CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213433Orig1s000

MULTI-DISCIPLINE REVIEW

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

NDA Multidisciplinary Review and Evaluation

Application Type	NME- In "The Program"
Application Number(s)	NDA 213433
Priority or Standard	Standard
Submit Date(s)	August 19, 2019
Received Date(s)	August 27, 2019
PDUFA Goal Date	August 27, 2020
Division/Office	Shari Targum, Deputy Director, Division of Dermatology and Dentistry Julie Beitz, Director Office of Immunology and Inflammation
Review Completion Date	
Established/Proper Name	Clascoterone cream, 1%
(Proposed) Trade Name	WINLEVI
Pharmacologic Class	NME
Code Name	N/A
Applicant	Cassiopea SpA
Dosage Form	Topical cream
Applicant proposed Dosing Regimen	Apply a thin layer (approximately 1 gram) to affected area twice daily (morning and evening)
Applicant Proposed Indication(s)/Population(s)	For the treatment of acne vulgaris in patients 9 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	
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 SNOMED CT Indication Disease Term for Each Indication (if applicable)	
Recommended Dosing Regimen	Apply a thin layer (approximately 1 gram) to affected area twice daily (morning and evening).

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
DHOT = Division of Hematology Oncology Toxicology
OCP = Office of Combination Products
OB = Office of Biostatistics
OHOP = Office of Hematology and Oncology Products

Signatures

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

Glossary

ACTH	adrenocorticotropic hormone
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
BID	twice daily
BLA	biologics license application
BLQ	below the lower limit of quantitation
BSA	body surface area
CFR	Code of Federal Regulations
CRF	case report form
CSR	clinical study report
CST	cosyntropin stimulation test
CYP	cytochrome P450
DALY	disability-adjusted life year
DBP	diastolic blood pressure
DHT	dihydrotestosterone
ECG	electrocardiogram
EOS	end-of-study
FDA	Food and Drug Administration
GD	gestational day
GLP	good laboratory practice
HD	high dose
HPA	hypothalamic-pituitary-adrenal
IGA	Investigator Global Assessment
IND	investigational new drug
ISS	integrated summary of safety
ITT	intent-to-treat
LD	low dose
LLOQ	lower limit of quantitation
LSR	local skin reaction
LTF	long-term follow-up
MD	mid dose
MRHD	maximum recommended human dose
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
OCP	Office of Clinical Pharmacology
OSI	Office of Scientific Investigation
OPDP	Office of Prescription Drug Promotion
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetics

PP	per-protocol
PPI	patient package insert
PT	preferred term
QD	once daily
SAE	serious adverse event
SBP	systolic blood pressure
SOC	system organ class
TEAE	treatment-emergent adverse event
TQT	thorough QT
UPT	urine pregnancy test
WOCBP	women of childbearing potential

1. Executive Summary

1.1. Product Introduction

The Applicant, Cassiopea SpA, is seeking approval for WINLEVI (clascoterone) cream, 1%, for the topical treatment of acne vulgaris in patients 9 years of age and older, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

The active ingredient is clascoterone, a new molecular entity (NME). Clascoterone is a novel androgen receptor inhibitor, with a chemical structure similar to dihydrotestosterone (DHT) and competes for binding to androgen receptors in the skin. Once absorbed in the skin, clascoterone is hydrolyzed to cortexolone. Currently, there are no topical androgen receptor inhibitor drug products marketed in the United States. The proposed indication is the treatment of acne vulgaris in patients 9 years of age and older. The recommended dosing regimen is an application to the affected areas twice daily (BID).

The Agency concluded that the proposed proprietary name, WINLEVI, was acceptable from both a promotional and safety perspective under new drug application (NDA) 213433 (Proprietary Name Review by Madhuri R. Patel, PharmD, Division of Medication Error Prevention and Analysis dated January 2, 2020).

1.2. Conclusions on Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials (CB-03-01/25 and CB-03-01/26). The data provided evidence of the effectiveness of clascoterone cream, 1%, for the topical treatment of inflammatory lesions, and noninflammatory lesions in the target population with acne vulgaris. The trials assessed the changes from baseline to week 12 for the following primary efficacy endpoints (hierarchical):

- P1: Proportion of subjects in each treatment group achieving “success,” with “success” defined as an Investigator Global Assessment (IGA) score of clear or almost clear and at least a two-point reduction in IGA compared to baseline.
- P2: Absolute change from baseline in noninflammatory lesion count in each treatment group.
- P3: Absolute change from baseline in inflammatory lesion count in each treatment group.

Clascoterone cream, 1%, was statistically superior to vehicle (p-value ≤ 0.003) on the coprimary endpoints in trials CB-03-01/25 and CB-03-01/26. The Applicant has demonstrated that clascoterone cream, 1%, is effective for its intended use and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126(a)(b) to support approval. Upon review of the benefits and risks, the review team recommends approval in subjects 12 years of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Cassiopea SpA submitted new drug application (NDA) 213433 for WINLEVI (clascoterone) cream, 1%, for the topical treatment of acne vulgaris under the 505(b)(1) regulatory pathway. Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles that primarily affects adolescents and young adults. WINLEVI is a new molecular entity. The active ingredient clascoterone is a novel androgen receptor inhibitor.

The Applicant submitted data from nonclinical studies, two pharmacokinetic (PK) maximal usage trials (MUsTs), one in pediatric subjects and one in adults, two vehicle controlled phase 3 efficacy and safety trials, and one long-term (12 months) safety trial to support the efficacy and safety of their product. Upon review of the benefits and risks, the review team recommends approval in subjects 12 years of age and older.

In two multicenter, randomized, double-blind clinical trials— CB-03-01/25 and CB-03-01/26—enrolling 1,440 subjects age 9 years and older with acne vulgaris, clascoterone cream, 1%, was statistically superior to a vehicle for the treatment of acne vulgaris on all coprimary endpoints evaluating the face. Success on the Investigator Global Assessment (IGA) was evaluated for the face and defined as at least a two-grade improvement from baseline and an IGA score of clear (0) or almost clear (1). The coprimary efficacy endpoints were success on the IGA (trial CB-03-01/25: 18.8% versus 8.7% and trial CB-03-01/26: 20.9% versus 6.6%), absolute change in inflammatory lesion count (trial CB-03-01/25: -19.3 versus -15.4 and trial CB-03-01/26: -20.1 versus -12.6), and absolute change in noninflammatory lesion count (trial CB-03-01/25: -20.4 versus -13.0 and trial CB-03-01/26: -19.5 versus -10.8) at week 12.

The safety profile for clascoterone cream, 1%, was adequately characterized during the drug development program. Treatment with clascoterone cream, 1%, was not associated with an increased risk of mortality or serious adverse events (SAEs). There were no deaths or drug-related serious adverse events in the phase 3 trials, trial CB-03-01/25, and trial CB-03-01/26 (referred to as study 1 and study 2 in labeling). In the pooled safety analysis set, SAEs occurred in 0% subjects in the clascoterone cream, 1% arm, and 0.3% in the vehicle arm. Review of the data supports the potential for pruritus, burning, skin redness or peeling, in section 5 WARNINGS AND PRECAUTIONS of labeling. The most frequent treatment-emergent Local Skin Reactions (LSRs) were erythema (12.2% CB-03-01, 15.3% vehicle) and scaling/dryness (10.5% CB-03-01, 10.3% vehicle).

Subgroup analysis for subjects 9 to <12 years old did not show a beneficial treatment effect, and the incidences of treatment-emergent adverse events (TEAEs) in this age group treated with clascoterone were higher compared to older adolescents and adults. One of the risks for clascoterone is the potential for hypothalamic-pituitary-adrenal (HPA) suppression. The proportion of subjects in the 9 to <12 years old, treated with clascoterone cream, 1%, that experienced HPA suppression, was three-times that of the HPA suppression observed in adults. Also, the

proportion of subjects in the 9- to <12-year-old group that saw a shift from normal to high potassium was substantially higher than in other age groups.

Taken together, the lack of demonstrated treatment effect as described below and rate and concern of adverse events (AEs) present an unfavorable benefit-risk profile for first-line therapy for patients 9 to <12 years old. Approval down to 12 years of age is recommended.

In summary, acne vulgaris is a common chronic disease that may be associated with impairment of quality of life. Clascoterone cream, 1%, provides an additional treatment option for prescribers. The available evidence of safety and efficacy supports the approval of WINLEVI (clascoterone) cream, 1%, for the topical treatment of acne vulgaris in the population 12 years of age and older. Given a favorable overall benefit/risk assessment, the review team recommends the approval of this product when used according to the recommended labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles that primarily affects adolescents and young adults. Acne occurs most frequently on the face and is characterized by two major types of lesions: noninflammatory (open or closed comedones) and inflammatory lesions (papules, pustules, and nodules). The etiology is multifactorial. Because of the chronic relapsing and remitting course and potential for scarring after lesions resolve, acne may be associated with impairment of quality of life.	Acne is a common chronic disorder with a range of disease severities that may impact the quality of life.
Current Treatment Options	Many topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies 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, nodulocystic acne. Treatment is individualized according to the types of lesions, the severity of disease, and patient preferences (Zaenglein et al. 2016).	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of acne vulgaris. However, the response to treatment varies with the lesion type, the severity of the disease, and compliance with the treatment regimen. There is a need for additional products that promote compliance by addressing patient preferences.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Data from two adequate and well-controlled trials (CB-03-01/25 and CB-03-01/26), provided substantial evidence of the effectiveness of clascoterone cream, 1%. These trials enrolled 1,440 subjects age 9 years and older with moderate to severe acne vulgaris. In subjects 12 years of age and older, clascoterone cream, 1%, was statistically superior to a vehicle in both trials for the coprimary efficacy endpoints of absolute change in noninflammatory lesion count, absolute change in inflammatory lesion count and IGA success. There was no observed benefit of treatment in the 9 to <12 age group.	Clascoterone cream, 1%, provides an effective treatment option for patients with moderate to severe acne vulgaris.
Risk and Risk Management	The primary safety database (study pool A) included 1,440 subjects who received clascoterone cream, 1%, twice daily for 12 weeks. There were no deaths or serious adverse events related to the trial product. The most common adverse reactions occurring in ≥1% of subjects and greater than the vehicle was localized to the applicate site: pruritus, burning, skin redness or peeling. Active assessment of local adverse reactions indicated that most were mild to moderate with a few severe. Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and identified during product development. No issues require further assessment with a postmarketing requirement or postmarketing commitment. Risk evaluation and mitigation strategy is not recommended.	The risks associated with the use of clascoterone cream, 1%, are primarily at the site of application. Local effects such as erythema, scaling, dryness, and burning/stinging may occur but are primarily mild to moderate in severity with a few severe reactions. Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

1.4. Patient Experience Data

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

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

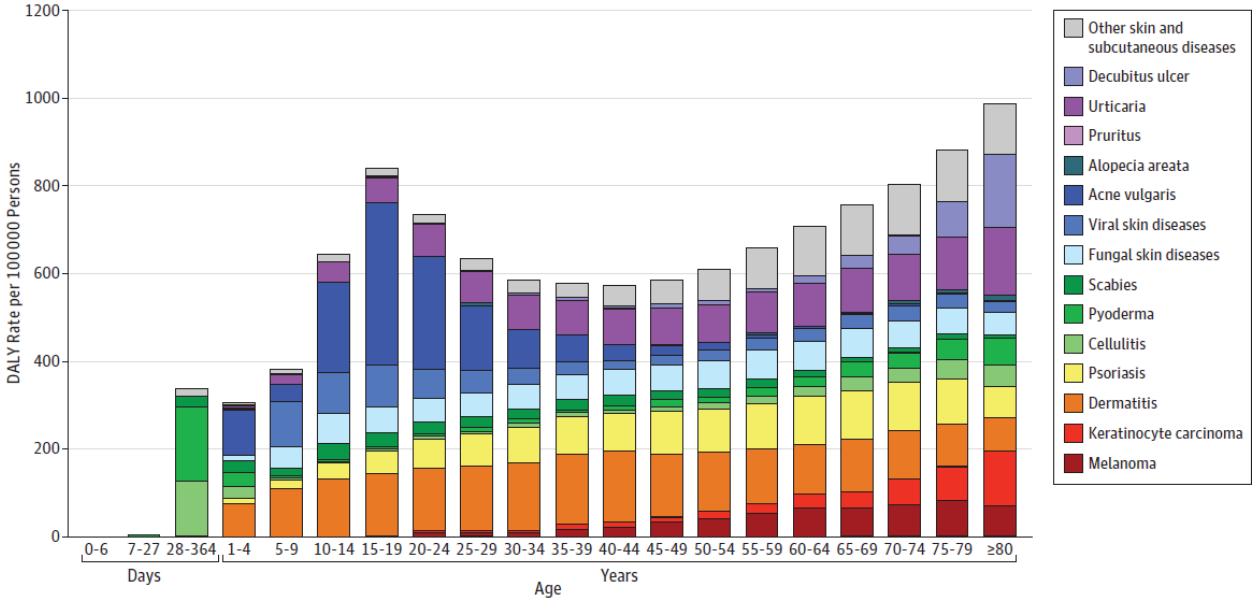
2. Therapeutic Context

2.1. Analysis of Condition

Acne is the most common skin condition in the United States, affecting up to 50 million Americans annually (Bickers et al. 2006). Acne usually begins in puberty and affects many adolescents, and young adults and approximately 85% of people between the ages of 12 and 24 experience at least minor acne (Bhate and Williams 2013). *Acne vulgaris* is a common subtype of acne that occurs most frequently in adolescents and young adults; the estimates of the prevalence in adolescents range from 35% to over 90% (Stathakis et al. 1997). Adolescent acne exhibits a male predominance in contrast to postadolescent acne that predominantly affects women (Goulden et al. 1997). The prevalence of acne in adult women is about 12% (Goulden et al. 1999).

