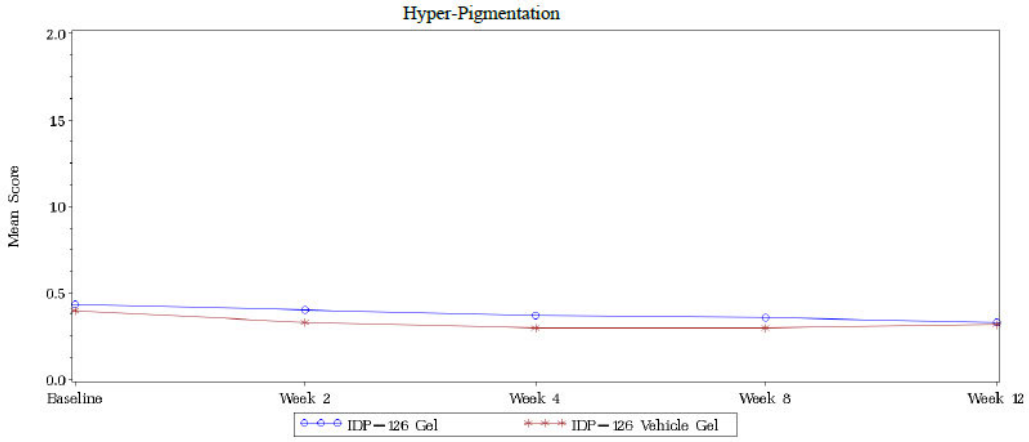
	Baseline			Week 2			Week 4			Week 8			Week 12		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
IDP-126 Gel (N=242)	242	0.57	0.82	228	0.65	0.77	217	0.55	0.73	213	0.44	0.68	214	0.37	0.63
IDP-126 Vehicle Gel (N=121)	121	0.57	0.76	119	0.55	0.71	112	0.47	0.73	111	0.43	0.70	110	0.36	0.59

SOURCE: AMOORE\BauschHealth\V01_126A_ISS\Stats\Outputs\Production\Tables\fscsaf (Jul 12, 2022 11:41)



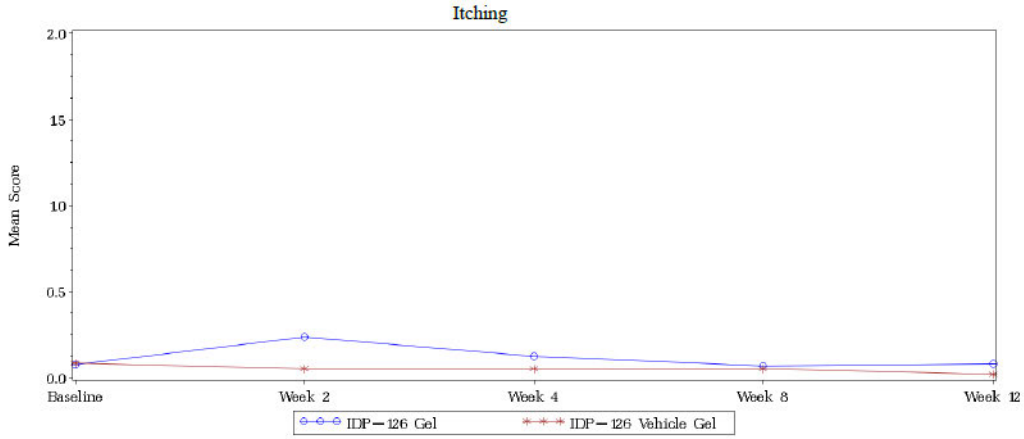
	Baseline			Week 2			Week 4			Week 8			Week 12		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
IDP-126 Gel (N=242)	242	0.03	0.19	228	0.02	0.13	217	0.01	0.10	213	0.00	0.07	214	0.00	0.07
IDP-126 Vehicle Gel (N=121)	121	0.04	0.30	119	0.03	0.18	112	0.01	0.09	111	0.03	0.16	110	0.00	0.00

SOURCE: AMOORE\BauschHealth\V01_126A_ISS\Stats\Outputs\Production\Tables\fscsaf (Jul 12, 2022 11:41)



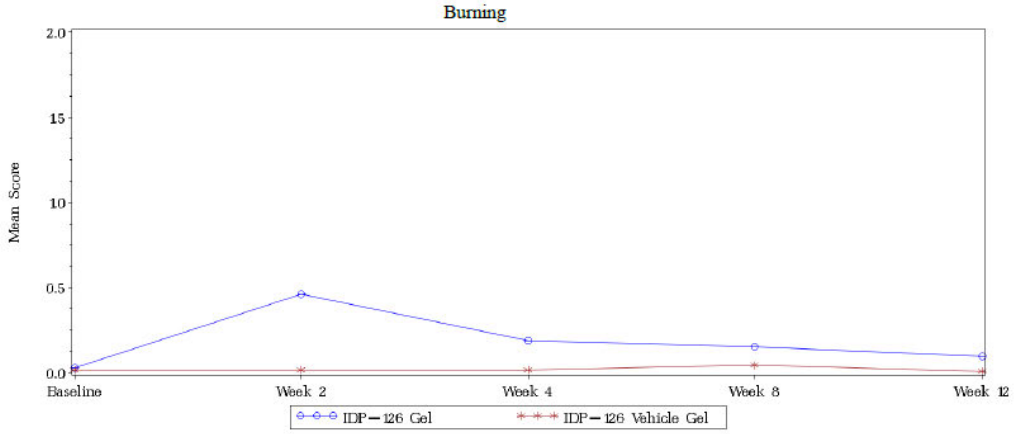
	Baseline			Week 2			Week 4			Week 8			Week 12		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
IDP-126 Gel (N=242)	242	0.43	0.69	228	0.40	0.64	217	0.37	0.63	213	0.36	0.63	214	0.33	0.64
IDP-126 Vehicle Gel (N=121)	121	0.40	0.65	119	0.33	0.58	112	0.29	0.61	111	0.30	0.64	110	0.32	0.66

SOURCE: AMOORE\BauschHealth\V01_126A_ISS\Stats\Outputs\Production\Tables\fscsaf (Jul 12, 2022 11:41)



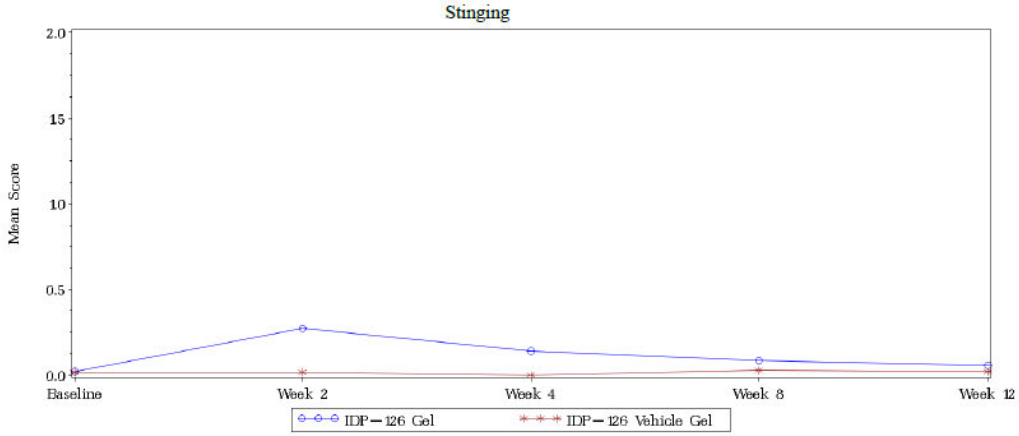
	Baseline			Week 2			Week 4			Week 8			Week 12		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
IDP-126 Gel (N=242)	242	0.07	0.36	228	0.24	0.52	223	0.13	0.36	219	0.07	0.25	215	0.08	0.30
IDP-126 Vehicle Gel (N=121)	121	0.08	0.33	119	0.05	0.26	116	0.05	0.22	115	0.05	0.22	111	0.02	0.13

SOURCE: AMOORE\BauschHealth\V01_126A_ISS\Stats\Outputs\Production\Tables\fscsaf (Jul 12, 2022 11:41)



	Baseline			Week 2			Week 4			Week 8			Week 12		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
IDP-126 Gel (N=242)	242	0.03	0.25	228	0.46	0.71	223	0.19	0.50	219	0.15	0.45	215	0.10	0.42
IDP-126 Vehicle Gel (N=121)	121	0.02	0.18	119	0.02	0.18	116	0.02	0.13	115	0.04	0.33	111	0.01	0.09

SOURCE: AMOORE\BauschHealth\V01_126A_ISS\Stats\Outputs\Production\Tables\fscsaf (Jul 12, 2022 11:41)



	Baseline			Week 2			Week 4			Week 8			Week 12		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
IDP-126 Gel (N=242)	242	0.02	0.14	228	0.27	0.60	223	0.14	0.44	219	0.08	0.32	215	0.06	0.32
IDP-126 Vehicle Gel (N=121)	121	0.02	0.18	119	0.02	0.13	116	0.00	0.00	115	0.03	0.21	111	0.02	0.13

SOURCE: AMOORE\BauschHealth\V01_126A_ISS\Stats\Outputs\Production\Tables\fscsaf (Jul 12, 2022 11:41)

Source: Applicant submitted ISS Tables and Figures

The incidences of scaling, erythema, hyperpigmentation, itching, burning, and stinging were more common in the IDP-126 gel group than the vehicle group at maximum postbaseline. The severity of the signs and symptoms of irritation is summarized in the following Table 45.

Table 45. Facial Cutaneous Tolerability Assessment at Week 12 in Subjects With Acne Vulgaris Treated With IDP-126 Gel in the Phase 3 Trials, 301 and 302

(b) (4)

Source: Sponsor provided table from draft PI (Reviewer confirmed based on ISS ADTOL dataset)
* (b) (4)

Local tolerability scores for erythema, scaling, itching, burning, and stinging increased during the first two weeks of treatment and decreased thereafter.

A modified version of Table 45 which will include the maximum postbaseline assessments presented by the Applicant in the ISS will be reflected in labeling.

The results of the active assessments of local safety indicate that patients may experience irritation and pigmentary changes during treatment with IDP-126 gel which may infrequently be severe. Therefore, language regarding the potential for irritation is included in Section 5 Warnings and Precautions. The results of the active assessments of local safety provide data regarding the course and severity of these irritant reactions.