The disease burden of *acne vulgaris* by age is presented in Figure 1, presented by disability-adjusted life year (DALY), which is the sum of years of life lost to disease plus years lived with disability; one DALY is equivalent to 1 year of healthy life lost (Karimkhani et al. 2017).

Figure 1. Age Distribution of Skin and Subcutaneous Disease Burden



Abbreviations: α-MSH = α-melanocyte-stimulating hormone; CRH = corticotropin-releasing hormone; DHEA = dehydroepiandrosterone; EGFR = epidermal growth factor receptor; IGF1 = insulin-like growth factor 1; LPS = lipopolysaccharide; MMP = matrix metalloproteinase; NF-κB = nuclear factor-κB; PPARγ = peroxisome proliferator-activated receptor-γ; TNF = tumor necrosis factor; VIP = vascular intestinal polypeptide

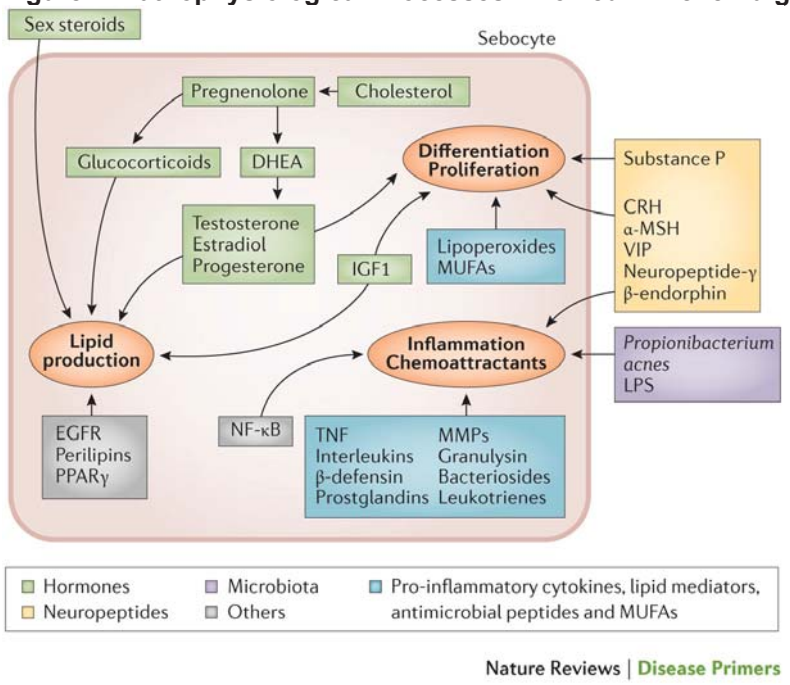
Of the 15 skin diseases, the DALY rate for acne vulgaris per 100,000 persons (navy color) illustrates the significant burden of this disease in the 10 to 34 age group (Karimkhani et al. 2017).

The American Academy of Dermatology estimates the economic burden of acne to be $846 million, with lost productivity among patients and caregivers at nearly $400 million (Dermatology 2017).

Acne is a chronic inflammatory skin disease, and *acne vulgaris* is dermatosis notable for open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules (also known as cysts) (Zaenglein et al. 2016).

Acne is a multifactorial inflammatory disease affecting the pilosebaceous follicles of the skin. The pathogenesis of acne involves several processes, including sebum production and sebocyte differentiation, proliferation, and inflammation. These processes are regulated by circulating sex hormone levels as well as locally synthesized hormones, neuropeptides, the microbiota, and pro-inflammatory cytokines, lipid mediators, antimicrobial peptides, and monounsaturated fatty acids (MUFAs). (Moradi Tuchayi et al. 2015).

Figure 2. Pathophysiological Processes Involved in Acne Vulgaris



Source: (Moradi Tuchayi et al. 2015)

The understanding of acne pathogenesis is continuously evolving. Key pathogenic factors that play an important role in the development of acne are follicular hyperkeratinization, microbial colonization with *Propionibacterium acnes*, sebum production, and complex inflammatory mechanisms involving both innate and acquired immunity. In addition, studies have suggested that neuroendocrine regulatory mechanisms, diet, and genetic and nongenetic factors all may contribute to the multifactorial process of acne pathogenesis (Zaenglein et al. 2016).

Clinically acne vulgaris can present as mild, moderate, or severe based on the number of comedones, papules and/or pustules, nodules, cysts, and sinus tracts on the face.

Table 1. Classification of Clinical Forms of Acne Vulgaris

Acne Severity	Clinical Type	Comedones	Papules and/or Pustules	Nodules	Nodules, Cysts and Sinus Tracts
Mild	Comedonal acne and papulopustular acne	Comedones are the main lesions (<20*)	Small and few in number (<10*)	None	None
Moderate	Papulopustular acne and nodular acne	10–40*	10–40*	0–10*	None
Severe	Nodulocystic acne and conglobate acne	40–100* and fused	>40*	>10*	Many

Source: (Moradi Tuchayi et al. 2015)
* Number of lesions on the face

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.

The American Academy of Dermatology developed an evidence-based guideline to address the management of adolescent and adult patients who present with acne vulgaris (Zaenglein et al. 2016). The algorithm for the treatment and management of acne in adolescents and young adults is shown in Table 2.

Table 2. Treatment Algorithm for Management of Acne Vulgaris

Treatment	Mild	Moderate	Severe
First line of treatment	Benzoyl peroxide (BP) or topical retinoid or topical combination therapy **	Topical combination therapy ** or oral antibiotic + topical retinoid + BP or oral antibiotic + topical retinoid + BP + topical antibiotic	Oral antibiotic + topical combination therapy ** or oral isotretinoin
Alternative treatment	Add topical retinoid or BP or consider alternate retinoid or consider topical dapsone	Consider alternate combination therapy or consider change in oral antibiotic or add combined oral contraceptive or oral spironolactone (females) or consider oral isotretinoin	Consider change in oral antibiotic or add combined oral contraceptive or oral spironolactone (females) or consider oral isotretinoin

Source: Treatment algorithm for the management of acne vulgaris in adolescents and young adults. The double asterisks (**) indicate that the drug may be prescr bed as a fixed combination product or as a separate component. BP, Benzoyl peroxide. (Zaenglein et al. 2016)
Topical Combination Therapy ** = BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic
Abbreviations: BP = benzoyl peroxide

The current medications, dose, partial list of preparation, and select adverse events (AEs) are summarized in Table 3.

Table 3. Acne Medications

Medications	Dose	Partial List of Preparations	Select Adverse Effects
Topical retinoids			
Tretinoin	Once daily, at bedtime	Standard vehicles – Creams: 0.025%, 0.0375%, 0.05%, 0.1% Gels: 0.01%, 0.025% Lotion: 0.05% Optimized vehicles – Microsphere gels: 0.04%, 0.08%, 0.1% Polyolprepolymer-2 cream:0.025% Polyolprepolymer-2 gel:0.025% Gel (micronized): 0.05%	Local skin irritation, dryness, and flaking; sun sensitivity NOTE: Micronized gel tretinoin 0.05% (Atralin) contains soluble fish proteins, use with caution in patients with known sensitivity or allergy to fish
Adapalene	Once daily, at bedtime	Cream: 0.1% Gels: 0.1%, 0.3% Lotion: 0.1%	Local skin irritation, dryness, and flaking; sun sensitivity
Tazarotene	Once daily, at bedtime	Creams: 0.05%, 0.1% Gels: 0.05%, 0.1% Foam: 0.1%	Contraindicated in pregnancy; local skin irritation, dryness, and flaking; sun sensitivity
Trifarotene	Once daily, in the evening	Cream: 0.005%	Local skin irritation, dryness, and flaking; sun sensitivity
Isotretinoin (not available in United States)	Once daily, at bedtime or twice per day	Gel: 0.05%	Contraindicated in pregnancy and lactation; local skin irritation, dryness, and flaking; sun sensitivity
Topical antimicrobials*			
Benzoyl peroxide	Twice daily	Multiple (prescription and nonprescription) 2.5 to 10% gels, lotions, creams, pads, masks, cleansers	Local skin irritation; may bleach hair or clothing
Clindamycin	Twice daily Once daily (foam)	1% gel, lotion, pledget, solution, foam	Rare risk of pseudomembranous colitis; usually prescribed with benzoyl peroxide to decrease resistance
Erythromycin	Twice daily	2% gel, solution, pledget	Usually prescribed with benzoyl peroxide to decrease resistance
Dapsone	Twice daily (5% gel) Once daily (7.5% gel)	5% gel, 7.5% gel	Yellow-orange skin discoloration when applied at the same time as benzoyl peroxide
Minocycline	Once daily	4% foam	Headache
Topical combination products			
Benzoyl peroxide 5%/clindamycin 1%	Twice daily	Gel	Local skin irritation; may bleach hair or clothing
Benzoyl peroxide 5%/clindamycin 1.2%	Once daily	Gel	Local skin irritation; may bleach hair or clothing

Medications	Dose	Partial List of Preparations	Select Adverse Effects
Benzoyl peroxide 2.5%/clindamycin 1.2%	Once daily	Gel	Local skin irritation; may bleach hair or clothing
Benzoyl peroxide 3.75%/clindamycin 1.2%	Once daily	Gel	Local skin irritation; may bleach hair or clothing
Benzoyl peroxide 5%/erythromycin 3%	Twice daily	Gel	Local skin irritation; may bleach hair or clothing
Clindamycin 1.2%/tretinoin 0.025%	Once daily, at bedtime	Gel	Local skin irritation
Benzoyl peroxide 2.5%/adapalene 0.1%	Once daily	Gel	Local skin irritation; may bleach hair or clothing
Benzoyl peroxide 2.5%/adapalene 0.3%	Once daily	Gel	Local skin irritation; may bleach hair or clothing
Azelaic acid	Twice daily	20% cream, 15% gel	Local skin irritation
Salicylic acid	Once to three times daily	Multiple (nonprescription) 0.5 to 2% creams, gels, pads, cleansers, solutions, soaps, pledget, foam	Local skin irritation; potential for salicylate absorption
Oral antibiotics¶Δ			
Tetracycline	500 mg twice daily		Photosensitivity, gastrointestinal distress; contraindicated in pregnancy and young children
Doxycycline	50 to 100 mg twice daily or 100 mg once daily **or** Delayed-release formulation: 100 mg every 12 hours for 1 day, then 100 mg per day Subantimicrobial dosing: 20 mg twice daily **or** Delayed-release formulation given as 40 mg once daily		Photosensitivity, gastrointestinal distress; contraindicated in pregnancy and young children
Minocycline	50 mg 1 to 3 times daily **or** Extended-release formulation: 1 mg/kg/day (round to nearest available strength)		Dizziness, drug-induced lupus, skin discoloration; contraindicated in pregnancy and young children

Medications	Dose	Partial List of Preparations	Select Adverse Effects
Sarecycline	Weight-based dosing: 33 to 54 kg: 60 mg once daily 55 to 84 kg: 100 mg once daily 85 to 136 kg: 150 mg once daily		Photosensitivity, gastrointestinal distress; contraindicated in pregnancy and young children
Erythromycin	500 mg twice daily (base)		Gastrointestinal distress
Trimethoprim-sulfamethoxazole	160 mg/800 mg once to twice daily		Stevens-Johnson syndrome, toxic epidermal necrolysis
Azithromycin	Intermittent dosing due to long drug half-life; optimum regimen unknown		Gastrointestinal distress
Hormonal agents¶			
Combination oral contraceptives (estrogen/progestin)	Once daily		Nausea, breast tenderness, weight gain, thromboembolic events
Spironolactone	50 to 100 mg/day in 1 or 2 equally divided doses§		Contraindicated in pregnancy; menstrual irregularity, breast tenderness, minor gastrointestinal symptoms, orthostatic hypotension, hyperkalemia, dizziness, headaches, fatigue
Oral retinoid			
Oral isotretinoin	0.5 mg/kg/day, increasing to 1 mg/kg/day in 1 or 2 equally divided doses; total dose 120 to 150 mg/kg over 20 weeks		Teratogenicity (absolutely contraindicated in pregnancy), mucocutaneous effects, hypertriglyceridemia, others

* Topical sulfacetamide (e.g., gels, creams, lotions, other) with and without sulfur are also available but not typically used and have limited data; refer to topic.
¶ Usual oral dose for adult or adolescent.
Δ Benzoyl peroxide may be prescribed with oral antibiotics to reduce resistance.
§ Initiating treatment with a total daily dose of 25 to 50 mg per day, with subsequent dose escalation based upon patient tolerance and response, helps to minimize side effects. Doses of up to 200 mg per day have been utilized for acne; however, limited data suggest that doses of 50 to 100 mg per day may be as effective and may reduce risk for side effects.
Source: UpToDade (Accessed May 2020)

From the listed treatments: Benzoyl peroxide is in an over-the-counter monograph approved products; azithromycin/erythromycin, ampicillin/amoxicillin are used off-label; spironolactone, flutamide, corticosteroids are used off-label.

Most FDA-approved therapies belong to the following pharmacologic classes: Antibiotics and antimicrobials (e.g., erythromycin, clindamycin, benzoyl peroxide, dapsone); hormonal agents (e.g., ethinyl estradiol/norgestimate); and retinoids (e.g., tretinoin, tazarotene, isotretinoin).

Other treatment options that are used less frequently include physical modalities (e.g., chemical peels, intralesional corticosteroids, and laser therapy), complementary/alternative therapies (e.g., tea tree oil, herbal supplements, and biofeedback), and dietary management (e.g., low glycemic index diets and low calcium diets). Factors that influence the choice of treatment are lesion type(s), disease severity, personal preference, and individual patient characteristics (e.g., age, sex, skin sensitivity, predisposition for hyperpigmentation/scarring). Topical products such as benzoyl peroxide, retinoids, and antibiotics are indicated for acne of mild to moderate severity (Zaenglein et al. 2016) whereas oral formulations of isotretinoin are indicated for severe, recalcitrant, nodule-cystic acne. Topical products may contain a single active ingredient or two active ingredients, which may address different lesion types.

Table 4. Summary of FDA-Approved Treatment Armamentarium Relevant to Proposed Indication Acne Vulgaris

Application Type/Number	Product Name	Submitter	Dosage Form	Year of Approval
NDA-020380	Differin (Adapalene)	GALDERMA LABORATORIES LP	Gel	5/31/1996
NDA-019931	Klaron (Sulfacetamide Sodium)	VALEANT PHARMACEUTICALS NORTH AMERICA LLC	Lotion	12/23/1996
NDA-020404	Avita (Tretinoin)	MYLAN PHARMACEUTICALS INC	Emulsion, cream	1/14/1997
NDA-020475	Retin-A Micro (Tretinoin)	VALEANT PHARMACEUTICALS NORTH AMERICA LLC	Gel	2/7/1997
NDA-020600	Tazorac (Tazarotene)	ALLERGAN INC	Gel	6/13/1997
NDA-020400	Avita (Tretinoin)	MYLAN PHARMACEUTICALS INC	Gel	1/29/1998
NDA-020748	Differin (Adapalene)	GALDERMA LABORATORIES LP	Emulsion, cream	5/26/2000
NDA-050769	Aktipak (erythromycin, benzoyl peroxide)	BIOFRONTERA BIOSCIENCE GMBH	Gel	11/27/2000
NDA-050782	Clindagel (Clindamycin Phosphate)	BAUSCH HEALTH US LLC	Gel	11/27/2000
NDA-050756	BenzaClin (Benzoyl Peroxide and Clindamycin Phosphate)	BAUSCH HEALTH AMERICAS INC	Gel; gel	12/21/2000
NDA-050741	Duac (Benzoyl Peroxide and Clindamycin Phosphate)	STIEFEL LABORATORIES INC	Gel	8/26/2002
NDA-050801	Evoclin (Clindamycin Phosphate)	MYLAN PHARMACEUTICALS INC	Emulsion, aerosol foam	10/22/2004
NDA-021794	Aczone (Dapsone)	ALLERGAN INC	Gel; gel	7/7/2005
NDA-050802	Ziana (Clindamycin Phosphate and Tretinoin)	MEDICIS PHARMACEUTICAL CORP	Gel	11/7/2006
NDA-022070	Atralin (Tretinoin)	DOW PHARMACEUTICAL SCIENCES INC	Gel	7/26/2007
NDA-021753	Differin (Adapalene)	GALDERMA LABORATORIES LP	Gel	12/23/2007
NDA-050819	Acanya (Benzoyl Peroxide and Clindamycin Phosphate) and Onexton (Benzoyl Peroxide and Clindamycin)	BAUSCH HEALTH AMERICAS INC	Gel	10/23/2008

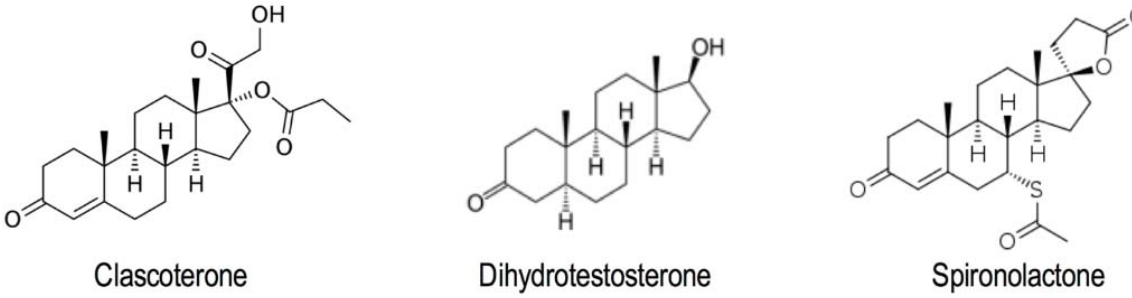
Application Type/Number	Product Name	Submitter	Dosage Form	Year of Approval
NDA-022320	Epiduo (Adapalene and Benzoyl Peroxide)	GALDERMA LABORATORIES LP	Gel	12/8/2008
NDA-022502	Differin (Adapalene)	GALDERMA LABORATORIES LP	Lotion	3/17/2010
NDA-050803	Veltin (Clindamycin and Tretinoin)	ALMIRALL LLC	Gel	7/16/2010
NDA-202428	Fabior (Tazarotene)	MAYNE PHARMA LLC	Emulsion, aerosol foam	5/11/2012
ANDA-200298	Adapalene	TOLMAR INC	Gel	6/14/2012
ANDA-202026	Tretinoin	MYLAN PHARMACEUTICALS INC	Gel	7/17/2013
ANDA-201000	Adapalene	ACTAVIS MID ATLANTIC LLC	Gel	10/27/2014
ANDA-205128	Benzoyl Peroxide and Clindamycin Phosphate	ACTAVIS LABORATORIES UT INC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC	Gel; gel	6/19/2015
NDA-207917	Epiduo Forte (Adapalene and Benzoyl Peroxide)	GALDERMA LABORATORIES INC	Gel	7/15/2015
ANDA-207955	Tretinoin	MYLAN PHARMACEUTICALS INC	Gel	8/13/2015
NDA-207154	Aczone (Dapsone)	ALMIRALL LLC	Gel	2/24/2016
ANDA-208322	Adapalene	TARO PHARMACEUTICALS USA INC	Gel; gel	6/23/2016
ANDA-208154	Erythromycin	TELIGENT PHARMA INC	Gel	7/19/2017
ANDA-209506	Dapsone	TARO PHARMACEUTICALS USA INC	Gel	10/16/2017
ANDA-206218	Benzoyl Peroxide and Clindamycin Phosphate	TARO PHARMACEUTICALS INC	Gel	12/15/2017
ANDA-205033	Adapalene and Benzoyl Peroxide	PERRIGO UK FINCO LTD PARTNERSHIP	Gel	1/23/2018
ANDA-206164	Adapalene and Benzoyl Peroxide	TOLMAR INC	Gel	5/23/2018
ANDA-208776	Benzoyl Peroxide and Clindamycin Phosphate	TARO PHARMACEUTICALS USA INC	Gel	5/25/2018
ANDA-208683	Benzoyl Peroxide and Clindamycin Phosphate	TARO PHARMACEUTICALS USA INC	Gel	6/5/2018
NDA-209353	Altreno (Tretinoin)	DOW PHARMACEUTICAL SCIENCES INC	Lotion	8/23/2018
ANDA-209148	Adapalene and Benzoyl Peroxide	TARO PHARMACEUTICALS USA INC	Gel	10/17/2018
ANDA-210794	Benzoyl Peroxide and Clindamycin Phosphate	ZYDUS PHARMACEUTICALS USA INC	Gel	12/28/2018
ANDA-209252	Benzoyl Peroxide and Clindamycin Phosphate	GLENMARK PHARMACEUTICALS SA	Gel	3/14/2019
ANDA-210191	Dapsone	TARO PHARMACEUTICALS INC	Gel	6/26/2019
ANDA-206575	Benzoyl Peroxide and Clindamycin Phosphate	TARO PHARMACEUTICALS USA INC	Gel; gel	8/19/2019
ANDA-207194	Benzoyl Peroxide and Clindamycin Phosphate	ANDA REPOSITORY LLC	Gel	8/19/2019

Application Type/Number	Product Name	Submitter	Dosage Form	Year of Approval
ANDA-205397	Benzoyl Peroxide and Clindamycin Phosphate	PERRIGO ISRAEL PHARMACEUTICALS LTD	Gel	9/9/2019
NDA-211527	Aklief	GALDERMA RESEARCH AND DEVELOPMENT INC	Cream	10/4/2019
NDA-212379	AMZEEQ (minocycline)	FOAMIX PHARMACEUTICALS INC	Foam dosage form	10/18/2019
NDA-211913	Absorica LD (isotretinoin)	SUN PHARMACEUTICAL INDUSTRIES LTD	Capsule	11/5/2019
NDA-211882	ARAZLO (tazarotene)	BAUSCH HEALTH AMERICAS INC	Lotion	12/18/2019

Source: Clinical Review Analysis

Clascoterone cream, 1%, is a new chemical entity, that is purported to target androgen receptors in the skin to block the effects of circulating endogenous androgens; chemically, it shares a four-ring backbone identical to dihydrotestosterone and spironolactone (Figure 3) (Kircik 2019).

Figure 3. Chemical Similarity Between Clascoterone, Dihydrotestosterone, and Spironolactone



Source: (Kircik 2019)

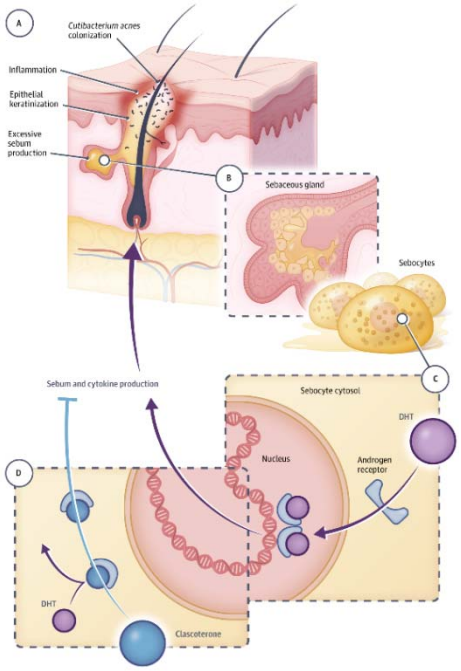
Androgen receptors belong to the nuclear receptor superfamily and contain a ligand-binding domain, a DNA-binding domain, and an N-terminal regulatory domain. Upon binding to its ligand (i.e., 5α-DHT or testosterone), the androgen receptor translocates from the cytosol into the nucleus and serves as a transcriptional factor to regulate the expression of its target genes, such as prostate-specific antigen. The exact mechanism by which clascoterone may ameliorate acne vulgaris when topically applied is unknown.

The proposed mechanism of action of clascoterone is presented in Figure 4. Clascoterone competes with dihydrotestosterone for binding to the androgen receptor to limit or block transcription of androgen-responsive genes and modify specific gene expression (Kircik 2019).

Acne is characterized by epithelial hyperkeratinization, excessive sebum production, *Cutibacterium acnes* colonization of the pilosebaceous unit, and inflammation. Within the sebaceous gland, sebocytes convert precursor molecules into androgens including DHT. Within sebocytes, DHT binds to androgen receptors in the cytosol. On binding, the DHT-androgen receptor complex dimerizes and translocates to the nucleus. There, it influences transcription

of genes involved in acne pathogenesis, including sebum and inflammatory cytokine production. Clascoterone, applied topically to the skin, binds to the androgen receptor with high affinity at the site of application, competing with DHT. Results from in vitro studies suggest it thereby limits the effect of DHT on transcription of genes that modulate sebum production and inflammation (Hebert et al. 2020).

Figure 4. Proposed Mechanism of Action of Clascoterone



Source: (Hebert et al. 2020)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The proposed medical product, WINLEVI (clascoterone) cream, 1%, is an original NDA and is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed clascoterone under investigational new drug (IND) application 112137. The IND was opened on January 31, 2012, with a phase 2, multicenter, randomized, double-blind, vehicle-controlled, dose escalating study to evaluate the safety and efficacy of cortexolone 17α- propionate (cb-03-01) cream applied once or twice-daily for 12 weeks in subjects with facial acne vulgaris (protocol number 171-7151-201) with a primary objective to compare the safety and efficacy of topical creams containing 0.1% (BID), 0.5% (BID) or 1% (once daily [QD] and BID) CB-03-01 and the vehicle cream (QD or BID) in subjects with facial acne vulgaris.

CB-03-01 1% cream had been assessed in four good clinical practice-compliant clinical studies conducted in Europe involving 156 subjects (106 subjects exposed to CB-03-01 1% cream):

1) A phase 1 randomized, double-blind, vehicle-controlled, single ascending dose, safety/tolerability and pharmacokinetics (PK) study in 24 healthy volunteers,
2) A phase 1 vehicle-controlled, 14-day repeat-dose pharmacokinetics study in 24 healthy volunteers,
3) A phase 1 3-week cumulative skin irritation study in 36 healthy volunteers, and
4) A phase 2 8-week randomized, double-blind, vehicle-controlled, active comparator (Retin-A® [tretinoin] 0.05% cream) study evaluating safety and efficacy in 72 adult subjects with facial acne vulgaris.

During its development program, the Applicant interacted with the Agency at the following milestones/meetings: End-of-phase 2 meeting on January 28, 2015, and a pre-NDA meeting on May 6, 2019. The Applicant also received the following correspondences during the development program:

- April 8, 2019, proprietary name granted
- March 23, 2018, advice/information request
- October 26, 2016, advice
- April 27, 2016, harmonized annual report due date granted
- March 25, 2016, advice
- March 22, 2016, advice
- December 15, 2015, pediatric study plan–initial agreement
- July 30, 2015, special protocol–agreement
- June 22, 2015, pediatric study plan–written response

- May 18, 2015, special protocol–no agreement
- February 26, 2014, advice
- January 8, 2014, special protocol–agreement (carcinogenicity)
- February 1, 2013, advice
- August 1, 2012, advice
- May 30, 2012, study may proceed

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

4.1. Office of Scientific Investigations

Site investigations through the Office of Scientific Investigations (OSI) were conducted by Jenn Sellers, M.D., Ph.D., Medical Officer, Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation OSI. Five clinical investigator sites were chosen to be inspected based on the large enrollments, treatment effect size, and prior inspection histories.