Photosensitivity

The Applicant requested a waiver for the conduct of clinical phototoxicity and photoallergy studies to evaluate IDP-126 gel. In support of the phototoxicity/photoallergenicity waiver, the Applicant investigated the absorbance of the active ingredients, clindamycin phosphate, benzoyl peroxide, and adapalene, as well as of the IDP-126 gel drug product (refer to NDA 216632 SDN 9 Section 1.12.5 Request for Waiver submitted on June 16, 2023). The data show that among the active ingredients, only adapalene absorbed in the (b) (4) nm range, exhibiting maximum absorbance at (b) (4) nm.

The Applicant also submitted UVB/UVA/Vis spectra ((b) (4) nm) for IDP-126 gel, DIFFERIN (adapalene 0.1%) Gel, and EPIDUO FORTE (adapalene 0.3%/benzoyl peroxide 2.5%) Gel which were similar. IDP-126 gel.

The Applicant submitted a right of reference to NDA 207917 EPIDUO FORTE Gel and the evaluation of phototoxicity and photoallergenicity for EPIDUO FORTE Gel was waived (refer to NDA 207917 EPIDUO FORTE Gel Medical Review dated November 05, 2014 and IND 67801 Pre-

NDA meeting minutes dated June 25, 2014). The Applicant proposes to include the following patient information in the IDP-126 gel package insert [redacted]

- [redacted]

Based on the overlapping UV spectrum with Epiduo Forte Gel (the adapalene component) and acceptable labeling pertaining to UV light precautions, the Agency grants the proposed waiver of clinical photo-studies for IDP-126 gel.

Hypersensitivity Reactions

No cases of anaphylaxis were reported in subjects exposed to IDP-126 gel in the development program. However, there was one reported TEAE of urticaria and one reported TEAE of face swelling. Case narratives are presented below.

Subject [redacted] was a 21-year-old, white, not Hispanic or Latino, female with a primary diagnosis of acne since [redacted] who started topical treatment with IDP-126 gel once daily on [redacted]. The subject had a history of pneumonia and shingles in [redacted]. The subject's prior medication included topical salicylic acid. At the time of entry into the study, the subject had no ongoing medical conditions other than acne and was not taking any concomitant medications. The subject experienced a non-serious TEAE of mild urticaria on [redacted]. The event of urticaria, that did not occur in the treatment area, was not considered by the investigator to be related to study drug. The subject administered cetirizine to treat the event. Study drug application was not interrupted due to occurrence of the event. The outcome of the event was reported as recovering. The subject applied the last dose of topical treatment with IDP-126 gel on [redacted]. The subject's Week 12 study visit was conducted on [redacted]

Given that the subject continued the study drug without any subsequent reported AEs of urticaria, the AE of urticaria is less likely attributable to the study drug.

Subject [redacted] was a 19-year-old, white, not Hispanic or Latino, male with a primary diagnosis of acne since [redacted] who started topical treatment with IDP-126 gel once daily on [redacted]. At the time of entry into the study, in addition to acne, the subject had ongoing medical conditions that included Tourette's syndrome, depression, Type 1 diabetes mellitus, seasonal allergy, and vitamin D deficiency. The subject was taking concomitant medications that

consisted of vitamin D, iron, Levemir (insulin detemir), Novolog (insulin aspart), and bupropion. The subject experienced non-serious TEAE of moderate swelling face (right side around the eye) on (b) (6). As a result of the event, study drug was withdrawn (last application (b) (6) and the subject discontinued the study on (b) (6) The event was reported as having resolved on (b) (6). The investigator considered the event to be study drug related.

The study drug was discontinued due to the AE of moderate swelling face. This subject also had reported AEs of erythema, application site pain, and application site exfoliation on the same day as the reported AE of swelling face, making the AE of swelling face more likely attributable to a local site reaction and less likely due to a systemic hypersensitivity reaction.

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

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Upon review of multiple analyses to evaluate the safety profile of IDP-126 gel in different populations, there were no substantial differences in the risk of adverse events or reactions in demographic subgroups. However, because the trials were not powered for these analyses, the data must be interpreted with caution.

Table 46. Treatment Emergent Adverse Reactions by Sex, Pooled Trials 301 and 302 (Safety Population)

	Female		Male		Total	
	IDP-126 gel (N=144)	IDP-126 Vehicle Gel (N=68)	IDP-126 gel (N=98)	IDP-126 Vehicle Gel (N=53)	IDP-126 gel (N=242)	IDP-126 Vehicle Gel (N=121)
Preferred Term						
Application site burn	1 (0.7)	0	0	0	1 (0.4)	0
Application site dermatitis	2 (1.4)	0	1 (1.0)	0	3 (1.2)	0
Application site dryness	3 (2.1)	0	4 (4.1)	0	7 (2.9)	0
Application site erythema	2 (1.4)	0	1 (1.0)	0	3 (1.2)	0
Application site exfoliation	3 (2.1)	0	1 (1.0)	0	4 (1.7)	0
Application site irritation	4 (2.8)	0	1 (1.0)	0	5 (2.1)	0
Application site pain	17 (11.8)	1 (1.5)	16 (16.3)	0	33 (13.6)	1 (0.8)
Application site paraesthesia	1 (0.7)	0	0	0	1 (0.4)	0
Application site pruritus	2 (1.4)	0	0	0	2 (0.8)	0
Dermatitis contact	2 (1.4)	0	0	0	2 (0.8)	0
Dry skin	0	0	1 (1.0)	0	1 (0.4)	0
Erythema	3 (2.1)	0	5 (5.1)	0	8 (3.3)	0
Folliculitis	0	1 (1.5)	0	0	0	1 (0.8)
Paraesthesia	1 (0.7)	0	1 (1.0)	0	2 (0.8)	0
Sunburn	1 (0.7)	0	0	0	1 (0.4)	0
Swelling face	0	0	1 (1.0)	0	1 (0.4)	0
Urticaria	1 (0.7)	0	0	0	1 (0.4)	0
Xerosis	3 (2.1)	1 (1.5)	0	0	3 (1.2)	1 (0.8)
Subjects	39 (27.1)	8 (11.8)	27 (27.6)	5 (9.4)	66 (27.3)	13 (10.7)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Preferred Term - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEDECOD = 'Erythema' or 'Application site burn' or 'Application site pain' or 'Application site exfoliation' or 'Application site irritation' or 'Application site pruritus' or 'Dermatitis contact' or 'Folliculitis' or 'Application site dermatitis' or 'Application site dryness' or 'Swelling face' or 'Sunburn' or 'Dry skin' or 'Paraesthesia' or 'Xerosis' or 'Application site paraesthesia' or 'Urticaria' or 'Application site erythema'.
Subjects - Dataset: Adverse Events; Filter: None.

Table 47. Treatment Emergent Adverse Reactions by Age, Pooled Trials 301 and 302 (Safety Population)

	Age < 12		Age 12 to <18		Age >= 18		Total	
	IDP-126 gel (N=3)	IDP-126 Vehicle Gel (N=2)	IDP-126 gel (N=123)	IDP-126 Vehicle Gel (N=50)	IDP-126 gel (N=116)	IDP-126 Vehicle Gel (N=69)	IDP-126 gel (N=242)	IDP-126 Vehicle Gel (N=121)
Preferred Term								
Application site burn	0	0	0	0	1 (0.9)	0	1 (0.4)	0
Application site dermatitis	0	0	1 (0.8)	0	2 (1.7)	0	3 (1.2)	0
Application site dryness	1 (33.3)	0	2 (1.6)	0	4 (3.4)	0	7 (2.9)	0
Application site erythema	0	0	1 (0.8)	0	2 (1.7)	0	3 (1.2)	0
Application site exfoliation	0	0	2 (1.6)	0	2 (1.7)	0	4 (1.7)	0
Application site irritation	0	0	1 (0.8)	0	4 (3.4)	0	5 (2.1)	0
Application site pain	1 (33.3)	0	17 (13.8)	0	15 (12.9)	1 (1.4)	33 (13.6)	1 (0.8)
Application site paraesthesia	0	0	0	0	1 (0.9)	0	1 (0.4)	0
Application site pruritus	0	0	0	0	2 (1.7)	0	2 (0.8)	0
Dermatitis contact	0	0	0	0	2 (1.7)	0	2 (0.8)	0
Dry skin	0	0	1 (0.8)	0	0	0	1 (0.4)	0
Erythema	1 (33.3)	0	4 (3.3)	0	3 (2.6)	0	8 (3.3)	0
Folliculitis	0	0	0	0	0	1 (1.4)	0	1 (0.8)
Paraesthesia	0	0	1 (0.8)	0	1 (0.9)	0	2 (0.8)	0
Sunburn	0	0	1 (0.8)	0	0	0	1 (0.4)	0
Swelling face	0	0	0	0	1 (0.9)	0	1 (0.4)	0
Urticaria	0	0	0	0	1 (0.9)	0	1 (0.4)	0
Xerosis	0	0	0	0	3 (2.6)	1 (1.4)	3 (1.2)	1 (0.8)
Subjects	1 (33.3)	0	31 (25.2)	3 (6.0)	34 (29.3)	10 (14.5)	66 (27.3)	13 (10.7)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Preferred Term - Dataset: Adverse Events; Filter: SAFFL = 'Y', AEDECOD = 'Erythema' or 'Application site burn' or 'Application site pain' or 'Application site exfoliation' or 'Application site irritation' or 'Application site pruritus' or 'Dermatitis contact' or 'Application site dermatitis' or 'Dry skin' or 'Swelling face' or 'Sunburn' or 'Application site dryness' or 'Paraesthesia' or 'Xerosis' or 'Application site paraesthesia' or 'Urticaria' or 'Folliculitis' or 'Application site erythema'.
Subjects - Dataset: Adverse Events; Filter: None.