Table 5. Clinical Inspection Summary

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification	Inspection Dates
Scott Guenthner, M.D. Site #0168 824 Edwards Dr. Suite 172 Plainfield, IN 46168	CB-03-01/25	31	NAI	5/28/2020–6/03/2020
Misael Gonzalez, M.D. Site #0199 1250 SW 27th Avenue, Suite 507 Miami, FL 33135	CB-03-01/25	20	NAI	2/24/2020–2/27/2020
Otto Marquez Mendoza, M.D. Site #0192 1414 NW 107th Ave., Suite 102 Doral, FL 33172	CB-03-01/25	36	NAI	2/24/2020–2/26/2020
Sandra Johnson, M.D. Site #0138 5921 Riley Park Drive Fort Smith, AR 72916	CB-03-01/26	23	NAI	6/09/2020–6/11/2020

Abbreviations: NAI = no action indicated
Source: OSI Review: Section III, Results in DARRTs dated July 1, 2020

In conclusion, the results of the inspection of these sites found that the quality of the clinical information in this application is adequate to support the proposed indication.

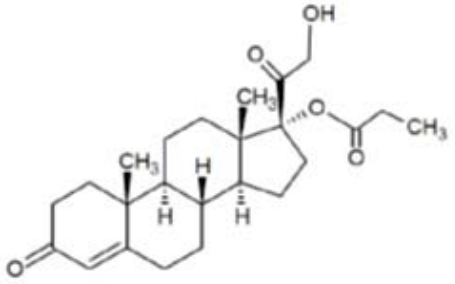
4.2. Product Quality

4.2.1. Drug Substance

The drug substance clascoterone is an androgen receptor inhibitor with a good skin permeation. It binds weakly to the human androgen receptor, thus blocking the receptor and preventing downstream androgenetic gene activation. Clascoterone has not been previously approved and therefore, has been classified as a new molecular entity (NME).

Clascoterone is a white or almost white powder. It is practically insoluble in water, slightly soluble in ether, and very soluble in methanol and ethanol. It has the chemical name, [(8R,9S,10R,13S,14S,17R)-17-(2-hydroxyacetyl)-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-17-yl] propanoate, a molecular formula of C24H34O5, a molecular weight of 402.5 g/mol, and the chemical structure in Figure 5 below.

Figure 5. Chemical Structure of Clascoterone



Clascoterone for this application is manufactured and supplied by (b) (4) in accordance current Good Manufacturing Practices (cGMP). It is tested against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of (b) (4) months when stored in a (b) (4). Information regarding the manufacture of clascoterone supplied by (b) (4) is provided in DMF (b) (4). This DMF has been reviewed and found to be adequate.

4.2.2. Drug Product

WINLEVI® (clascoterone) cream, 1%, for topical administration has been developed for the treatment of acne vulgaris in patients 12 years of age or older. It is intended for twice a day topical application as uniform thin layer to cleaned and dried affected skin area.

WINLEVI has been formulated as a white to almost white (b) (4) cream. Each gram of the cream contains 10 mg (1%) clascoterone as the active ingredient and cetyl alcohol, mono and diglycerides, mineral oil, propylene glycol, vitamin E, edetate disodium, polysorbate 80, citric acid monohydrate, and purified water as inactive ingredients. Inactive ingredients used in the composition of the drug product are all compendial materials. (b) (4)

(b) (4) Therefore, the pH of final cream formulation was adjusted to (b) (4) for the phase 3 studies. (b) (4) storage condition of 5°C + 3°C was used and recommended as the shelf-life storage condition for the commercial drug product.

WINLEVI cream is manufactured in accordance to cGMP requirements by Cassiopea SpA and is packaged as 60g in epoxy-lined blind-end aluminum tubes with polypropylene caps. The drug product is tested against a specification that includes testing and acceptance criteria for all physical and chemical attributes that are essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed shelf-life of 36 months. The Applicant has provided sufficient stability data that supports the expiration dating period of 36 months for the drug product stored at 2°C – 8°C (38°F – 46°F). The Applicant has also provided sufficient stability data that supports the storage of the drug product at room temperature, 20°C – 25°C (68°F – 78°F) while in use.

4.2.3. OPQ Recommendation

- The Applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance (clascoterone) and the drug product, WINLEVI (clascoterone) cream, 1%
- Labels/labeling issues have been satisfactorily addressed
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA
- The claim for categorical exclusion from the preparation of environmental assessment has been granted

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

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(1) application for WINLEVI (clascoterone) cream, 1%, for the treatment of acne vulgaris in patients 9 years of age and older. Clascoterone is a new molecular entity androgen receptor inhibitor.

The Applicant submitted the following nonclinical studies to support the NDA: Subcutaneous repeat dose toxicity studies in rats (up to 26 weeks in duration); dermal repeat dose toxicity studies in minipigs (up to 39 weeks in duration); a battery of in vitro and in vivo genetic toxicity studies; a 2-year dermal carcinogenicity study in rats; a fertility and early embryonic development study in rats; embryofetal development studies in rats and rabbits; a prenatal and

postnatal development study in rats; an ocular irritation study in rabbits; and a skin sensitization study in guinea pigs. The Applicant also submitted several studies to support the safety of the primary degradation product of clascoterone, cortexolone-21-propionate, including a 13-week subcutaneous repeat dose toxicity study in rats and in vitro genotoxicity studies.

In a pivotal 26-week subcutaneous repeat dose toxicity study in rats, clascoterone (doses: 0, 0.1 mg/kg/day, 0.5 mg/kg/day, and 2.5 mg/kg/day) was well-tolerated; no clascoterone-related adverse effects were noted. The no observed adverse effect level (NOAEL) was 2.5 mg/kg/day, which corresponds to day 182 $AUC_{0\text{-}tlast}$ and C_{max} of 173.19 ng·hr/mL and 71.33 ng/mL, respectively, in females and 298.61 ng·hr/mL and 84.35 ng/mL, respectively, in males.

In a pivotal 39-week dermal repeat dose toxicity study in minipigs, clascoterone cream (concentrations: 0% [untreated], 0% [vehicle], 1%, 2.5%, and 5% applied to ~10% body surface area (BSA); doses: 0, 0, 5 mg/kg/day, 12.5 mg/kg/day, and 25 mg/kg/day) produced minimal systemic clascoterone exposure and no adverse effects. The NOAEL in both sexes was 5% cream, which corresponds to day 272 $AUC_{0\text{-}24}$ and C_{max} of 269 ng·hr/mL and 16.8 ng/mL, respectively, in females, and 401 ng·hr/mL and 30.1 ng/mL, respectively, in males.

Clascoterone did not display clear genotoxic potential in a standard battery of genetic toxicity studies. Clascoterone was not mutagenic in an in vitro reverse bacterial mutation assay or clastogenic in an in vitro chromosome aberration assay. In a micronucleus assay in rats, a single subcutaneous dose of clascoterone produced a slight, statistically significant increase in bone marrow micronuclei at the high dose (2000 mg/kg), but not lower doses (500 mg/kg and 1000 mg/kg); this result was considered equivocal because only two out of five HD animals exceeded the historical negative control range and none of the HD animals were within the historical positive control range.

In a dermal carcinogenicity study, clascoterone cream (concentrations: 0% [untreated], 0% [vehicle], 0.1%, 1%, and 5%; doses: 0, 0, 0.052 mg/kg/day, 0.52 mg/kg/day, and 2.6 mg/kg/day) was applied once daily to 10% BSA for 96 weeks. Clascoterone cream did not affect survival or produce systemic toxicity. No clascoterone-related tumor findings were noted.

In a fertility and early embryonic development study in rats (doses: 0, 0.5 mg/kg/day, 2.5 mg/kg/day, and 12.5 mg/kg/day, subcutaneous), 12.5 mg/kg/day clascoterone decreased body weight in both sexes, decreased testicular sperm count, increased caudal epididymis sperm count, and increased pre-implantation loss. No adverse effects were noted at ≤2.5 mg/kg/day (NOAEL: 2.5 mg/kg/day). No effects on mating and fertility were noted at doses up to 12.5 mg/kg/day.

In an embryofetal development study in rats, subcutaneous clascoterone (doses: 0, 1, 5, and 25 mg/kg/day) did not produce maternal toxicity (maternal NOAEL: 25 mg/kg/day, corresponding to gestational day (GD) 17 $AUC_{0\text{-}t}$ and C_{max} of 2850 ng·hr/mL and 589 ng/mL,

respectively); a developmental NOAEL could not be determined because clascoterone-related malformations were noted in three fetuses at the low dose (LD) and 1 fetus each at the mid dose (MD) and HD. In an embryofetal development study in rabbits (doses: 0, 0.1, 0.4, and 1.5 mg/kg/day), the HD increased postimplantation loss and resorptions and slightly delayed ossification of several bones in fetuses; no fetal malformations were noted at any dose level.

In a pre- and postnatal development study in rats, subcutaneous clascoterone (doses: 0, 0.5, 2.5, and 12.5 mg/kg/day) was well-tolerated; no clascoterone-related adverse effects were noted in F_0 dams or F_1 offspring (NOAEL: 12.5 mg/kg/day). Notably, although developmental toxicity to male fetuses is scientifically plausible based on its mechanism of action, clascoterone did not display any developmental toxicity specific to males at any dose evaluated in the submitted developmental and reproductive toxicology studies.

A 5% clascoterone solution did not cause sensitization in a guinea pig dermal sensitization study. Clascoterone cream, 1%, was a weak ocular irritant in rabbits. Clascoterone cream does not pose a phototoxic risk based on a lack of absorption in the ultraviolet/visible spectrum between 290 and 700 nm.

Cortexolone-21-propionate, a clascoterone degradation product and metabolite, was well-tolerated in a good laboratory practice (GLP) 13-week subcutaneous repeat dose toxicity study in rats, (doses: 0 [saline control], 0 [vehicle control], 0.6 mg/kg/day, 1.2 mg/kg/day, and 2.4 mg/kg/day); no cortexolone-21-propionate-related adverse effects were noted (NOAEL: 2.4 mg/kg/day). Additionally, cortexolone-21-propionate was not mutagenic in an in vitro reverse bacterial mutation assay and was not clastogenic in an in vitro chromosome aberration assay.

Clascoterone cream, 1%, does not contain novel excipients. One excipient, vitamin E, is present at higher concentrations than in approved topical products, but has been qualified and does not present safety concerns. All other excipients are present at the same or lower levels as previously-approved topical drug products.

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

None

5.3. Pharmacology

Clascoterone is a new molecular entity androgen receptor inhibitor. Clascoterone and its metabolite, cortexolone-21-propionate, bind to the human androgen receptor (IC_{50} using LNCaP cells: 50nM and 20nM for clascoterone and cortexolone-21-propionate, respectively). These data support a statement made in section 12.1 of labeling. The mechanism of action of

clascoterone in the proposed indication is unknown. The Applicant submitted in vitro data (b) (4) related to the mechanism of action (b) (4) however, the data provided were inadequate (b) (4)

Clascoterone did not display systemic anti-androgenic activity when subcutaneously administered to rats or topically applied to hamsters; topical application, however, displayed local anti-androgenic effects.

Clascoterone did not display in vitro activity at a panel of off-target receptors at clinically-relevant concentrations. Clascoterone and its metabolite, cortexolone-21-propionate, did not display in vitro binding to the gonadotropin releasing hormone receptor. Clascoterone did not have estrogenic effects in immature female mice, but had some progestational activity in immature female rabbits.

5.3.1. Safety Pharmacology

Neurological Effects

Male Wistar rats (eight per group) received one subcutaneous dose of clascoterone (doses: 0 [vehicle: polysorbate 80 (b) (4) and (b) (4) alcohol (b) (4) in saline], 10 mg/kg, 50 mg/kg, and 250 mg/kg) or positive control (10 mg/kg chlorpromazine). Behavior was evaluated using an Irwin observational battery at 0.5 hours, 1 hour, 2 hours, 4 hours, and 8 hours postdose and body temperatures were recorded. No clascoterone-related effects were noted (NOAEL: 250 mg/kg).

Respiratory Effects

A respiratory safety pharmacology study was not conducted. However, no clascoterone-related adverse respiratory effects or histopathological changes to the lungs were noted in repeat dose toxicity studies in nonclinical species.