Table 48. Treatment Emergent Adverse Reactions by Race, Pooled Trials 301 and 302 (Safety Population)

	ASIAN		BLACK OR AFRICAN AMERICAN		NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER		OTHER		WHITE		Total	
	IDP-126 gel (N=21)	IDP-126 Vehicle Gel (N=5)	IDP-126 gel (N=40)	IDP-126 Vehicle Gel (N=14)	IDP-126 gel (N=1)	IDP-126 Vehicle Gel (N=1)	IDP-126 gel (N=11)	IDP-126 Vehicle Gel (N=3)	IDP-126 gel (N=169)	IDP-126 Vehicle Gel (N=98)	IDP-126 gel (N=242)	IDP-126 Vehicle Gel (N=121)
Preferred Term												
Application site burn	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0
Application site dermatitis	1 (4.8)	0	0	0	0	0	0	0	2 (1.2)	0	3 (1.2)	0
Application site dryness	1 (4.8)	0	1 (2.5)	0	0	0	0	0	5 (3.0)	0	7 (2.9)	0
Application site erythema	0	0	1 (2.5)	0	0	0	0	0	2 (1.2)	0	3 (1.2)	0
Application site exfoliation	0	0	1 (2.5)	0	0	0	0	0	3 (1.8)	0	4 (1.7)	0
Application site irritation	0	0	0	0	0	0	0	0	5 (3.0)	0	5 (2.1)	0
Application site pain	3 (14.3)	0	5 (12.5)	0	0	0	0	0	25 (14.8)	1 (1.0)	33 (13.6)	1 (0.8)
Application site paraesthesia	0	0	1 (2.5)	0	0	0	0	0	0	0	1 (0.4)	0
Application site pruritus	0	0	2 (5.0)	0	0	0	0	0	0	0	2 (0.8)	0
Dermatitis contact	1 (4.8)	0	0	0	0	0	0	0	1 (0.6)	0	2 (0.8)	0
Dry skin	0	0	0	0	0	0	1 (9.1)	0	0	0	1 (0.4)	0
Erythema	0	0	0	0	0	0	0	0	8 (4.7)	0	8 (3.3)	0
Folliculitis	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (0.8)
Paraesthesia	0	0	0	0	0	0	0	0	2 (1.2)	0	2 (0.8)	0
Sunburn	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0

	ASIAN		BLACK OR AFRICAN AMERICAN		NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER		OTHER		WHITE		Total	
	IDP-126 gel (N=21)	IDP-126 Vehicle Gel (N=5)	IDP-126 gel (N=40)	IDP-126 Vehicle Gel (N=14)	IDP-126 gel (N=1)	IDP-126 Vehicle Gel (N=1)	IDP-126 gel (N=11)	IDP-126 Vehicle Gel (N=3)	IDP-126 gel (N=169)	IDP-126 Vehicle Gel (N=98)	IDP-126 gel (N=242)	IDP-126 Vehicle Gel (N=121)
Swelling face	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0
Urticaria	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0
Xerosis	0	0	1 (2.5)	0	0	0	0	0	2 (1.2)	1 (1.0)	3 (1.2)	1 (0.8)
Subjects	5 (23.8)	2 (40.0)	9 (22.5)	1 (7.1)	0	1 (100.0)	1 (9.1)	0	51 (30.2)	9 (9.2)	66 (27.3)	13 (10.7)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Preferred Term - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEDECOD = 'Erythema' or 'Application site burn' or 'Application site pain' or 'Application site exfoliation' or 'Application site irritation' or 'Application site pruritus' or 'Dermatitis contact' or 'Folliculitis' or 'Application site dermatitis' or 'Application site dryness' or 'Swelling face' or 'Sunburn' or 'Dry skin' or 'Paraesthesia' or 'Xerosis' or 'Application site paraesthesia' or 'Urticaria' or 'Application site erythema'.
Subjects - Dataset: Adverse Events; Filter: None.

8.2.8. Specific Safety Studies/Clinical Trials

Clinical Dermal Safety Studies

The Applicant conducted two phase 1 dermal safety studies (V01-126A-101 and V01-126A-102) in healthy adult volunteers with IDP-126 gel to support the dermal safety of IDP-126 gel. The trials evaluated the potential for IDP-126 gel for irritation and sensitization. The results of the trials are presented below.

V01-126A-101 (Cumulative Irritant Patch Test)

This study was a 21-day, randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of the investigational products (IPs) (IDP-126 gel and vehicle gel), comparator product (EpiDuo Forte Gel), and positive (0.5% sodium lauryl sulfate (SLS) and negative (0.9% saline) controls under semi-occlusive conditions in healthy volunteer adult subjects. Forty-five (45) subjects were randomized, and 42 subjects completed the study.

All subjects had fields designated for IDP-126 gel, vehicle gel, comparator product, and the positive and negative control patches at 5 randomly assigned, adjacent sites, for the purpose of determining irritation potential. The IPs, comparator, and controls were applied to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation. A total of 21 consecutive applications of each product were made over a study period of 22 days.

Assessment of the patch sites was conducted by a trained evaluator once at Baseline (Day 1) and then 21 times post-baseline during the study. The following symbols and their respective numerical equivalent Grades were used to express the response observed at the time of examination (Table 49 and Table 50).

Table 49. 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 edema
5	3	Erythema, edema, and papules
6	3	Vesicular eruption
7	3	Strong reaction spreading beyond test site

*Scores were utilized only during the statistical analysis process of the study; Grades were conducted throughout the trial by the clinical staff.

Source: Applicant's submission, study report body for Study V01-126A-101, Table 3. Page 31

Table 50. Effects on Superficial Layers of the Skin

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

*Scores were utilized only during the statistical analysis process of the study; Grades were conducted throughout the trial by the clinical staff.

Source: Applicant's submission, study report body for Study V01-126A-101, Table 4. Page 31

Results

The IP, IDP-126 gel, yielded a mean (standard deviation, SD) irritation score of 1.29 (0.57), Vehicle (vehicle gel) yielded a mean (SD) irritation score of 0.32 (0.47), the Comparator (EpiDuo Forte Gel) yielded a mean (SD) irritation score of 1.96 (0.47), 0.9% Saline yielded a mean (S) irritation score of 0.30 (0.50), and the 0.5% SLS yielded a mean (SD) irritation score of 1.17 (0.74). The normalized total score for IDP-126 gel was 264 (moderately irritating). The normalized total score for vehicle gel was 66 (slightly irritating). The normalized total score for EpiDuo Forte Gel was 401 (moderately irritating). The normalized total score for 0.9% Saline was 63 (slightly irritating). The normalized total score for 0.5% SLS was 232 (moderately irritating).

There was 1 AE among 1 subject (2.2%) during this study. The AE was a TEAE (an injury (fracture of the right pelvis), serious and led to study drug withdrawal. This AE is not likely related to the study drug.

The Applicant's proposed label for IDP-126 gel is adequate to convey the risk of potential skin irritation.

V01-126A-102 (Repeat Insult Patch Test)

This study was a randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of the investigational products (IPs: IDP-126 gel and Vehicle gel), and a negative control, (under semi- occlusive conditions), in healthy volunteer adult subjects. All subjects had fields designated for IDP-126 gel, Vehicle gel, and the negative control at randomly assigned, adjacent sites, for the purpose of determining sensitization potential.

During the Induction Phase of the study, the IPs and control were applied to adjacent sites on the infrascapular area of the back. Evaluation of dermal reactions at the

application sites were assessed clinically using a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation.

Following Induction, subjects had a 10 to 14-day Rest Phase, after which they entered the Challenge Phase, which consisted of one 48 (± 5)-hour patch application to a naive site on the opposite side of the back. Observations at the naive site during Challenge and the patterns of reactivity during the Induction Phase provided a basis for an interpretation of contact sensitization.

If a cutaneous response observed in the Challenge Phase indicated possible sensitization, or at the discretion of the Investigator, a Rechallenge occurred. A narrative description of reactions in the Challenge and Rechallenge phases are reported together with the opinion of the Investigator as to whether such reactions are felt to be indicative of contact sensitization.

A total of 10 patch applications were made over a period of approximately 6-8 weeks. Subjects who participated in rechallenge had a total of 11 patch applications made over a period of approximately 10-12 weeks.

Assessment of the patch sites were done once at Baseline (Day 1), 9 times during the Induction Phase, 4 times during Challenge and, if applicable, 4 times during Rechallenge. The following symbols and their respective numerical equivalents (Table 51) were used to express the response observed at the time of examination (Table 52).

Table 51. Response Symbols and Numerical Equivalents

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 edema
5	3	Erythema, edema, and papules
6	3	Vesicular eruption
7	3	Strong reaction spreading beyond test site

*Scores are utilized only during the statistical analysis process of the study. Grades were conducted throughout the study by the trained evaluator.
Source: Applicant's submission, study report body for Study V01-126A-102, Table 3. Page 36

Table 52. Effects on Superficial Layers of the Skin

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

*Scores are utilized only during the statistical analysis process of the study. Grades will be conducted throughout the study by the trained evaluator.

Source: Applicant's submission, study report body for Study V01-126A-102, Table 4. Page 36

Results

Two hundred thirty-four (234) subjects were randomized to study product and 210 subjects completed the Induction Phase and received the Challenge Phase application, and 206 subjects completed the Challenge Phase. Of the 206 subjects who completed the Challenge Phase, 4 subjects received and completed the Re-challenge Phase application.

The IDP-126 gel yielded a mean (SD) cumulative irritation index of 0.37 (0.57), vehicle gel yielded a mean (SD) cumulative irritation index of 0.07 (0.32), and the 0.9% Saline yielded a mean (SD) cumulative irritation index of 0.05 (0.19). IDP-126 gel yielded a mean (SD) total cumulative irritation score of 3.21 (5.04), vehicle gel yielded a mean (SD) total cumulative irritation score of 0.65 (2.81), and 0.9% Saline yielded a mean (SD) total cumulative irritation score of 0.48 (1.70). All three products were classified as having no clinically significant irritation.

There were 206 subjects in the Sensitization Population. Four (4) subjects (2.0%) required a rechallenge in the study. Of the 4 subjects rechallenged, Subject No. (b) (6) had no significant reactions at challenge; therefore the PI considered the subject not sensitized. Subject No. (b) (6) had reactions that were identical in vehicle gel and IDP-126 gel, the reactions tapered to a low level by the end of rechallenge. Therefore, the PI concluded the subject was not sensitized to the test products. For Subject No. (b) (6) and Subject No. (b) (6), the challenge/rechallenge data, however, seemed to suggest evidence of sensitization (with Subject No. (b) (6) borderline and Subject No. (b) (6) more strongly suggestive of sensitization).

There were 4 AEs among 4 subjects (1.7%) during this study. There were 3 subjects discontinued from the study due to AEs: 2 due to Covid-19 and 1 due to a vaccination adverse reaction. There was one SAE, suspected Covid-19, and the subject died during hospitalization. These TEAEs were not likely to be related to the study drug.

Given the two subjects with evidence suggestive of sensitization, labeling regarding the potential risk of sensitization is recommended under Section 4 Contraindications Subsection 4.1 Hypersensitivity and Section 5 Warnings and Precautions Subsection 5.3 Skin Irritation, discussing the potential risk of allergic contact dermatitis (refer to Section 11.1 in this review).

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 IDP-126 gel, the trial designs did not include specific assessments to evaluate for carcinogenicity or screen for safety signals related to malignancy. In addition, the short duration of the phase 3 trials (12 weeks) precludes any determinations regarding the risk of human carcinogenicity or tumor development with IDP-126 gel. Nevertheless, no subjects enrolled in the phase 3 trials reported malignant neoplasms and each individual moiety of IDP-126 gel is well characterized without any known malignancy risk.

Information from the nonclinical carcinogenicity studies conducted to support the listed drug, EPIDUO FORTE gel (NDA 207917), and the Applicant's owned and right of reference drugs, ACANYA, ONEXTON (NDA 050819), and BENZACLIN (NDA 050756) gels are included in Section 13.1 of labeling. Refer to Section 5 of this review for a discussion of the nonclinical data.

Human Reproduction and Pregnancy

Pregnancies

There was 1 IDP-126 gel-exposed subject with a positive serum pregnancy test in trial 301. There was 1 IDP-126 Component C [clindamycin phosphate 1.2%/adapalene 0.15% gel]) - exposed and 1 IDP-126 Component A [BPO 3.1%/adapalene 0.15% gel]-exposed subject with a positive serum pregnancy test in trial 201. There was 1 IDP-126 gel-exposed subject and 2 Epiduo Forte Gel-exposed subjects with a positive serum pregnancy test in trial 202. As of the 120-safety update, there were 3 unknown pregnancy outcomes/lost to follow-up randomized to IDP-126 gel, Component A [BPO 3.1%/adapalene 0.15% gel], and Epiduo Forte Gel, respectively, 1 unknown pregnancy outcome/estimated date of delivery after the 120-day safety update in a subject randomized to Epiduo Forte Gel, 1 elective abortion at 6 weeks gestational age (no complications associated with the abortion procedure or during the immediate post procedure period reported) in a subject randomized to IDP-126 Component C (Clindamycin Phosphate 1.2%/Adapalene 0.15%), and 1 live birth (male) via Cesarean delivery with epidural (no labor/delivery complication, no abnormal placenta, no malformations/anomalies at birth, no neonatal illness, hospitalization, or drug therapies

reported) in a subject randomized to IDP-126 gel. See Pregnancy Narratives in the Appendices below.

There is insufficient data to assess the pregnancy risk with use of IDP-126 gel based on the pregnancies reported in the development program.

DPMH-Maternal Health was consulted. Refer to review by Dr. Kristie Baisden, DPMH, from August 18, 2023. Recommend the label for IDP-126 gel for NDA 216632 reflect the recommendations by Dr. Baisden, DPMH-Maternal Health (Refer to Section 11).

Pediatrics and Assessment of Effects on Growth

Effects on growth were not assessed in the development program for IDP-126 gel. Refer to Section 10 for discussion on pediatrics.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No information regarding overdose is available and no subject in any of the clinical studies conducted with IDP-126 gel experienced an overdose. There were no unexpected or untoward AEs reported in Study V01-126A-501, which evaluated IDP-126 gel under maximal use conditions.

Based on the pharmacodynamic properties of IDP-126 gel, no drug abuse is to be expected and a Controlled Substance Staff consultation was not obtained. There were no reports of abuse in any of the clinical studies conducted with IDP-126 gel

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

IDP-126 gel is not marketed in any country, and there are no postmarketing safety data available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of IDP-126 gel safety data identified no unexpected 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 IDP-126 gel in the postmarket setting. A Pediatric Research Equity Act (PREA) PMR will be recommended to evaluate the safety, PK, and treatment effect of IDP-126 gel in pediatric subjects ages 9 to 11 years 11 months with acne vulgaris (refer to Section Section 10, and Section 13 of this review).

8.2.11. Integrated Assessment of Safety

The safety profile for IDP-126 gel was adequately characterized during the drug development program. The primary safety database consisted of 363 subjects (242 subjects treated with IDP-126 gel and 121 subjects treated with vehicle gel) from the two phase 3 trials, Studies 301 and 302 (the pooled safety analysis set). All randomized subjects who were included in the safety analysis set were to have used the study drug at least once.

The safety profile for IDP-126 gel was similar to the safety profile for other topical clindamycin, adapalene, and benzoyl peroxide products. The data on IDP-126 gel support advising patients about the potential for skin irritation and effects of ultraviolet light and environmental exposure in Section 5 WARNINGS AND PRECAUTIONS of labeling. Active assessment of local tolerability indicated that the percentage of subjects who reported signs and symptoms (erythema, scaling, hyperpigmentation, itching, burning, and stinging) at maximum postbaseline was greater in the IDP-126 gel group than the Vehicle group. In addition, all the adverse which occurred in $\geq$1% of subjects treated with IDP-126 gel and greater than Vehicle related to the application site (pain, erythema, dryness/xerosis, irritation, exfoliation, and dermatitis).

Treatment with IDP-126 gel was not associated with an increased risk of mortality or serious adverse events.

The Applicant defined pregnancy as a serious adverse event. Subjects who became pregnant withdrew from treatment and, where feasible, were followed until delivery. There was 1 subject with a positive serum pregnancy test in the phase 3 trial with an unknown/lost to follow-up pregnancy outcome. Section 8 of labeling will convey the uncertainty regarding a drug-associated risk of major birth defect, miscarriage, or adverse maternal or fetal outcomes with exposure of the drug product in pregnancy.

The currently available safety data from the two 12-week phase 3 trials demonstrate that IDP-126 gel appears safe for the treatment of acne vulgaris in patients 12 years of age and older. The Applicant relied on long-term safety data from other topical clindamycin phosphate, adapalene, and benzoyl peroxide products, the listed drug, EPIDUO FORTE [adapalene 0.3%/BPO 2.5%] Gel (NDA 207917) and ACANYA Gel [clindamycin 1.2%/benzoyl peroxide 2.5%] (NDA 050819), ONEXTON Gel [clindamycin 1.2%/benzoyl peroxide 3.75%]) (NDA 050819) and BENZACLIN [clindamycin phosphate 1.2%/BPO 5%] Gel (NDA 050756), for which they submitted a right of reference or have ownership. Postmarketing risk management will include professional labeling and routine pharmacovigilance. As the moiety is well characterized, the review team recommends no other risk management tools (i.e., a risk evaluation and mitigation strategy). However, the review team recommends a postmarketing requirement to evaluate the drug product in pediatric patients aged 9 to 11 years and 11 months as additional

information is needed about systemic exposure and safety after exposure to IDP-126 gel applied to acne vulgaris in this age cohort (refer to Section 10 and Section 13).

8.3. Statistical Issues

There were no notable statistical issues with the review of the two Phase 3 trials included in this application to support evidence of efficacy.

One minor concern arose regarding the appropriate efficacy results to present in Section 14 of the label. These trials were planned with an eligibility criterion of age 9 and older. IDP-126 gel is a combination of three separate components, each of which is approved (at a range of concentrations) for treatment of moderate to severe acne vulgaris. However, the approved indications for some of these, limit the lower age to 12 years. IDP-126 gel contains adapalene at 0.15% concentration and this application relied on a bridging study to a product with adapalene at 0.3% concentration for safety. The comparator product in that bridging study is only approved for ages 12 and older.

A total of 5 subjects out of 363 total randomized in the two Phase 3 trials were in the 9-11 age range. Two were in Study 301 (both in IDP-126 gel arm) and three were in Study 302 (1 in IDP-126 gel arm; 2 in vehicle gel arm). There are too few to make any determination about safety and efficacy in this age group without relying on the bridging study. Results from reanalysis of each trial without those subjects provided almost identical results for all the coprimary efficacy endpoints.

For Section 14 of the label, my recommendation is that results of the two trials be described and presented for all randomized subjects, as planned in the protocols, and including the 5 subjects in the 9-11 age group. A sentence in the study description was added to note the difference in the minimum age for enrollment versus the anticipated indication (limit to 12 and older) and specifies the number of subjects under age 12 in each study. This is an appropriate way to address the issue.

From a statistical perspective, the two Phase 3 trials in this application and the phase 2 trial which supports the combination policy provide sufficient evidence of efficacy to support the indication of treatment of moderate to severe acne vulgaris.

8.4. Conclusions and Recommendations

To establish the effectiveness of IDP-126 gel, the Applicant submitted data from two randomized, multicenter, vehicle-controlled, phase 3 trials (Study 301 and Study 302). The trials enrolled subjects 10 years of age and older (inclusion criteria included subjects 9 years of age and older) with moderate (3) or severe (4) acne vulgaris on the EGSS. Enrolled subjects had 30 to 100 inflammatory lesions (papules, pustules, and nodules), 35 to 150 noninflammatory lesion (open and closed comedones) and two or fewer facial nodules. In both trials, subjects were

randomized in a 2:1 ratio to receive IDP-126 gel or Vehicle applied once daily for 12 weeks in a sufficient amount to cover the entire face, excluding the mouth, eyes, inside the nose, and lips. The three co-primary efficacy endpoints were the absolute change in inflammatory lesion count, absolute change in noninflammatory lesion count, and "treatment success" at Week 12. Treatment success was defined as at least a 2-grade improvement from Baseline in EGSS and an EGSS score of clear (0) or almost clear (1). Secondary efficacy endpoints included percent change in noninflammatory lesion counts and percent change in inflammatory lesion counts from baseline to Week 12. In both trials, IDP-126 gel was statistically superior to Vehicle (all p-values ≤ 0.005) for these co-primary efficacy endpoints and secondary efficacy endpoints at Week 12 (see Section 8.1.2).