Cardiovascular Effects

In a pilot hERG assay, clascoterone produced low potency dose-related inhibition of the hERG potassium current (up to 40% inhibition at the highest concentration evaluated [10µM]) (b) (4)

Conscious unrestrained Beagles (three per sex) received subcutaneous doses of clascoterone (doses: 0 [vehicle], 10 mg/kg, 50 mg/kg, and 250 mg/kg) in a crossover study with a minimum washout period of 48 hours. Cardiovascular parameters were monitored predose through 24 hours postdose, including arterial blood pressure, heart rate, and electrocardiogram (ECG) (including PR, PQ, QT interval duration, and QRS complex duration). No clascoterone-related cardiovascular effects or changes in body temperature were noted (NOAEL: 250 mg/kg).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
CB-03-01: In vitro dermal penetration studies / CPS/01	Clascoterone cream, 1%, in the clinical formulation was applied to dermatomed human skin in Franz diffusion cells for up to 24 hours. Clascoterone was absorbed at a rate of 389 ng/cm^2/hour, with a lag time of 5.82 hr. (b) (4)
Distribution	
Protein binding study of cortexolone 17α-propionate in mouse, rat, rabbit, minipig and human plasma by ultrafiltration / (b) (4) 11M-0048	Clascoterone (concentrations: 100 ng/mL, 1000 ng/mL, and 5000 ng/mL) binding to plasma proteins was similar between species and was not concentration dependent. The percent plasma protein binding ranged from 84.4% to 88.5% in humans; 91.8% to 93.2% in rats; 86.8% to 91.7% in minipigs; 80.2% to 85.7% in mice; and 79% to 86.3% in rabbits. These data support statements made in section 12.3 of labeling.
Metabolism	
In vitro Drug Metabolism report / PF11M-0047	Clascoterone metabolism was evaluated in vitro using humans, CD1 mice, Wistar rats, New Zealand white rabbits, and Gottingen minipig hepatocytes. Fifteen metabolites were detected after a 2-hour incubation. M2 (cortexolone) was the primary metabolite in all species except rats. No unique human metabolites were noted.
Ex-vivo metabolic profile for CB-03-01 in human plasma / B37653	Clascoterone metabolism into M1 (cortexolone-21-α-propionate) and M2 (cortexolone) was evaluated in vitro using plasma from human donors. After a 6-hour incubation at 37°C, 11% of the parent drug remained, and the metabolites M1 and M2 accounted for 24% and 65% of total drug.
Excretion	
TK data from general toxicology studies CB-03-01: 26 Week Subcutaneous Toxicity Study in Rats Followed by a 4 Week Recovery Period / CB-03-01/22	<u>Rat @ NOAEL (2.5 mg/kg/day) on day 182</u> $t_{1/2}$: 2.1 hour (females); not calculable in males t_{max}: 0.5 (females) and 2 hour (males) $AUC_{0\text{-}tlast}$: 173.19 (females) and 298.61 ng·hr/mL (males) C_{max}: 71.33 (females) and 84.35 ng/mL (males) Accumulation: None Dose proportionality: Exposure generally increased less than dose proportionally on day 1 and day 182.

Type of Study	Major Findings
A 9-Month Dermal Toxicity Study in Gottingen Minipigs with a 1-Month Recovery / CB-03-01/31	Minipig @ NOAEL (5% cream) on day 272 t_{max}: 10.3 (females) and 9.0 hour (males) AUC_{0-24}: 269 (females) and 401 ng·hour/mL (males) C_{max}: 16.8 (females) and 30.1 ng/mL (males) Increased clascoterone cream concentration generally resulted in increased exposure, but accumulation and dose proportionality could not be meaningfully assessed because overall exposure was minimal.
TK data from reproductive toxicology studies Study for effects on embryo-fetal development in the rat / CB-03-01/8	Rat @ maternal NOAEL (HD; 25 mg/kg/day) and LD (1 mg/kg/day) on GD 17 t_{max}: 0.5 (LD) and 1 hour (HD) $t_{1/2}$: 0.55 (LD) and 4.6 hour (HD) AUC_{0-t}: 93.6 (LD) and 3750 ng·hour/mL (HD) C_{max}: 98.6 (LD) and 981 ng/mL (HD) Note: A developmental NOAEL could not be determined.
CB-03-01: Study for effects on embryo-fetal development in the rabbit / CB-03-01/10	Rabbit @ maternal & developmental NOAEL (0.4 mg/kg/day) on GD 18 t_{max}: 0.5 to 1.0 hour $t_{1/2z}$: 2.2 hour AUC_{0-t}: 136 ng·hour/mL C_{max}: 48.6 ng/mL TK evaluation was not performed for the clascoterone metabolite, cortexolone, because it was usually below the lower limit of quantification (200 ng/mL).

5.5. Toxicology

5.5.1. General Toxicology

Study Title/Number

CB-03-01: 26-Week Subcutaneous Toxicity Study in Rats Followed by a 4-Week Recovery Period / CB-03-01/22

Key Study Findings

- Clascoterone was well-tolerated in both sexes; no clascoterone-related mortality, clinical signs, body weight effects, or microscopic findings were noted
- In HD males, slightly decreased adrenal weight and increased spleen weight were noted and considered nonadverse
- Clascoterone exposure increased less than dose proportionally, differed between sexes without any apparent pattern, and did not display accumulation

- The NOAEL in both sexes is 2.5 mg/kg/day, which corresponds to day 182 $AUC_{0\text{-tlast}}$ and C_{max} of 173.19 ng·hr/mL and 71.33 ng/mL, respectively, in females and 298.61 ng·hr/mL and 84.35 ng/mL, respectively, in males

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

Methods

- Dose and frequency of dosing: 0, 0.1 mg/kg/day, 0.5 mg/kg/day, and 2.5 mg/kg/day, once daily
- Route of administration: Subcutaneous
- Formulation/vehicle: Polysorbate 80 (b) (4) alcohol (b) (4) in saline
- Species/strain: Rat/Wistar Han
- Number/sex/group: 20
- Age: 6 weeks to 7 weeks (140 g-175 g) upon arrival and acclimated at least 13 days prior to treatment
- Satellite groups/unique design: 3/sex and 9/sex/group for toxicokinetic assessment in control and treated animals, respectively; 10/sex control and HD animals for 4-week recovery
- Deviation from study protocol affecting interpretation of results: No

Observations and Results: Changes From control

Parameters	Major Findings
Mortality	No clear clascoterone-related mortalities. One MD female was found dead on day 127; cause of death was unknown.
Clinical signs	No clascoterone-related effects
Body weights	No clascoterone-related effects
Ophthalmoscopy	No clascoterone-related effects
Hematology	No clascoterone-related effects
Clinical chemistry	Nonadverse decreases in alkaline phosphatase and alanine aminotransferase in males during week 13 and week 27. No other clascoterone-related effects were noted.
Urinalysis	No clascoterone-related effects
Gross pathology	No clascoterone-related effects
Organ weights	HD males: decreased adrenal gland weight and increased spleen weight No other clascoterone-related effects
Histopathology Adequate battery: Yes	No clascoterone-related effects

Abbreviations: LD = low dose; MD = mid dose; HD = high dose

Study Title/Number

CB-03-01: A 9-Month Dermal Toxicity Study in Gottingen Minipigs With a 1-Month Recovery/CB-03-01/31

Key Study Findings

- Clascoterone cream produced minimal systemic clascoterone exposure and had no effects on survival, clinical signs, or body weight
- At the MD and HD, adrenal gland weight decreased in both sexes, corresponding with the microscopic finding of cortical atrophy; these findings were fully reversible in females but not males
- Reversible clascoterone cream-related microscopic findings (minimal to mild atrophy and mucinous change) were noted at all dose levels in treated skin and at the MD and HD in untreated skin
- Minimal severity microscopic findings (decreased dermal thickness and fibroblast hypertrophy) were noted in treated and untreated skin of all HD animals at the end of recovery, but not at terminal sacrifice
- Minimal bilateral interstitial cell hypertrophy was present in the testes of one HD male at the end of treatment, but not after recovery
- The NOAEL in both sexes was 5% cream, which corresponds to day 272 AUC_{0-24} and C_{max} of 269 ng·hr/mL and 16.8 ng/mL, respectively, in females and 401 ng·hr/mL and 30.1 ng/mL, respectively, in males

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

Methods

- Dose and frequency of dosing: 0% (untreated control), 0% (vehicle control), 1%, 2.5%, and 5% cream (0, 0, 5, 12.5, and 25 mg/kg/day), once daily to 10% BSA
- Route of administration: Topical
- Formulation/vehicle: Propylene glycol (b) (4) cetyl alcohol (b) (4), polysorbate 80 (b) (4) edetate sodium (b) (4) (b) (4)
- Species/strain: Pig/minipig
- Number/sex/group: 4
- Age: 4 months to 5 months
- Satellite groups/unique design: 2/sex vehicle and HD animals for 4-week recovery
- Deviation from study protocol affecting interpretation of results: no

Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	No clascoterone cream-related effects
Clinical signs	No clascoterone cream-related effects
Body weights	No clascoterone cream-related effects
Ophthalmoscopy	No clascoterone cream-related effects
ECG	No clascoterone cream-related effects
Hematology	No clascoterone cream-related effects
Clinical chemistry	No clascoterone cream-related effects
Urinalysis	No clascoterone cream-related effects

Parameters	Major Findings
Gross pathology	No clascoterone cream-related effects
Organ weights	MD & HD: decreased adrenal gland weight (both sexes)
Histopathology Adequate battery: Yes	Treated skin: reversible minimal-to-mild atrophy and mucinous change in both sexes at all dose levels; minimally decreased dermal thickness and fibroblast hypertrophy in HD recovery animals (both sexes) Untreated skin: reversible minimal-to-mild atrophy and mucinous change in both sexes at the MD and HD; minimally decreased dermal thickness and fibroblast hypertrophy in HD recovery animals (both sexes) Adrenal glands: minimal-to-moderate cortical atrophy at the MD and HD in both sexes; reversible in HD females, partially reversible in males Testes: minimal interstitial cell hypertrophy in one HD male (not observed in either HD recovery male)
Dermal irritation scoring	Vehicle cream and all clascoterone cream dose levels produced sporadic, reversible erythema. The majority of observations (>80%) were of very slight severity. Incidence and severity were not dose-related.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose

5.5.2. Genetic Toxicology

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

Study Title/Number

Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay With CB-03-01/ (b) (4) 1013900

Key Study Findings

- Clascoterone was not mutagenic under the conditions of the assay. These data support statements made in section 13.1 of labeling.

GLP compliance: Yes
Test system: *Escherichia coli* strains TA98, TA100, TA1535, and TA1537 and *Salmonella typhimurium* strain WP2 uvrA; up to 5000 µg/plate; ±S9
Study is valid: Yes

5.5.2.2. In Vitro Assays in Mammalian Cells

Study Title/Number

Chromosome Aberration Test In Human Lymphocytes In Vitro With CB-03-01 / (b) (4) 1093200

Key Study Findings

- Clascoterone did not induce chromosome aberrations under the conditions of the assay. These data support statements made in section 13.1 of labeling.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes; up to 600.1 µg/mL; ±S9
Study is valid: Yes

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

Study Title/Number

Rat Bone Marrow Erythrocyte Micronucleus Test Following Subcutaneous Administration of CB-03-01 / AD33DF.125M.(b) (4)

Key Study Findings

- Clascoterone did not induce micronuclei at 500 mg/kg or 1000 mg/kg dose levels
- A slight, statistically significant increase in micronuclei was noted at 2000 mg/kg at 24 hours postdose (20 MPCEs/10,000 PCEs); this exceeded the historical control range (0 to 15 MPCEs/10,000 PCEs)
- No difference was noted at 48 hours postdose. These data support statements made in section 13.1 of labeling

GLP compliance: Yes
Test system: Rat, bone marrow micronuclei; single subcutaneous dose of 0 (vehicle), 500 mg/kg, 1000 mg/kg, or 2000 mg/kg; assessments at 24-hour or 48-hour postdose
Study is valid: Yes

5.5.3. Carcinogenicity

Study Title/Number

CB-03-01 Cream: A 24-Month Dermal Carcinogenicity Study in Rats / V01-CB01-601

In a 2-year dermal carcinogenicity study in rats, clascoterone cream (concentrations: 0% [untreated], 0% [vehicle], 0.1%, 1%, and 5%; doses: 0, 0, 0.052 mg/kg/day, 0.52 mg/kg/day, and 2.6 mg/kg/day) was topically applied once daily to 10% of the BSA. The study was terminated early because of decreasing control animals in both sexes. Clascoterone cream did not increase mortality, affect body weight, or produce adverse clinical observations. Clascoterone cream-related microscopic findings were limited to minimal to marked dose-related atrophy at the application site in both sexes at concentrations ≥1%. No clascoterone cream-related tumors were noted in either sex. These data support statements made in section 13.1 of labeling.

5.5.4. Reproductive and Developmental Toxicology

5.5.4.1. Fertility and Early Embryonic Development

Study Title/Number

A Subcutaneous Study of Fertility and Early Embryonic Development to Implantation in Rats / 13-4399

Key Study Findings

- One HD (12.5 mg/kg/day) male was found dead on day 14 postmating; because the cause of death could not be determined, this is potentially clascoterone-related.
- At the HD in males, clascoterone decreased body weight gain, overall body weight, seminal vesicle weight, and testicular sperm count; clascoterone increased testes weight and caudal epididymis sperm count.
- At the HD in females, clascoterone transiently decreased body weight gain during GD 0 to 4 and body weight on GD 4 and 7 and increased pre-implantation loss.
- No other clascoterone-related effects on other reproductive parameters were noted (NOAEL: 2.5 mg/kg/day). No clascoterone-related effects on fertility were noted at doses up to 12.5 mg/kg/day. These data support statements made in sections 8.1 and 13.1 of labeling. (b) (4) .

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

Methods

- Dose and frequency of dosing: 0, 0.5, 2.5, and 12.5 mg/kg/day, once daily
- Route of administration: Subcutaneous
- Formulation/Vehicle: Polysorbate 80 (b) (4) alcoho (b) (4) in saline
- Species/Strain: RAT/SPRAGUE-DAWLEY
- Number/Sex/Group: 25
- Satellite groups: None
- Study design: Females were dosed beginning 2 weeks prior to mating and continuing through GD 6. Males were dosed beginning 4 weeks prior to mating and continuing for approximately 10 weeks. Toxicokinetic assessment was not performed.
- Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	One HD male was found dead on day 14 postmating. Because the cause of death was not determined, this is potentially clascoterone-related.
Clinical signs	No clascoterone-related findings

Parameters	Major Findings
Body weights	HD: Male body weight gain and overall body weight was decreased. Female body weight gain and body weight were transiently decreased at the beginning of gestation.
Necropsy findings [Mating/fertility index, *Corpora lutea*, preimplantation loss, etc.]	LD & MD: No clascoterone-related findings HD: Increased pre-implantation loss, decreased seminal vesicle weight, decreased testicular sperm count, increased testes weight, and increased caudal epididymis sperm count

Abbreviations: LD = low dose; MD = mid dose; HD = high dose

5.5.4.2. Embryo-Fetal Development

Study Title/Number

Study For Effects on Embryo-Fetal Development in the Rat / CB-03-01/8

Key Study Findings

- Clascoterone slightly decreased maternal body weight at the HD; no clinical signs or effects on Cesarean-section data were noted. The maternal NOAEL was the HD (25 mg/kg/day), which corresponds to GD 17 AUC0-t and Cmax of 2850 ng·hr/mL and 589 ng/mL, respectively.
- A developmental NOAEL could not be determined because clascoterone-related external and/or visceral malformations were observed at all dose levels.