The Applicant also conducted a phase 2 randomized, double-blind, dual-component and vehicle-control trial, V01-126A-201 (201), to provide evidence that each of the 3 separate components in the IDP-126 gel combination contributed to efficacy over that of the other two combined. The three coprimary endpoints were the same as in the phase 3 trials. IDP-126 gel demonstrated superiority for all three efficacy endpoints versus each of the dual-component arms as well as the vehicle gel arm (all p-values ≤ 0.026).

The Applicant conducted a comprehensive assessment of the safety of IDP-126 gel in the target population for the indication recommended for approval. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

Submitted safety and efficacy data support approval of this NDA for IDP-126 gel for the topical treatment of acne vulgaris in the population 12 years and older.

For pediatric patients aged 9 to 11 years and 11 months, additional information is needed about systemic exposure and safety after exposure to IDP-126 gel applied to acne vulgaris (refer to Section 10 and Section 13).

9 Advisory Committee Meeting and Other External Consultations

The application was not presented to an Advisory Committee or other external consult.

10 Pediatrics

The listed drug, Epiduo Forte gel, and the drugs for which Applicant has ownership and right of reference, Acanya gel, Onexton gel, and Benzaclin gel are approved for patients 12 years of age and older.

The Applicant (b) (4) In the pivotal phase 3 trials (301 and 302) 3/242 subjects (1.2%) in the IDP-126 gel cohort and 2/121 subjects (1.7%) in the vehicle gel cohort were ages 10 to <12 years (enrollment allowed down to 9 years of age). All 3 of the subjects randomized to IDP-126 gel achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to clear or almost clear (defined as treatment success). All 3 of the subjects randomized to IDP-126 gel also had reduction in both inflammatory and noninflammatory lesion counts from baseline to Week 12. One subject of the 3 randomized to IDP-126 gel reported AEs (application site pain, application site dryness, erythema). None of the 2 subjects randomized to vehicle gel achieved treatment success and their noninflammatory lesion counts increased from baseline to Week 12. Neither of the 2 subjects randomized to vehicle gel reported any AEs.

In one phase 2 trial (Study 201), 16/605 (2.6%) subjects (2/146 in the IDP-126 gel (Clindamycin Phosphate 1.2%/BPO 3.1%/Adapalene 0.15%), 2/150 in the IDP-126 Component A (BPO 3.1%/Adapalene 0.15%), 6/146 in the IDP-126 Component B (Clindamycin Phosphate 1.2%/BPO 3.1%), 4/150 in the IDP-126 Component C (Clindamycin Phosphate 1.2%/Adapalene 0.15%), and 2/148 in the IDP-126 vehicle gel) were ages 10 to <12 years (enrollment allowed down to 9 years of age). Both subjects randomized to IDP-126 gel achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to clear or almost clear (defined as treatment success). Both subjects randomized to IDP-126 gel also had reduction in both inflammatory and noninflammatory lesion counts from baseline to Week 12. Neither of the 2 subjects randomized to IDP-126 gel reported any AEs. None of the 2 subjects randomized to IDP-126 Component A (BPO 3.1%/Adapalene 0.15%) achieved treatment success. One of the 2 subjects randomized to IDP-126 Component A (BPO 3.1%/Adapalene 0.15%) reported an AE of mild sunburn. Four of the 6 subjects randomized to IDP-126 Component B (Clindamycin Phosphate 1.2%/BPO 3.1%) achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to clear or almost clear (defined as treatment success). These subjects also had reduction in both inflammatory and noninflammatory lesion counts from baseline to Week 12. There were no notable reported AEs in these 4 subjects. Of the 2 subjects randomized to IDP-126 Component B (Clindamycin Phosphate 1.2%/BPO 3.1%) who did not achieve treatment success, one reported a mild sunburn. One of the 4 subjects randomized to IDP-126 Component C (Clindamycin Phosphate 1.2%/Adapalene 0.15%) achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to clear or almost clear (defined as treatment success) and had reduction in both inflammatory and noninflammatory lesion counts from baseline to Week 12. This subject did not report any AEs. Of the 3 subjects randomized to IDP-126 Component C (Clindamycin Phosphate 1.2%/Adapalene 0.15%) who did not achieve treatment success, one reported an AE of gastroenteritis. Neither of the subjects randomized to vehicle gel achieved treatment success and did not report any AEs.

Clinically, efficacy can be extrapolated for the 9 to <12-year-old cohort from the 12 to <18-year-old population as preadolescent acne has similar pathogenesis (i.e., heralds the start of puberty amongst other similar pathogenic factors) and treatment principles as for adolescent acne, with the exception of hormonal therapies as these are not indicated for preadolescent acne. While preadolescent acne may present with more of a comedonal component, these patients can also present with inflammatory lesions and this new fixed triple combination product targets both comedonal and inflammatory acne.

However, a limited and insufficient number of subjects ages 10 to 11 years and 11 months (enrollment permitted down to age 9 years) were treated with IDP-126 gel in the phase 3 trials (5/363 (1.4%) subjects (3/242 (1.2%) in the IDP-126 gel cohort and 2/121 (1.7%) in the vehicle gel cohort) to inform safety. Additionally, in the phase 1b PK bridging, maximal use study, systemic exposure was assessed in only 8 subjects ages 9 years to 11 years and 11 months and higher systemic exposures were noted with IDP-126 gel in the 9 to 11 years and 11 months cohort compared to the 12 years and older cohort (refer to Section 6). Thus, for pediatric patients ages 9 to 11 years and 11 months, additional information is needed about systemic exposure and safety after exposure to IDP-126 gel applied to acne vulgaris. Refer to Section 13.

The Division of Pediatrics and Maternal Health-Pediatrics team was consulted to provide input to labeling, give recommendations on the age of the proposed indication, and assist with PMRs.

Pediatric Labeling

DPMH-Pediatrics recommends the following for Section 8.4 Pediatric Use:

The safety and effectiveness of CABTREO for the topical treatment of acne vulgaris have been established in pediatric patients 12 years of age and older. Use of CABTREO for this indication is supported by data from two randomized, double-blind, vehicle-controlled trials [see Clinical Studies (14)]. The safety and effectiveness of CABTREO have not been established in pediatric patients younger than 12 years of age.

PREA PMR

The Applicant submitted an Agreed iPSP in their marketing application that included (1) a planned waiver of assessment in pediatric patients < 9 years old because the number of patients in this age group is small enough to make necessary clinical studies impossible or highly impracticable (Section 505B(a)(4)(B)(i) of the Act) and (2) (b) (4) DPMH-Pediatrics recommends a deferred pediatric assessment for patients 9 to 11 years old with issuance of a PREA PMR.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed PI and carton/container labels for IDP-126 gel. The review team provided recommendations regarding the PI which are provided throughout this review. Labeling negotiations are ongoing at the time of this review.

The following table (Table 53) provides the location of the labeling discussion for each section.

Table 53. Location of the Labeling Discussion for Significant High Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 Indications and Usage	Sections 1.1, 1.2, 8.2.9, 10
5 Warnings and Precautions	8.2.5
6 Adverse Reactions	8.2
7 Drug Interactions	6
8 Use in Specific Populations	8, 10
12 Clinical Pharmacology	6
14 Clinical Studies	8
17 Patient Counseling Information	Reflects the data in other sections of labeling, Sections 4, 5, 6 and 14.

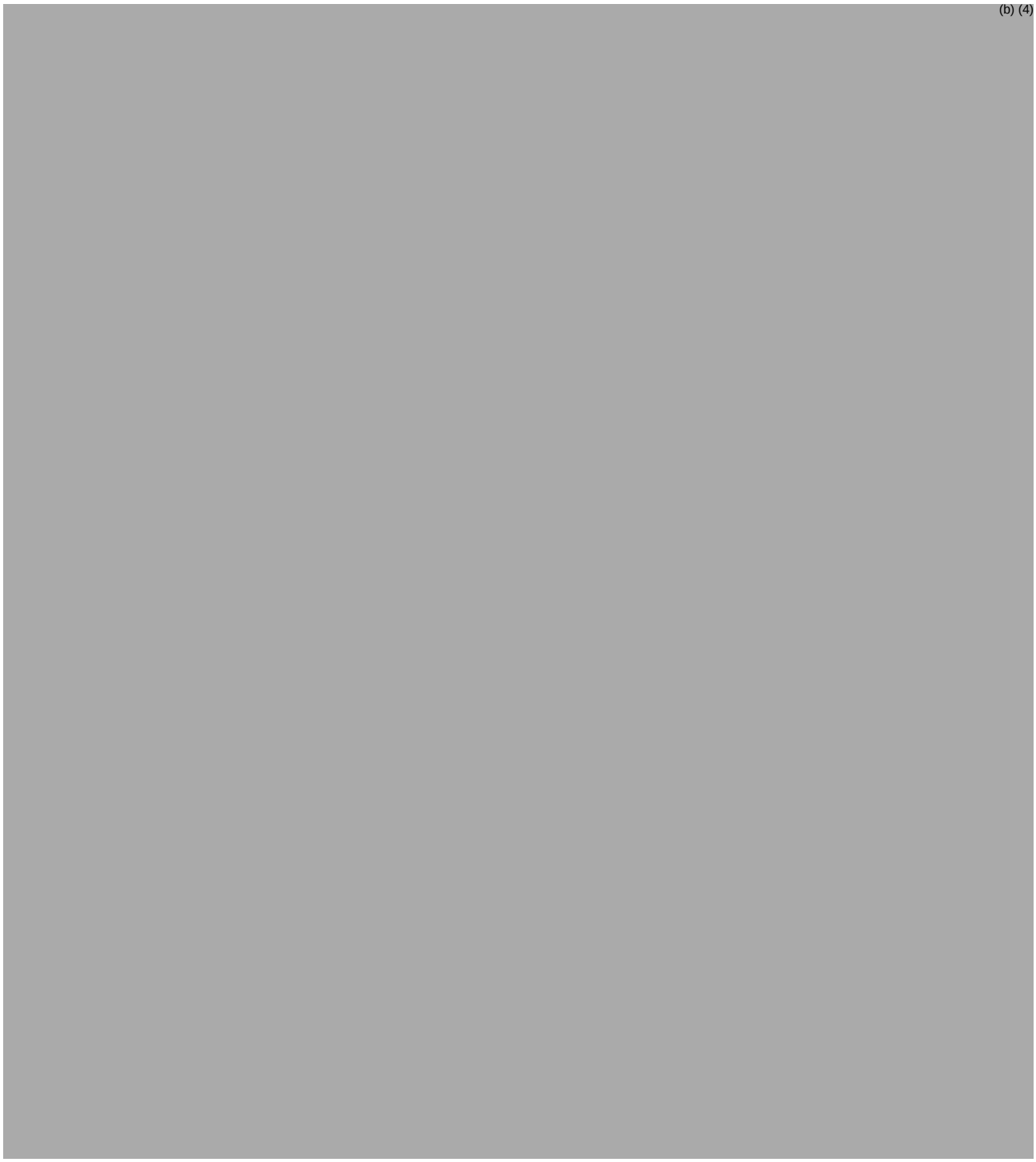
Source: Clinical reviewer's table

Dr. Corwin Howard from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI for IDP-126 gel and the carton and container labels and provided comments. DMEPA concluded that the proposed PI, Patient Packet Insert, Instructions for Use, container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective (refer to review by Dr. Corwin Howard, DMEPA, from May 22, 2023). The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, and carton/container. Refer to the OPDP review by Dr. Elvy Varghese, dated September 06, 2023. These comments are reflected in final labeling.