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

Methods

- Dose and frequency of dosing: 0, 1, 5, and 25 mg/kg/day, once daily
- Route of administration: Subcutaneous
- Formulation/Vehicle: Polysorbate 80 ((b) (4) alcohol (b) (4) in saline
- Species/Strain: RAT/WISTAR HAN
- Number/Sex/Group: 22 (vehicle and HD) or 24 females (LD and MD)
- Satellite groups: 3 females per group for toxicokinetic assessment
- Study design: Females were dosed daily from GDs 6 through 17 and sacrificed on GD 20. Blood samples were collected on GDs 6 and 17.
- Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	No clascoterone-related findings.
Clinical signs	No clascoterone-related findings.
Body weights	LD: No clascoterone-related findings. MD: No clascoterone-related findings.

Parameters	Major Findings
	HD: Clascoterone slightly decreased body weight gain during treatment, resulting in approximately 7% lower body weight at the end of dosing and approximately 5% lower body weight at the end of the study compared to controls.
Necropsy findings Cesarean-section data	No clascoterone-related findings.
Necropsy findings Offspring	LD: Clascoterone-related malformations were noted in three fetuses from three litters. One fetus had multiple abnormalities (small size, thin skin, and protruding tongue); one fetus had severe dilation of the lateral and third cerebral ventricles; and one fetus had omphalocele. MD: One fetus was observed with omphalocele. No other clascoterone-related findings. HD: One fetus was observed with omphalocele. No other clascoterone-related findings.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose

Study Title/Number

CB-03-01: Study for Effects on the Embryo-Fetal Development in the Rabbit / CB-03-01/10

Key Study Findings

- At the HD, postimplantation loss and resorptions were increased
- No fetal malformations were noted at any dose level
- Slightly delayed ossification of limbs, pelvis, sternum, and cranium were noted in fetuses at the HD
- The maternal and developmental NOAEL was 0.4 mg/kg/day, which corresponds to GD 18 AUC_{0-t} and C_{max} of 136 ng·hr/mL and 48.6 ng/mL, respectively

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

Methods

- Dose and frequency of dosing: 0, 0.1, 0.4, and 1.5 mg/kg/day, once daily
- Route of administration: Subcutaneous
- Formulation/Vehicle: Polysorbate 80 ((b) (4) alcohol (b) (4) in saline
- Species/Strain: RABBIT/NEW ZEALAND WHITE
- Number/Sex/Group: 20 females
- Satellite groups: 3 females per group for toxicokinetic assessment
- Study design: Females were dosed daily from GD 6 through 18 and sacrificed on GD 28. Blood samples were collected on GD 6 and 18.
- Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	No clascoterone-related findings.
Clinical signs	No clascoterone-related findings.
Body weights	Reversible, dose-related increases in body weight and body weight gain were noted at the MD and HD.
Necropsy findings Cesarean-section data	LD: No clascoterone-related findings. MD: No clascoterone-related findings. HD: Increased postimplantation loss and resorptions were noted. No other effects on uterine parameters.
Necropsy findings Offspring	LD: No clascoterone-related findings. MD: No clascoterone-related findings. HD: No clascoterone-related findings.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose

5.5.4.3. Prenatal and Postnatal Development

Study Title/Number

CB-03-01: Pre- and Postnatal Developmental Study in Rats Via Subcutaneous Injection / 15-4440

Key Study Findings

- No clascoterone-related mortality, clinical signs, body weight effects, macroscopic findings, or reproductive effects were noted in F_0 dams
- No clascoterone-related pre- or postnatal effects were noted in F_1 offspring
- The F_0 and F_1 NOAEL was 12.5 mg/kg/day

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

Methods

- Dose and frequency of dosing: 0, 0.5, 2.5, and 12.5 mg/kg/day, once daily
- Route of administration: Subcutaneous
- Formulation/Vehicle: Polysorbate 80 ((b) (4) alcohol (b) (4) in saline
- Species/Strain: Rat/Sprague-Dawley
- Number/Sex/Group: F_0: 22 females/group; F_1: 20/sex/group
- Satellite groups: None
- Study design: F_0 dams were dosed once daily from gestation day 6 through lactation day 20. On postnatal day 21, F_1 animals were either selected for the next generation (20-21/sex/group; 1/sex/litter was selected when feasible) or necropsied. The following parameters were evaluated in the selected F_1 animals: mortality, body weight, clinical observations, food consumption, preweaning functional assessments (righting reflex, auditory function, and visual function), sexual maturation, mating and fertility, motor

activity, learning and memory, reproductive parameters, macroscopic observations, and organ weights.

- Deviation from study protocol affecting interpretation of results: No

Observations and Results

Generation	Major Findings
F_0 Dams	No clascoterone-related findings.
F_1 Generation	No clascoterone-related findings.

5.5.5. Other Toxicology Studies

5.5.5.1. Ocular Irritation Potential

Study Title/Number

CB-03-01: Primary Eye Irritation Study in Rabbits / 0421LT28.006

The clinical formulation and concentration of clascoterone cream, 1%, was instilled into the conjunctival sac of the right eyes of three female rabbits. At 1 hour postdose, conjunctival chemosis was noted in the treated eye of one animal and discharge was noted in the other two treated eyes. All signs of irritation were resolved by 24 hours postdose. Clascoterone cream, 1%, was considered a weak ocular irritant.

5.5.5.2. Sensitization Potential

Study Title/Number

CB-03-01: Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test / A62921

In a guinea pig maximization test, clascoterone (vehicle: PEG (b) (4)) was not a sensitizer.

5.5.5.3. Phototoxic Potential

Clascoterone cream, 1%, did not display significant absorption between 290 nm and 700 nm and therefore does not present a phototoxic risk.

5.5.5.4. Degradation Product Toxicity

Cortexolone-21-propionate is the main degradation product and a metabolite of clascoterone. Cortexolone-21-propionate was evaluated for its potential to induce toxicity upon repeat exposure and for its genotoxic potential in vitro. In a GLP 13-week repeat dose toxicity study in Wistar Han rats, cortexolone-21-propionate, a clascoterone metabolite, was administered subcutaneously once daily (doses: 0 [saline control], 0 [vehicle control], 0.6 mg/kg/day, 1.2 mg/kg/day, and 2.4 mg/kg/day; 10/sex/group, plus 5/sex control and HD animals for 4-week recovery). No adverse cortexolone-21-propionate-related effects were noted on mortality, clinical signs, body weight, food consumption, or other in-life measures. All macroscopic or microscopic findings were either associated with needle injuries or incidental

(NOAEL: 2.4 mg/kg/day). In a GLP in vitro bacterial reverse mutation assay, cortexolone-21-propionate was not mutagenic. In a GLP in vitro chromosome aberration assay in human lymphocytes, cortexolone-21-propionate was not clastogenic.

6. Clinical Pharmacology

6.1. Executive Summary

Clascoterone (WINLEVI, also known as CB-03-01), chemically identified as cortexolone 17α-propionate, is an NME, purportedly acting as an androgen receptor inhibitor. The mechanism of action in the treatment of acne vulgaris is unknown.

- Proposed indication: For the topical treatment of acne vulgaris in subjects 9 years of age and older
- Proposed dosing regimen: Apply a thin layer of clascoterone cream, 1% (approximately 1 gram) to affected area of skin twice daily, in the morning and evening
- Proposed dosage form: Cream 1%

The Applicant evaluated the safety and efficacy of clascoterone cream, 1%, in two pivotal phase 3 trials in which clascoterone cream, 1%, was applied to the affected skin areas of the subjects with facial acne vulgaris twice daily for 12 weeks. The Applicant conducted a phase 2 dose-ranging study and an active-controlled trial (Retin-A cream 0.05%) to support the dose selection for phase 3 trials. The Applicant also submitted the results of six phase 1 trials in healthy subjects or subjects with facial acne vulgaris and the results of two pivotal PK studies under maximal use conditions in subjects 9 years of age and older with acne vulgaris to support clinical pharmacology information of clascoterone.

Key review findings with specific recommendations and comments are summarized in Table 6.

Table 6. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy is established in two pivotal phase 3 trials (CB-03-01/25 and CB-03-01/26). See section 8.1 for efficacy studies and their results.
General dosing instructions	The efficacy data from phase 3 trials support the proposed dosing regimen, i.e., topical application of clascoterone cream, 1%, twice daily to the affected areas of the skin for 12 weeks.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Therapeutic individualization based on intrinsic or extrinsic factors is not necessary due to lack of effect of age on systemic exposure and lack of drug-drug interaction concerns.
Drug interactions	The results of in vitro studies (CB-03-01/16, CB-03-01/18, and GT050709) suggest that under the conditions of clinical use, clascoterone is neither an inducer of cytochrome P450 (CYP) 1A2, 2B6, and 3A4 nor an inhibitor of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

Review Issues	Recommendations and Comments
Pediatric subjects	The PK profiles were characterized in pediatric subjects ≥9 years of age in study 171-7151-202 and study CB-03-01/28 under maximal use conditions. A partial waiver for conducting studies in patients younger than 9 years of age with acne vulgaris has been agreed to in the initial Pediatric Study Plan.
Bridge between to-be-marketed and clinical trial formulations	Any kind of bridging is not needed because the to-be-marketed formulation was used in phase 3 trials and maximal use PK studies.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable to support the approval of WINLEVI (clascoterone) cream, 1%, for the topical treatment of acne vulgaris in subjects 12 years of age and older. Approval in subjects aged 9 years to 11 years is not supported due to unfavorable benefit (lack of efficacy)/risk (an increase rate of hypothalamic-pituitary-adrenal [HPA] axis suppression) profile of this product.

6.1.2. Postmarketing Requirements and Commitment

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Mechanisms of Action

Clascoterone is an NME purportedly acting as an androgen receptor inhibitor; however, the exact mechanism of action in the treatment of acne vulgaris is unknown. The pharmacodynamic (PD) effect of clascoterone in humans has not been characterized.

6.2.1.2. Pharmacodynamics

HPA Axis Suppression

HPA axis suppression was evaluated under maximal use conditions in adults aged ≥18 years (n=20), adolescents aged 12 years to 17 years (n=22), and pediatric subjects aged 9 years to 11 years (n=27) with acne vulgaris following twice daily application of clascoterone cream, 1%, for 2 weeks. Of the 69 subjects who had a cosyntropin stimulation test (CST), seven subjects (10%) had an abnormal HPA axis response (30 minutes poststimulation serum cortisol level of ≤18 mcg/dL) at day 14, and all subjects returned to normal HPA axis function at follow-up 4 weeks after the end of treatment. There was an increase in HPA axis suppression rate with decrease in age. Specifically, the data showed that HPA axis suppression was observed in 1/20 (5%) of adult subjects, 2/22 (9%) of adolescent subjects, and 4/27 (15%) of pediatric subjects 9 years to 11 years.

Reviewer's comment: *The lack of efficacy in subjects 9 years to 11 years of age (see clinical review in section 8.1) coupled with an increase in HPA axis suppression rate with decrease in age does not support the use of this product in subjects 9 years to 11 years of age.*

Cardiac Electrophysiology

The effect of clascoterone 225 mg twice daily at steady-state on the QTc interval was evaluated in 32 healthy subjects. The results indicated that at up to 1.6-times higher systemic exposure of clascoterone compared with that observed in the maximal usage study , clascoterone did not have significant QTc prolongation effect (see QT Study Consultation Review dated November 15, 2019, in the Document Archiving, Reporting, and Regulatory Tracking System).

6.2.1.3. Pharmacokinetics

Following topical application of a mean dose of 5.7 grams or 4.7 grams of clascoterone cream, 1%, to entire face, shoulders, upper chest, and/or upper back of adult or adolescent subjects with moderate to severe acne vulgaris, respectively, every 12 hours for 14 days, steady-state clascoterone concentration was achieved by 96 hours (day 5). The PK results are summarized in Table 7. Overall, systemic clascoterone exposures were quantifiable in all subjects and were similar between adults and adolescents (Table 7). There was a small degree of accumulation (~twofold) upon repeat dosing with clascoterone cream, 1%, in adult and adolescent subjects (Table 7). In addition, the plasma concentrations of cortexolone, a possible primary metabolite of clascoterone and an endogenous substance, were generally below the lower limit of quantitation (BLQ) (0.5 ng/mL) in both adult and adolescent subjects. The PK parameters for cortexolone could not be calculated due to lack of sufficient data points.

Table 7. Pharmacokinetics of Clascoterone in Adults and Adolescents With Acne Vulgaris

	Mean (SD)								
	C_{max} (ng/mL)			AUCτ (h*ng/mL)			C_{avg} (ng/mL)		
Subjects*	D1	D14	D14/D1	D1	D14	D14/D1	D1	D14	D14/D1
Adults (n=20) (≥18 years)	3.23 (1.95)	4.46 (2.93)	1.4	22.02 (13.46)	37.14 (22.30)	1.7	1.84 (1.11)	3.10 (1.86)	1.7
Adolescents (n=22) (12to 17 years)	3.58 (4.20)	4.61 (4.63)	1.3	22.55 (22.03)	30.97 (24.06)	1.4	1.88 (1.84)	2.58 (2.00)	1.4

Abbreviations: AUCτ = area under the plasma concentration-time over the dosing interval (i.e., 0 to 12 hours), C_{avg} = the average plasma concentrations over the dosing interval, C_{max} = the maximum plasma concentration, D1 = day 1, D14 = day 14, SD = standard deviation

*Under maximal use conditions: subjects received 6 grams of WINLEVI cream per each application, except for adolescent subjects with a body surface area (BSA)<1.6m^2 who received 4 grams of WINLEVI per each application.

Source: Reviewer's summary based on clinical study report 171-7151-202

PK in Subjects 9 Years to Less Than 11 Years

Following topical application of a mean dose of 2.1 grams of clascoterone cream, 1%, to the entire face, shoulders, upper chest and upper back of pediatric subjects aged 9 years to 11 years with acne vulgaris every 12 hours for 14 days, the mean ± SD morning trough plasma concentrations of clascoterone and cortexolone on day 7 were approximately 0.58±1.01 ng/mL (range: BLQ to 4.9 ng/mL) and 0.42±0.51 ng/mL (range: BLQ to 1.4 ng/mL), respectively, with the trough concentrations of clascoterone and cortexolone being similar on day 7 and day 14.

The mean ± SD trough levels (predose) of clascoterone on day 14 (i.e., at 312 hours) in adults and adolescents were 2.22±2.30 ng/mL and 2.42±3.50 ng/mL, respectively.

6.2.1.4. Drug-Drug Interactions

In vitro, clascoterone inhibited cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or CYP3A4 with an IC_{50}>40µM. Clascoterone up to 30µM did not induce CYP 1A2, 2B6, or 3A4. These findings suggest that clascoterone cream, 1%, has no clinically meaningful effect on the PK of drugs metabolized by CYPs tested. See section 18.3 Clinical Pharmacology for details. Due to this, clinical studies evaluating the drug interaction potential of clascoterone cream, 1%, have not been conducted.

6.2.1.5. Systemic Safety—Incidence of Hyperkalemia

The purpose of a maximal usage study is to inform systemic safety. Hyperkalemia was observed in some subjects in the phase 1 and phase 2 studies. This reviewer conducted exposure-response analysis to explore whether there was any correlation between systemic exposure under maximal use conditions and incidence of hyperkalemia, and the results indicated lack of any correlation (see section 18.3 Clinical Pharmacology for details).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's proposed dosing regimen is to apply a thin layer of clascoterone cream, 1%, (approximately 1 gram) to affected area of skin twice daily, in the morning and in the evening. This dosing regimen in subjects 12 years of age and older is supported by systemic safety data from the maximal use study (171-7151-202) and efficacy and safety data from the phase 2 comparative pilot study (CB-03-01/03) and dose-ranging study (171-7151-201) and the two phase 3 pivotal trials (CB-03-01/25 and CB-03-01/26). See section 8 for efficacy and safety findings from phase 3 trials.

For subjects aged 9 to 11 years with acne vulgaris, lack of efficacy coupled with an increase in HPA axis suppression rate does not justify approval in this age range (see clinical review under sections 8 and 18.3 for details).

6.2.2.2. Therapeutic Individualization

Therapeutic individualization was not evaluated in this NDA.

6.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of clascoterone cream, 1%, in subjects 12 years of age and older from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, PK, and PD characteristics of clascoterone are summarized in Table 8.

Table 8. Summary of Clinical Pharmacology, Pharmacokinetics and Pharmacodynamics of Clascoterone

Pharmacology	
Mechanism of action	Clascoterone is an NME acting as an androgen receptor inhibitor.
Pharmacodynamics	The PD effect of clascoterone in subjects with acne vulgaris has not been characterized. HPA Axis Suppression Seven of 69 subjects ≥9 years of age (10%) had abnormal HPA axis response (30 minutes poststimulation serum cortisol level of ≤18 mcg/dL) by the end of treatment on day 14, and all subjects returned to normal HPA axis function at follow-up 4 weeks after the end of treatment. There was an increase in HPA axis suppression rate with decrease in age. Specifically, the data showed that HPA axis suppression was observed in 1/20 (5%) of adult subjects, 2/22 (9%) of adolescent subjects and in 4/27 (15%) of pediatric subjects 9 years to 11 years old. Cardiac Electrophysiology The effect of clascoterone 225 mg twice daily at steady-state on the QTc interval was evaluated in 32 healthy subjects. The results indicated that at up to 1.6-times higher systemic exposure of clascoterone compared with that observed in the maximal usage study clascoterone did not have significant QTc prolongation effect.
General Information	
Bioanalysis	Clascoterone and cortexolone (a metabolite as well as an endogenous substance) concentrations in human plasma were quantified using high-performance LC/MS/MS assays with the sensitivity of 0.25 ng/mL and 0.5 ng/mL, respectively. Clascoterone, cortexolone, and tetrahydrocortexolone (a metabolite) concentrations in human urine were quantified using validated LC/MS/MS assays with the sensitivity of 0.5 ng/mL for all of three. Cortisol in human serum was determined using the ADVIA Centaur® XP analyzers with the sensitivity of 0.5 mcg/mL (13.8 nmol/L or 0.5 mcg/dL)
PK model	The Applicant has not conducted any PK modeling and simulation analysis.
Healthy versus patients	For topical dermatological indications, the healthy subject PK data are considered exploratory and maximal use PK data are considered pivotal. Due to differences in drug application in terms of % BSA, disease state and dose, cross trial comparison of systemic exposure between healthy subject and patients is not considered a viable approach.

Drug exposure at steady state	Following topical application of a mean dose of 5.7 grams of clascoterone cream, 1%, every 12 hours to adult subjects with moderate to severe acne vulgaris, systemic exposure to clascoterone on day 1 was low with a mean ± SD of maximum plasma concentration (C_{max}) of 3.2±2.0 ng/mL, average plasma concentration (C_{avg}) of 1.8±1.1 ng/mL, and area under the plasma concentration curve over the dosing interval ($AUC_{□}$) of 22.0±13.5 ng*h/mL, associated variability was ~62%. A steady-state clascoterone concentration was achieved by 96 hours (day 5). On day 14, plasma concentrations of clascoterone increased by approximately twofold compared to the first dose with a mean ± SD C_{max} of 4.5±2.9 ng/mL, C_{avg} of 3.1±1.9 ng/mL, and $AUC_{□}$ of 37.1±22.3 ng*h/mL.
Dose proportionality	PK profile of clascoterone was independent of doses in healthy subjects at the dose range of 10 – 40 mg following single-dose topical application of clascoterone cream, 1%.
ADME	
Absorption	Following a single application of 5.7 grams clascoterone cream, 1%, to adult subjects with moderate to server acne vulgaris, the mean ± SD C_{max} and $AUC_{□}$ were estimated to be 3.2±2.0 ng/mL and 22.0±13.5 ng*h/mL, respectively, suggesting a low systemic absorption.
Distribution	Plasma protein binding of clascoterone is 84% to 89% and is independent of concentrations, in vitro.
Elimination	
Metabolism	Following topical application of clascoterone cream or solution, the plasma concentrations of cortexolone, a possible primary metabolite of clascoterone, were detectable and generally below or near the lower limit of quantitation (0.5 ng/mL) in subjects ≥9 years of age with acne vulgaris. The in vitro study indicated that incubation of 10 µmol/L clascoterone with cryopreserved hepatocytes from humans generated cortexolone and other unidentified metabolites.
Excretion	Excretion of calscoterone has not been fully characterized in humans.
Drug-drug interaction	In vitro studies suggest that clascoterone cream, 1%, has no clinically meaningful effect on the PK of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4.
Pediatric subjects	Following topical application of a mean dose of 4.7 grams of clascoterone cream, 1%, to adolescent subjects with acne vulgaris every 12 hours for 14 days, systemic exposure to clascoterone and cortexolone in adolescent subjects aged 12 years to <17 years were similar to those observed in adults under maximal use conditions. Following topical application of a mean dose of 2.1 grams of clascoterone cream, 1%,, the average steady-state trough concentrations of clascoterone in pediatric subjects 9 years to 11 years were generally lower than those observed in adults and adolescents (~0.6 ng/mL vs. ~2 ng/mL).

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; NME = new molecular entity; HPA = hypothalamic-pituitary-adrenal; LC/MS/MS = liquid chromatography with tandem mass spectrometry; PK = pharmacokinetic; BSA = body surface area

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The purpose of the pivotal clinical pharmacology studies was to assess systemic safety (i.e., determination of the adrenal suppression potential, see section 18.3 Clinical Pharmacology for details) and to evaluate the PK of clascoterone under maximal use conditions. These studies did not directly provide any efficacy data. See clinical review under section 8 for details on efficacy.

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

Based on the systemic safety under maximal use conditions and the efficacy and safety results from phase 3 trials, the proposed dosing regimen is appropriate for subjects ≥12 years of age with acne vulgaris. For subjects aged 9 years to 11 with acne vulgaris, lack of efficacy coupled with an increase rate in HPA axis suppression does not support benefit /risk profile of this product.

The mean total daily amount of clascoterone cream, 1%, used in maximal use trails in adult, adolescent, and pediatric subjects is about 5.7-fold, 4.9-fold, and 2.2-fold higher than that used in the two pivotal phase 3 trials, respectively (Table 9).

Table 9. Total Daily Amount of Clascoterone Cream 1% Evaluated in Maximal Use and Phase 3 Studies

	Daily Amount of Clascoterone Cream 1% Used (grams)		
	Mean ± SD	Range (minimum-maximum)	Clinical Study#
Maximal use studies*			
Adults aged ≥18 (n=20)	11.3±0.83	9.4 - 13.0	171-7151-202
Adolescents aged 12-17 (n=20)	9.3±2.47	3.9 - 11.9	
Pediatrics aged 9-11 (n=23)	4.2±0.80	2.3 - 6.0	CB-03-01/28
Phase 3 trials*			
Subjects aged ≥18 (n=368)	2.0±0.56	0.17 - 4.8	CB-03-01/25 CB-03-01/26
Subjects aged 12-17 (n=303)	1.9±0.56	0.25 - 4.3	
Subjects aged 9-11 (n=13)	1.9±0.44	1.27 - 2.85	

*To-be-marketed formulation was used in both phase 3 and maximal use PK studies.
Source: Reviewer's summary based on the clinical study reports

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 by the Applicant in this NDA, however this reviewer's analysis shows that the PK in adults and adolescent subjects is comparable and furthermore there are no drug-drug interaction concerns. Based on this information and efficacy and safety data from the phase 3 trials, dose adjustment will not be needed.

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

Clascoterone as a perpetrator has no clinically meaningful effect on the PK of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2E1, or 3A4 (see section 18.3 Clinical Pharmacology for details). As a victim, clascoterone was extensively metabolized to form cortexolone (an endogenous substrate) and other unidentified metabolites in vitro (see section 18.3 Clinical Pharmacology for details) and drug metabolizing enzymes involved in the metabolism of clascoterone have not been characterized yet. Food-drug interaction study is not needed for topical products.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 10. Clinical Trials in NDA 213433 Development Program

Study No./ Report Location/ No. of Sites/ Country/Dates	Study Objectives	Study Design Type of Control	Key Entry Criteria	Treatment (Number Enrolled or Randomized/Completed)	Total Subjects[a] Sex/Mean Age (Range)/Race[b]
Studies in healthy subjects					
CB-03-01/02 Module 5.3.3.1 1 site in Austria 4/9/2008 to 6/20/2008	To assess safety and tolerability and evaluate single-dose PK of CB-03-01 cream 1% versus control at increasing volumes (1, 2, or 4 mL) in healthy subjects	Phase 1, first-in-human, randomized, double-blind, placebo-controlled, single ascending dose	Healthy male subjects, 18 to 65 years	CB-03-01 cream 1%: 1 mL: 6/6 2 mL: 6/6 4 mL: 6/6 Placebo: 6/6 Single dose	24/24/24 24M 26.5 to 34.0 by cohort (18-48) White: 24
CB-03-01/04 Module 5.3.3.1 1 site in Switzerland 4/19/2010 to 5/9/2010	To evaluate 2-week repeat- dose PK of CB-03-01 cream 1% at increasing volumes (4 or 8 mL) and evaluate safety and tolerability of CB-03-01 versus placebo in healthy subjects	Phase 1, CB-03-01 on half of back, placebo on contralateral half	Healthy subjects, 18 to 65 years	CB-03-01 cream 1%: 4 mL: 12/12 8 mL: 12/12 QD (morning) for 14 days	24/24/24 12F, 12M 45.5 (18-64) White: 24
CB-03-01/05 Module 5.3.3.1 1 site in Switzerland 9/6/2010 to 11/8/2010	To evaluate potential cumulative skin irritation	Cumulative irritation study of CB-03-01 versus white petrolatum (negative control) and SLS 0.2% (positive control)	Healthy subjects, 18 to 65 years	CB-03-01 cream 1% (2 mL): 36/35 Applied to the back under occlusion QD on weekdays for 3 weeks (15 applications total)	36/36/35 12F, 24M 40.7 (19-62) White: 36