NDA 216632
Cabtreo (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel, 1.2%/0.15%/3.1%

DPMH, maternal health, was consulted for NDA 216632 (refer to review by Dr. Kristie Baisden, DPMH, from August 18, 2023). Labeling recommendations by Dr. Baisden includes the following:

(b) (4)



Version date: October 12, 2018

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

12 Risk Evaluation and Mitigation Strategies (REMS)

Risk mitigation measures beyond professional labeling and a Medication Guide are not warranted at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 11. As no additional risk management strategies are required, this section is not applicable for this review.

13 Postmarketing Requirements and Commitment

Refer to Section 10. Deferred pediatric studies in pediatric patients ages 9 to 11 years 11 months will be conducted as required by PREA. The product will be recommended to be approved for the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older.

A proposal for the PMR is as follows:

Conduct an open-label study to assess safety, pharmacokinetics, and treatment effect of CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel, 1.2%/0.15%/3.1% in 100 pediatric subjects ages 9 to 11 years 11 months with acne vulgaris.

14 Appendices

14.1. References

The references are included as footnotes.

14.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for IDP-126 gel. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trial 301and Trial V01-126A-302 which provided the primary data to establish effectiveness and safety of this product.

There were 2 investigators who reported significant payments of other sorts from the sponsor of the covered study [21 CFR 54.4(a) (3) (ii), 54.2(f)]. These disclosures were as follows:

- V01-126A-301:

(b) (6)

- V01-126A-302:

(b) (6)

The steps taken by the Applicant to prevent bias included monitoring to ensure protocol compliance and data integrity. Furthermore, the enrollment numbers at each of these sites were not disproportionate to the other sites (b) (6)

Covered Clinical Study (Name and/or Number): 301 and 302

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

14.3. Nonclinical Pharmacology/Toxicology

14.3.1. Calculations for Dose Margins

The following table summarizes the dose margins based on dose comparisons between the MRHD (2.5 g CABTREO gel per day) and human equivalent doses from nonclinical studies referenced in the label.

Table 54. Dose Margin Calculations for Labeling

Drug Substance	Study Type (Route)	Species	API Dose at NOAEL or LO(A)EL (mg/kg/day)	HED[a] (mg/kg/day)	API Dose Margin[b]
Clindamycin phosphate	Developmental toxicity (oral)	Mouse	600 (NOAEL)	48	96
		Rat	600 (NOAEL)	96	192
	Developmental toxicity (SC)	Mouse	200 (NOAEL)	16	32
		Rat	200 (NOAEL)	32	64
	Fertility (oral)	Rat	300 (NOAEL)	48	96
	Carcinogenicity (dermal)	Mouse	150 (NOAEL)[c]	12	24
	Carcinogenicity (oral)	Rat	30 (NOAEL)[d]	4.8	10
	Carcinogenicity (dermal)	Rat	20 (LOAEL)[e]	3.2	2
Adapalene	Developmental toxicity (oral)	Rat	5 (NOAEL)	0.8	13
		Rat	25 (LOAEL)	4	63
		Rabbit	25 (LOAEL)	8	127
	Developmental toxicity (dermal)	Rat	6 (LOEL)	0.96	15
		Rabbit	6 (LOEL)	1.92	30
	Carcinogenicity (dermal)	Mouse	4 (NOAEL)	0.32	5.1
		Rat	1.5 (LOAEL)	0.24	3.8
	Fertility (oral)	Rat	20 (NOAEL)	3.2	51

Drug Substance	Study Type (Route)	Species	API Dose at NOAEL or LO(A)EL (mg/kg/day)	HED[a] (mg/kg/day)	API Dose Margin[b]
Benzoyl peroxide	Carcinogenicity (dermal)	Mouse	750 (NOAEL)[c]	60	47
	Carcinogenicity (oral)	Rat	150 (NOAEL)[d]	24	19
	Carcinogenicity (dermal)	Rat	100 (LOAEL)[e]	16	32

Source: NDA submission
[a] dose multiplied by 0.08, 0.16, and 0.32 for mice, rats, and rabbits, respectively
[b] margin calculated by dividing the HED by the human dose for each API (i.e., 0.5, 0.06, and 1.29 mg/kg/day for clindamycin phosphate, adapalene, and benzoyl peroxide, respectively, assuming a 60 kg human and 2.5 g gel per day)
[c] 15000 mg/kg/day Acanya gel, containing 1% clindamycin phosphate and 5% benzoyl peroxide
[d] 3000 mg/kg/day Acanya gel, containing 1% clindamycin phosphate and 5% benzoyl peroxide
[e] 2000 mg/kg/day BenzaClin gel, containing 1% clindamycin phosphate and 5% benzoyl peroxide
Abbreviations: API, active pharmaceutical ingredient; NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect level; LOEL, lowest observed effect level; HED, human equivalent dose; SC, subcutaneous

14.3.2. Nonclinical Labeling

Recommended changes to nonclinical information in sections 8.1, 8.3, 12.1, and 13.1 of the Applicant's proposed labeling are provided below. The Applicant's proposed labeling is largely adapted from the labeling of the listed drugs. Notably, the Applicant calculated the dose margins assuming a 50 kg human body weight. Because the rationale for this decision is unclear and the listed drugs calculated dose margins using a 60 kg human body weight, the margins have been recalculated for consistency across labeling. Additionally, a 2-year dermal rat carcinogenicity study did not include a dose margin and the Applicant's proposed labeling was not clear that tumor incidence only increased at the high dose (2000 mg/kg/day); a dose margin has been added and clearer language suggested. Reviewer-recommended deletions and additions are indicated by ~~struck through~~ and underlined text, respectively.

The pharmacologic class for clindamycin phosphate and adapalene are lincosamide antibacterial and retinoid, respectively, and are provided in the Highlights of Prescribing Information, Indications and Usage section of the label.

(b) (4)

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Summary of Bioanalytical Method Validation and Performance

The PK samples collected from Study V01-126A-501 were analyzed using validated LC-MS/MS methods to quantify plasma concentrations of clindamycin and adapalene. The validation results for the methods used for quantitation of clindamycin and adapalene are summarized in Table 55 and Table 56, respectively. The bioanalysis performance results for quantitation of clindamycin and adapalene are summarized in Table 57 and Table 58, respectively.

The bioanalytical methods were adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance. Incurred sample reanalysis for plasma samples were acceptable in terms of both sample size (at least 10% of the first 1000

samples and 5% of the remaining samples) and the results (>67% of the study samples evaluated within ±20% of the original sample concentrations). All samples were analyzed within the established long-term stability window.

Table 55. Summary of Bioanalytical Method Validation Results for Clindamycin

Validation Report	VVALN1701P1
Matrix	Plasma
Anticoagulant	Dipotassium Ethylene Diamine Tetra Acetic Acid (K_2EDTA)
Analyte	Clindamycin
Internal standard (ISTD)	Clindamycin-^{13}C-d_4
Linearity (calibration curve range)	0.0500 - 15.0 ng/mL
Precision (% CV)	
Intra-assay	2.6 to 5.5% (LLOQ); 1.1 to 3.2% (above LLOQ)
Inter-assay	4.0% (LLOQ); 1.6 to 3.2% (above LLOQ)
Accuracy (% Nominal)	
Intra-assay	3.1 to 7.4% (LLOQ); 2.3 to 7.0% (above LLOQ)
Inter-assay	5.4% (LLOQ); 3.2 to 6.1% (above LLOQ)
Dilution (2x, 5x)	
Precision	6.3%, 4.5%
Accuracy	5.8%, -4.3%
Stability: Clindamycin	
Freeze/Thaw (-20 °C/RT)	Stable 5 cycles
Freeze/Thaw (-70 °C /RT)	Stable 5 cycles
Benchtop	Stable 16 hours
Long-term (-20 °C)	Stable 202 days
Long-term (-70 °C)	Stable 202 days
Stability: Clindamycin in the presence of 10 ng/mL adapalene and 300 ng/mL benzoic acid	
Freeze/Thaw (-20 °C/RT)	Stable 5 cycles
Freeze/Thaw (-70 °C /RT)	Stable 5 cycles
Benchtop	Stable 16 hours
Long-term (-20 °C)	Stable 202 days
Long-term (-70 °C)	Stable 418 days
Reproducibility (% Bias)	
Individual sample	1.8 to 2.8%
Whole batch	2.2 to 14.6%
Extraction Recovery	
Clindamycin	92.2%
Clindamycin-^{13}C-d_4	94.4%

Source: Applicant's Report VVALN1701P1

Table 56. Summary of Bioanalytical Method Validation Results for Adapalene

Validation Report	VVALN1701P2
Matrix	Plasma
Anticoagulant	Dipotassium Ethylene Diamine Tetra Acetic Acid (K_2EDTA)
Analyte	Adapalene
Internal standard (ISTD)	Adapalene-d_4
Linearity (calibration curve range)	0.100 - 10.0 ng/mL
Precision (% CV)	
Intra-assay	6.4 to 7.3% (LLOQ); 1.5 to 5.6% (above LLOQ)
Inter-assay	7.8% (LLOQ); 2.3 to 4.0% (above LLOQ)
Accuracy (% Nominal)	
Intra-assay	-3.6 to 7.2% (LLOQ); -1.7 to 4.0% (above LLOQ)
Inter-assay	2.2% (LLOQ); -0.3 to 3.7% (above LLOQ)
Dilution (2x, 5x)	
Precision	4.1%, 3.9%
Accuracy	3.5%, -3.6%
Stability	
Freeze/Thaw (-20 °C/RT)	Stable 4 cycles
Freeze/Thaw (-70 °C /RT)	Stable 4 cycles
Benchtop	Stable 20.5 hours
Long-term (-20 °C)	Stable 189 days
Long-term (-70 °C)	Stable 380 days
Reproducibility (% Bias)	
Individual sample	-1.8 to 4.7%
Whole batch	1.3 to 3.6%
Extraction Recovery	
Adapalene	86.4%
Adapalene-d_4	120.8%

Table 57. Summary of Bioanalysis Performance for Clindamycin

Relevant Clinical Trial	V01-126A-501
Bioanalysis Report	BVALN1802P1
Matrix	Human plasma
Anticoagulant	Dipotassium Ethylene Diamine Tetra Acetic Acid (K_2EDTA)
Analytes	Clindamycin
Internal standard	Clindamycin-^{13}C-d_4
Linearity (calibration curve range)	0.0500 - 15.0 ng/mL
Precision (% CV)	3.0 to 6.2
Accuracy (% Nominal)	0.0 to 4.7

Incurred Sample Reanalysis	
Total no. of incurred sample reanalysis	132 (10.8% of samples)
Total no. of sample whose % differences are within 20%	132
% of total no. of samples whose % differences are within 20 %	100
Duration from time sample was first drawn to date of last sample analysis including ISR	317 days (within the established stability window of 418 days)
Actual sample storage temperature	-70 °C

Table 58. Summary of Bioanalysis Performance for Adapalene

Relevant Clinical Trial	V01-126A-501
Bioanalysis Report	BVALN1802P2
Matrix	Human plasma
Anticoagulant	Dipotassium Ethylene Diamine Tetra Acetic Acid (K_2EDTA)
Analytes	Adapalene
Internal standard	Adapalene-d_4
Linearity (calibration curve range)	0.100 - 10.0 ng/mL
Precision (% CV)	3.6 to 12.4
Accuracy (% Nominal)	-4.6 to 1.0
Incurred Sample Reanalysis	
Total no. of incurred sample reanalysis	125 (10.2% of samples)
Total no. of sample whose % differences are within 20%	122
% of total no. of samples whose % differences are within 20 %	97.6
Duration from time sample was first drawn to date of last sample analysis including ISR	316 days (within the established stability window of 380 days)
Actual sample storage temperature	-70 °C

14.5. Clinical Supporting Data

Table 59. TEAEs Reported, Trial 202

		Description of Actual Arm								
		IDP-126 gel		Epiduo Forte Gel		IDP-126 vehicle gel (stored at CRT)		IDP-126 vehicle gel (stored at 2-8°C)		
		(N = 230)		(N = 226)		(N = 115)		(N = 113)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Total
General disorders and administration site conditions	Application site pain	23	10.0%	16	7.1%	.	.	.	.	39
	Application site dryness	9	3.9%	11	4.9%	1	0.9%	1	0.9%	22
	Application site dermatitis	3	1.3%	8	3.5%	.	.	.	.	11
	Application site irritation	3	1.3%	6	2.7%	1	0.9%	1	0.9%	11
	Application site erythema	4	1.7%	4	1.8%	.	.	1	0.9%	9
	Application site exfoliation	4	1.7%	4	1.8%	.	.	.	.	8
	Application site pruritus	3	1.3%	2	0.9%	.	.	.	.	5
	Application site swelling	3	1.3%	2	0.9%	.	.	.	.	5
	Application site rash	4	1.7%	.	.	.	.	.	.	4
	Pyrexia	.	.	.	.	1	0.9%	2	1.8%	3
	Influenza like illness	.	.	1	0.4%	.	.	1	0.9%	2
	Application site oedema	1	0.4%	.	.	.	.	.	.	1
	Application site photosensitivity reaction	1	0.4%	.	.	.	.	.	.	1
	Application site urticaria	.	.	1	0.4%	.	.	.	.	1
	Chest pain	.	.	1	0.4%	.	.	.	.	1
	Chills	.	.	.	.	1	0.9%	.	.	1
	Fatigue	1	0.4%	.	.	.	.	.	.	1
	Malaise	.	.	1	0.4%	.	.	.	.	1

		Description of Actual Arm								
		IDP-126 gel		Epiduo Forte Gel		IDP-126 vehicle gel (stored at CRT)		IDP-126 vehicle gel (stored at 2-8°C)		
		(N = 230)		(N = 226)		(N = 115)		(N = 113)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Total
	Pain	.	.	.	.	.	.	1	0.9%	1
	Vessel puncture site bruise	1	0.4%	.	.	.	.	.	.	1
	Vessel puncture site hemorrhage	.	.	1	0.4%	.	.	.	.	1
Infections and infestations	COVID-19	8	3.5%	4	1.8%	5	4.3%	5	4.4%	22
	Nasopharyngitis	6	2.6%	3	1.3%	.	.	1	0.9%	10
	Upper respiratory tract infection	3	1.3%	2	0.9%	.	.	1	0.9%	6
	Bronchitis	1	0.4%	1	0.4%	1	0.9%	1	0.9%	4
	Urinary tract infection	1	0.4%	3	1.3%	.	.	.	.	4
	Sinusitis	1	0.4%	2	0.9%	.	.	.	.	3
	Otitis media	1	0.4%	.	.	1	0.9%	.	.	2
	Pharyngitis	1	0.4%	.	.	1	0.9%	.	.	2
	Bacterial vaginosis	.	.	.	.	.	.	1	0.9%	1
	Disseminated varicella zoster virus infection	.	.	1	0.4%	.	.	.	.	1
	Gastroenteritis	.	.	.	.	.	.	1	0.9%	1
	Gingivitis	.	.	.	.	.	.	1	0.9%	1
	Herpes zoster	.	.	1	0.4%	.	.	.	.	1
	Hordeolum	.	.	1	0.4%	.	.	.	.	1
	Impetigo	.	.	.	.	.	.	1	0.9%	1
	Influenza	1	0.4%	.	.	.	.	.	.	1
	Periorbital cellulitis	.	.	.	.	1	0.9%	.	.	1
	Pharyngitis streptococcal	1	0.4%	.	.	.	.	.	.	1

		Description of Actual Arm								
		IDP-126 gel		Epiduo Forte Gel		IDP-126 vehicle gel (stored at CRT)		IDP-126 vehicle gel (stored at 2-8°C)		
		(N = 230)		(N = 226)		(N = 115)		(N = 113)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Total
	Pneumonia mycoplasma	1	0.4%	.	.	.	.	.	.	1
	Skin papilloma	1	0.4%	.	.	.	.	.	.	1
	Tinea infection	.	.	.	.	.	.	1	0.9%	1
	Tooth abscess	.	.	1	0.4%	.	.	.	.	1
	Tooth infection	.	.	1	0.4%	.	.	.	.	1
	Vaginal infection	.	.	1	0.4%	.	.	.	.	1
	Vulvovaginal candidiasis	.	.	1	0.4%	.	.	.	.	1
	Vulvovaginal mycotic infection	.	.	1	0.4%	.	.	.	.	1
Skin and subcutaneous tissue disorders	Rash	3	1.3%	4	1.8%	1	0.9%	.	.	8
	Dermatitis contact	2	0.9%	3	1.3%	.	.	.	.	5
	Pruritus	1	0.4%	2	0.9%	.	.	.	.	3
	Seborrhea	1	0.4%	1	0.4%	.	.	.	.	2
	Urticaria	.	.	1	0.4%	1	0.9%	.	.	2
	Androgenetic alopecia	.	.	1	0.4%	.	.	.	.	1
	Dermal cyst	1	0.4%	.	.	.	.	.	.	1
	Dermatitis	1	0.4%	.	.	.	.	.	.	1
	Ecchymosis	1	0.4%	.	.	.	.	.	.	1
	Eczema	.	.	1	0.4%	.	.	.	.	1
	Skin reaction	1	0.4%	.	.	.	.	.	.	1
	Skin tightness	.	.	1	0.4%	.	.	.	.	1

		Description of Actual Arm								
		IDP-126 gel		Epiduo Forte Gel		IDP-126 vehicle gel (stored at CRT)		IDP-126 vehicle gel (stored at 2-8°C)		
		(N = 230)		(N = 226)		(N = 115)		(N = 113)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Total
Injury, poisoning and procedural complications	Sunburn	4	1.7%	3	1.3%	.	.	.	.	7
	Ligament sprain	2	0.9%	.	.	.	.	.	.	2
	Skin laceration	1	0.4%	.	.	.	.	1	0.9%	2
	Thermal burn	.	.	1	0.4%	1	0.9%	.	.	2
	Arthropod bite	.	.	1	0.4%	.	.	.	.	1
	Foot fracture	1	0.4%	.	.	.	.	.	.	1
	Limb injury	.	.	1	0.4%	.	.	.	.	1
	Road traffic accident	1	0.4%	.	.	.	.	.	.	1
	Soft tissue foreign body	.	.	.	.	.	.	1	0.9%	1
Gastrointestinal disorders	Nausea	.	.	.	.	2	1.7%	2	1.8%	4
	Diarrhea	1	0.4%	1	0.4%	.	.	.	.	2
	Abdominal pain	.	.	.	.	1	0.9%	.	.	1
	Abdominal pain upper	.	.	.	.	1	0.9%	.	.	1
	Aphthous ulcer	.	.	.	.	1	0.9%	.	.	1
	Cheilitis	.	.	.	.	1	0.9%	.	.	1
	Food poisoning	1	0.4%	.	.	.	.	.	.	1
	Gastritis	.	.	1	0.4%	.	.	.	.	1
	Vomiting	.	.	1	0.4%	.	.	.	.	1

		Description of Actual Arm								
		IDP-126 gel		Epiduo Forte Gel		IDP-126 vehicle gel (stored at CRT)		IDP-126 vehicle gel (stored at 2-8°C)		
		(N = 230)		(N = 226)		(N = 115)		(N = 113)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Total
Nervous system disorders	Headache	4	1.7%	1	0.4%	2	1.7%	2	1.8%	9
	Dizziness	.	.	.	.	.	.	1	0.9%	1
	Migraine	.	.	1	0.4%	.	.	.	.	1
	Presyncope	1	0.4%	.	.	.	.	.	.	1
	Syncope	.	.	.	.	.	.	1	0.9%	1
Respiratory, thoracic and mediastinal disorders	Cough	2	0.9%	1	0.4%	1	0.9%	1	0.9%	5
	Nasal congestion	1	0.4%	2	0.9%	.	.	.	.	3
	Oropharyngeal pain	.	.	1	0.4%	.	.	1	0.9%	2
	Epistaxis	.	.	1	0.4%	.	.	.	.	1
	Pharyngeal erythema	.	.	1	0.4%	.	.	.	.	1
	Rhinitis allergic	.	.	.	.	.	.	1	0.9%	1
Investigations	Blood creatine phosphokinase increased	2	0.9%	.	.	1	0.9%	.	.	3
	Blood glucose increased	1	0.4%	1	0.4%	.	.	.	.	2
	Alanine aminotransferase increased	1	0.4%	.	.	.	.	.	.	1
	Aspartate aminotransferase increased	1	0.4%	.	.	.	.	.	.	1
	Blood creatinine increased	.	.	.	.	.	.	1	0.9%	1
	Blood triglycerides increased	.	.	1	0.4%	.	.	.	.	1
	Gamma-glutamyl transferase increased	.	.	1	0.4%	.	.	.	.	1
	SARS-CoV-2 test positive	.	.	.	.	.	.	1	0.9%	1

		Description of Actual Arm								
		IDP-126 gel		Epiduo Forte Gel		IDP-126 vehicle gel (stored at CRT)		IDP-126 vehicle gel (stored at 2-8°C)		
		(N = 230)		(N = 226)		(N = 115)		(N = 113)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Total
Blood and lymphatic system disorders	Anemia	1	0.4%	.	.	1	0.9%	.	.	2
	Iron deficiency anemia	1	0.4%	.	.	.	.	.	.	1
	Lymphopenia	.	.	.	.	.	.	1	0.9%	1
	Neutropenia	.	.	.	.	.	.	1	0.9%	1
	Neutrophilia	1	0.4%	.	.	.	.	.	.	1
Eye disorders	Blepharitis	1	0.4%	1	0.4%	.	.	.	.	2
	Dry eye	1	0.4%	.	.	.	.	.	.	1
Musculoskeletal and connective tissue disorders	Arthralgia	1	0.4%	.	.	.	.	.	.	1
	Myalgia	.	.	.	.	.	.	1	0.9%	1
	Rotator cuff syndrome	1	0.4%	.	.	.	.	.	.	1
Ear and labyrinth disorders	Ear pain	.	.	.	.	.	.	1	0.9%	1
	Ear pruritus	1	0.4%	.	.	.	.	.	.	1
Psychiatric disorders	Anxiety	1	0.4%	1	0.4%	.	.	.	.	2
Reproductive system and breast disorders	Menometrorrhagia	1	0.4%	.	.	.	.	.	.	1
Vascular disorders	Hematoma	.	.	1	0.4%	.	.	.	.	1

Source: JMP Clinical derived table based on Applicant provided 202 ADAE

Pregnancy Narratives

Study V01-126A-301

Subject [redacted] (b) (6) was a 24-year-old, black or African American, not Hispanic or Latino, female with a primary diagnosis of acne since [redacted] (b) (6) who started topical treatment with IDP-126 gel once daily on [redacted] (b) (6). At the time of entry into the study, the subject had no ongoing medical conditions other than acne and was not taking any concomitant medications other than levonorgestrel ethinyl estradiol for birth control. The subject did not experience any TEAEs

during the study. At the last study visit (Week 12, (b) (6) [Day 85]), the subject had a negative urine pregnancy test result; nevertheless, a serum pregnancy test administered at the same visit was positive. Because the positive result occurred at the last study visit, the subject had already completed the 12-week study drug application period (having not reported any missing applications) and was considered to have completed the study. Following completion, the subject did not return for an expected repeat urine/serum pregnancy test that was scheduled for (b) (6). Additional information received from the investigator on (b) (6) indicated that the subject was contacted but declined any further testing and stated she was not pregnant and did not want to be contacted again. The subject is considered lost to follow-up and continued to be considered lost to follow up at the time of the 120-day safety update.

Study V01-126A-302

No subject had a positive pregnancy test result during the study.

Study V01-126A-201

Subject (b) (6) was a 23-year-old, black or African American (not Hispanic or Latino), female. The subject had a medical history of acne. The subject had concomitant medications (either ongoing from the start of the study or added during the study) that included CeraVe cleaner, CeraVe moisturizing lotion, and CeraVe sunscreen. On (b) (6), the subject started using IDP-126 Component C [clindamycin phosphate 1.2%/adapalene 0.15% gel]) for acne. The subject's last application of study drug was on (b) (6). The subject had no TEAEs during the study but had a positive pregnancy test after the Week 4 study visit. The subject was discontinued from the study on (b) (6) and had an elective pregnancy termination (coded as abortion induced) on (b) (6) The pregnancy termination was serious, moderate in intensity, and, in the opinion of the investigator, not related to study drug. Regarding the event itself, the subject informed the study center on (b) (6) that she had received an elective abortion on (b) (6). The subject's gestational age at the time of elective termination was 6 weeks. No complications associated with the abortion procedure or during the immediate post procedure period were reported. No follow up information available as of and per the 120-day safety update.

Subject (b) (6) was a 24-year-old, native Hawaiian or other Pacific islander (Hispanic or Latino), female. The subject had a medical history of drug hypersensitivity and acne. The subject had concomitant medications (either ongoing from the start of the study or added during the study) that included Mononessa, CeraVe cleaner, CeraVe moisturizer, and CeraVe sunscreen. During the study, the subject had no TEAEs. On (b) (6), the subject started using IDP-126 Component A [BPO 3.1%/adapalene 0.15% gel] for acne. The subject's last application of study drug was on (b) (6). The subject had her first positive pregnancy test at the Week 12 study visit, after completing the treatment period. Because the first positive pregnancy test did

not occur until Week 12, the subject was considered to have completed the study. At the time of study completion (b) (6) the subject was estimated to have been 12 weeks and 4 days pregnant, based on the date of the last menstrual period. The subject confirmed that she was not aware of the pregnancy prior to the positive test results at Week 12. On (b) (6), the subject underwent an ultrasound, which showed she was 12 weeks pregnant. The pregnancy outcome is unknown as it was reported that the subject was lost-to-follow-up and continued to be considered lost to follow up at the time of the 120-day safety update.

Subject (b) (6) was a 19-year-old, white (not Hispanic or Latino), female. The subject had a medical history of drug hypersensitivity, vitamin D deficiency, anxiety, attention deficit/hyperactivity disorder, depression, drug use disorder, and acne. The subject had no concomitant medications or TEAEs during the study. On (b) (6), the subject was randomized to the IDP-126 gel group for acne treatment. The subject had a positive pregnancy test at baseline, however, and was randomized in error. The study drug was not dispensed or applied at the study center (i.e., the subject never used the study drug). The subject discontinued the study due to pregnancy. No information regarding the outcome of the pregnancy is available. No follow up information is available per the 120-day safety update as the subject was never treated with any study drug.

Study V01-126A-202

IDP-126 Gel Group

Subject (b) (6) was a 20-year-old, White, not Hispanic or Latino, female with a primary diagnosis of acne since (b) (6) who started topical treatment with IDP-126 gel once daily on (b) (6) At the time of entry into the study, the subject had no ongoing medical conditions other than acne and was not taking any concomitant medications. The subject experienced nonserious, mild TEAEs of application site dryness on (b) (6) (Day 5) (b) (6) (Day 15), and (b) (6) (Day 19). Study drug application on the face was interrupted at the time of each occurrence of the event. These events were considered by the investigator to be study drug related and resolved. At the last study visit (Week 12, (b) (6) [Day 82]), the subject had a negative urine pregnancy test result; nevertheless, a serum pregnancy test administered at the same visit was positive. Because the positive result occurred at the last study visit, the subject had already completed the 12-week study drug application period and was considered to have completed the study. As of and per the 120-day safety update, this pregnancy resulted in a live birth (male) via Cesarean delivery with epidural (no labor/delivery complication, no abnormal placenta, no malformations/anomalies at birth, no neonatal illness, hospitalization, or drug therapies reported).

Epiduo Forte Gel Group

Subject (b) (6) was a 20-year-old, Asian, not Hispanic or Latino, female with a primary diagnosis of acne since (b) (6) who started topical treatment with Epiduo Forte Gel once daily on (b) (6). At the time of entry into the study, the subject had no ongoing medical conditions other than acne and was taking concomitant medications that consisted of Isibloom (desogestrel and ethinyl estradiol tablets) for birth control, vitamins, and chlorophyll. The subject did not experience any TEAEs during the study. At the last study visit (Week 12, (b) (6) [Day 93]), the subject had a negative urine pregnancy test result; nevertheless, a serum pregnancy test administered at the same visit was positive. Because the positive result occurred at the last study visit, the subject had already completed the 12-week study drug application period and was considered to have completed the study. As of and per the 120-day safety update, the pregnancy outcome is unknown as the estimated date of delivery is after the 120-day safety update.

Subject (b) (6) was a 34-year-old, White, Hispanic or Latino, female with a primary diagnosis of acne since (b) (6) who started topical treatment with Epiduo Forte Gel once daily on (b) (6) At the time of entry into the study, the subject had no ongoing medical conditions other than acne and was not taking any concomitant medications. The subject did not experience any TEAEs during the study. On (b) (6), the subject had positive urine and serum pregnancy test results. Study drug application was discontinued (last application on (b) (6) and the subject discontinued the study on (b) (6) (Day 30) due to the pregnancy. No additional information related to the subject's pregnancy was available at the time of the 120-day safety update.

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY S WOITACH
10/19/2023 05:11:45 PM
Signing for myself and on behalf of Mary Kim

JOHN P DOUGHERTY
10/19/2023 05:18:41 PM

BARBARA A HILL
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KAREN R FRATANTONI
10/20/2023 09:57:09 AM
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10/20/2023 10:03:03 AM

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