Study No./ Report Location/ No. of Sites/ Country/Dates	Study Objectives	Study Design Type of Control	Key Entry Criteria	Treatment (Number Enrolled or Randomized/Completed)	Total Subjects[a] Sex/Mean Age (Range)/Race[b]
CB-03-01/32 Module 5.3.3.1 1 site in the US 11/3/2016 to 2/24/2017	To determine potential to induce contact sensitization by repeated topical application (repeat insult patch test [RIPT])	Phase 1 RIPT of CB-03-01 versus vehicle cream and normal saline (negative control)	Healthy subjects, 18 to 65 years	CB-03-01 cream 1% (2 mL): 250/2029 applications to the back over 3 weeks under occlusion for 24-72 hours with 48-hour challenge/ rechallenge after 2-week rest	200 evaluable/ 250/202 190F, 60M 44.3 (18-65) White: 126 Black: 118 Asian: 2 Other: 4
CB-03-01/33 Module 5.3.3.1 1 site in the UK 6/6/2018 9/12/2018	To evaluate effect of CB-03-01 on QT prolongation	Phase 1, randomized, double-blind, placebo-controlled	Healthy adult (18 to 40 years) subjects	CB-03-01 solution 7.5% (3 mL): 24/23 Vehicle: 8/8 BID on days 1-3, QD on day 4	32/32/31 5F/27M 26.1 (18-38) White: 20 Black: 6 Asian: 1 Other: 5
PK and maximum use studies in subjects with acne vulgaris					
171-7151-203 Module 5.3.3.2 1 site in the US 10/23/2012 to 12/10/2012	To evaluate safety and 6-week repeat-dose PK of CB-03-01 cream 1% (6 grams daily) in subjects with acne vulgaris	Phase 1, open-label	Adults (≥18□ years) with moderate to severe acne of the face and chest/ back	CB-03-01 cream 1% (6 grams): 8/8 QD (morning) for 6 weeks	8/8/8 5F, 3M 23.6 (18-36) White: 7 Black: 1
171-7151-202 Module 5.3.3.2 3 sites in the US 5/7/2013 to 11/11/2013	Maximum use HPA/PK study to evaluate adrenal suppression potential and PK in adults and adolescents with acne vulgaris	Phase 2, open-label, sequential cohorts	Adults (≥18 years, cohort 1) and adolescents (12 to <18 years, cohort 2) with moderate to severe facial acne and obvious acne on chest/back	CB-03-01 cream 1% (6 grams or 4 grams for subjects <18 years with BSA <1.6 m^2) Adults: 20/20 Adolescents: 22/22 BID for 2 weeks	40/42/42 Cohort 1: 15F/5M 24.4 (18-41) White: 17 Black: 1 Asian: 1 Other: 1 Cohort 2: 12F/10M 15.6 (13-18) White: 21 Other: 1

Study No./ Report Location/ No. of Sites/ Country/Dates	Study Objectives	Study Design Type of Control	Key Entry Criteria	Treatment (Number Enrolled or Randomized/Completed)	Total Subjects[a] Sex/Mean Age (Range)/Race[b]
CB-03-01/28 Module 5.3.3.2 4 sites in the US, 7 sites in Poland 10/28/2016 to 3/21/2018	Maximum use HPA/PK study to evaluate adrenal suppression potential and PK in pediatric subjects with acne vulgaris	Phase 2, open-label	Pediatric subjects (9 to <12 years) with moderate to severe facial acne and obvious acne on the trunk	CB-03-01 cream 1%: 27/27 2 grams BID for 2 weeks	24/27/27 5M, 22F 10.2 (9-11) White: 25 Black: 1 Asian: 1
Active-controlled study in subjects with acne vulgaris					
CB-03-01/03 Module 5.3.5.1 4 sites in Romania 1/13/2009 to 9/1/2009	To compare safety and efficacy of CB-03-01 cream 1% versus vehicle and versus tretinoin 0.05% cream	Phase 2, randomized, double-blind, active- controlled	Adult males (18 to 45 years) with acne vulgaris of the face	CB-03-01 cream 1%: 30/27 Retin-A® 0.05% cream: 32/26 Vehicle: 15/14 QD (evening) for 8 weeks	80/77/67 Safety population (N=72): 72M 20.8 (18-29) White: 72
Vehicle-controlled studies in subjects with acne vulgaris					
171-7151-201 Module 5.3.5.1 13 sites in the US 6/11/2012 to 2/19/2014	To compare safety and efficacy of CB-03-01 cream at various concentrations and regimens versus vehicle	Phase 2, double-blind, parallel-group, vehicle-controlled, dose response	Subjects ≥12□ years old with mild to severe facial acne vulgaris (IGA Grade 2 to 4)	CB-03-01 cream 0.1% BID: 72/58 0.5% BID: 76/64 1% QD (evening): 70/61 1% BID: 70/59 Vehicle QD or BID: 75/62 Applied for 12 weeks	360/363/304 196F/167M 19.7 (12-43) White: 257 Black: 74 Asian: 16 Other: 14 (NR: 2)
CB-03-01/25 Module 5.3.5.1 45 sites in the US, 7 sites in Ukraine, 3 sites in Republic of Georgia 1/21/2016 to 4/11/2018	To determine safety and efficacy of CB-03-01 cream 1% versus vehicle cream BID for 12 weeks in subjects with facial acne vulgaris	Phase 3, multicenter, randomized, double- blind, vehicle-controlled, parallel- group	Subjects ≥9□ years old with moderate or severe facial acne vulgaris (IGA Grade 3 or 4)	CB-03-01 cream 1%: 353/287 Vehicle:355/290 BID for 12 weeks	700/708/577 436F/272M 19.9 (9-58) White: 595 Black: 69 Asian: 19 Other: 25

Study No./ Report Location/ No. of Sites/ Country/Dates	Study Objectives	Study Design Type of Control	Key Entry Criteria	Treatment (Number Enrolled or Randomized/Completed)	Total Subjects[a] Sex/Mean Age (Range)/Race[b]
CB-03-01/26 Module 5.3.5.1 12 sites in Poland, 10 sites in the US, 9 sites in Romania, 8 sites in Bulgaria, 6 sites in Republic of Georgia, 3 sites in Serbia 11/16/2015 to 2/21/2018	Same as for CB-03-01/25	Same as for CB-03-01/25	Same as for CB-03-01/25	CB-03-01 cream 1%: 369/302 Vehicle:363/282 BID for 12 weeks	700/732/584 464F/268M 19.2 (10-50) White: 705 Black: 13 Asian: 4 Other: 10
Open-label long-term study in subjects with acne vulgaris					
CB-03-01/27 Module 5.3.5.2 40 sites in the US, 11 sites in Poland, 8 sites in Romania, 6 sites in Bulgaria, 4 sites in Ukraine, 3 sites in Serbia, 3 sites in Republic of Georgia 3/9/2016 to 8/31/2018	To evaluate the 12-month long-term safety in subjects exposed to CB-03-01 cream 1% BID for up to 12 months	Phase 3, open-label, long-term follow-up	Subjects who completed study CB-03-01/25 or CB-03-01/26	CB-03-01 cream 1%: 609 BID for up to 9 months	600/609/347 381F/228M 19.2 (10-50) White: 541 Black: 35 Asian: 14 Other: 19

BID = twice daily; BSA = body surface area; CSR = clinical study report; F = female; HPA = hypothalamic-pituitary-adrenal; IGA = Investigator's Global Assessment; M = male; PK = pharmacokinetics; QD = once daily; SLS = sodium lauryl sulfate; vs = versus

Note: CB-03-01 was applied topically in all studies.

a Total subjects is shown as the number planned/randomized or enrolled (based upon study design)/completed
b "Other" includes American Indian or Alaska native, native Hawaiian or other Pacific Islander, those reported as "other," and those reported as multiple.

7.2. Review Strategy

7.2.1. Data Sources

The data sources used for the evaluation of the efficacy and safety of clascoterone cream, 1%, included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in the Electronic Common Technical Document format and was entirely electronic. Both Study Data Tabulation Model datasets and Analysis Data Model (ADaM) datasets were submitted. The analysis datasets used in this review are archived at Application 213433–Sequence 0001–Analysis Data.

7.2.2. Data and Analysis Quality

The statistical and clinical teams evaluated data fitness. The databases for the study required minimal data management before performing analyses. In general, the data submitted by the Applicant to support the safety and efficacy of clascoterone cream, 1%, for the proposed indication appeared adequate. The finalized Statistical Analysis Plans were submitted to the Agency; they are discussed in more detail in section 8.1.2 of this review.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

The Applicant conducted two phase 3 trials (CB-03-01/25 and CB-03-01/26). Both were identically-designed, randomized, multicenter, double-blind, vehicle-controlled, parallel-group trials to investigate the safety and efficacy of WINLEVI (clascoterone) cream, 1%, for the treatment of moderate to severe acne vulgaris. For enrollment, the protocols specified the following key inclusion criteria:

- Male or female, 9 years of age or older
- IGA score of 3 (moderate) or 4 (severe), see Table 11 for details on the IGA scale
- 30 to 75 inflammatory lesions (papules, pustules, and nodules)
- 30 to 100 noninflammatory lesions (open and closed comedones)
- No more than two facial nodules

Each trial was designed to enroll and randomize approximately 700 subjects in a 1:1 ratio to receive either WINLEVI cream (n=350) or vehicle cream (n=350). Subjects applied study product to the face twice daily for 12 weeks. Subjects were scheduled to be evaluated at the following four visits: baseline (day 1), and week 4, week 8, and week 12.

The protocols specified the following coprimary efficacy endpoints:

- Proportion of subjects achieving IGA success at week 12, with success defined as an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-point reduction from baseline
- Absolute change from baseline in noninflammatory lesion counts at week 12
- Absolute change from baseline in inflammatory lesion counts at week 12

The protocols specified the following secondary efficacy endpoints:

- Absolute change from baseline in total lesion counts (inflammatory and noninflammatory) at week 12
- Percent change from baseline in total lesion counts (inflammatory and noninflammatory) at week 12
- Percent change from baseline in noninflammatory lesion counts at week 12
- Percent change from baseline in inflammatory lesion counts at week 12

Table 11. Investigator Global Assessment (IGA) Scale

Score	Grade	Definition
0	Clear	Absence of active disease with no inflammatory or noninflammatory lesions.
1	Almost clear	Rare noninflammatory lesions with no more than one small inflammatory lesions.
2	Mild	Some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only; no nodular/cystic lesions).
3	Moderate	Up to many noninflammatory lesions and may have some inflammatory lesions but no more than one nodular/cystic lesion.
4	Severe	Up to many noninflammatory lesions and inflammatory lesions but no more than a few nodular/cystic lesions.

Source: Page 27 of the protocol

8.1.2. Statistical Methodologies

The protocol-specified primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocols also specified conducting supportive analyses using the per-protocol (PP) population. The PP population was defined as all subjects in the ITT population who complete the study without any significant protocol deviations. The statistical analysis plan specified that subjects will be excluded from the PP population if they meet any of the following criteria:

- Lack of compliance to the test article (subjects with an overall compliance not evaluable due to missing data or less than 80%)
- Exposure to a test article different from the one assigned to the subject
- Lack of the primary variables assessments at baseline or at week 12
- Failure to satisfy any inclusion/exclusion criteria (eligibility violations)
- Intake of prohibited medications.

The protocols specified that the trials were to be conducted in such a manner as to have a minimum of eight ITT subjects in each treatment group at each center. Centers that did not meet this minimum were specified to be combined. The protocols specified combining centers

based on geographical and climatic similarities. The sequence of combination was specified to be based on the total number of subjects enrolled in each center (combining the lowest with the second lowest, and so on). These combined centers, as well as individual centers with sufficient subjects per treatment group, are then referred to as "analysis centers."

For the analysis of binary efficacy endpoints, protocols specified using logistic regression with treatment group and analysis center as factors in the model. The protocols specified analyzing continuous efficacy endpoints using analysis of covariance with treatment group, baseline value, and analysis center as factors in the model.

The protocols specified using a sequential gatekeeping approach to control the Type I error rate for testing multiple secondary efficacy endpoints. The protocols specified that the secondary efficacy endpoints would be tested only if all three coprimary efficacy endpoints were statistically significant at the 0.05. The protocols specified analyzing the secondary efficacy endpoints in the order specified in section 8.1.1.

The protocols specified primary method for handling missing data were the multiple imputation approach. Missing data were imputed 10 times using the Markov Chain Monte Carlo method. The protocol specified using the following methods as sensitivity analyses for the handling of missing data:

- Missing as Worst Value: missing data imputed as the worst value (failure for binary endpoints and highest value observed for the respective lesion count) regardless of the treatment arm.
- Worst Case: missing data for subjects in the WINLEVI group is imputed as the worst value (failure for binary endpoints and highest observed for the respective lesion count). Missing data for subjects in the vehicle group is imputed as the best value (success for binary endpoints and lowest value for the respective lesion count).
- Last Observation Carried Forward
- Baseline Observation Carried Forward

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Study CB-03-01/25 enrolled and randomized 708 subjects (353 to WINLEVI and 355 to vehicle) from 55 centers (45 in United States, 7 in Ukraine, and 3 in Republic of Georgia). Study CB-03-01/26 enrolled and randomized 732 subjects (369 to WINLEVI and 363 to vehicle) from 48 centers (10 in United States, 12 in Poland, 9 in Romania, 6 in Bulgaria, 6 in Republic of Georgia, and 3 in Serbia). Table 12 presents the disposition of subjects for study CB-03-01/25 and study CB-03-01/26. The discontinuation rates were generally similar between the two treatment groups in study CB-03-01/25; however, the discontinuation rate for the vehicle group was slightly higher compared to WINLEVI group in study CB-03-01/26.

Table 12. Disposition of Subjects

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=353)	Vehicle (N=355)	WINLEVI (N=369)	Vehicle (N=363)
Discontinued, n (%)	66 (18.7)	65 (18.3)	67 (18.2)	81 (22.3)
Adverse event	3 (0.8)	6 (1.7)	2 (0.5)	8 (2.2)
Lack of efficacy	0	3 (0.8)	3 (0.8)	1 (0.3)
Lost to follow-up	39 (11.0)	32 (9.0)	24 (6.5)	24 (6.6)
Noncompliance with study drug	0	2 (0.6)	1 (0.3)	5 (1.4)
Other	0	2 (0.6)	0	1 (0.3)
Physician decision	0	1 (0.3)	1 (0.3)	0
Pregnancy	0	1 (0.3)	0	1 (0.3)
Progressive disease	1 (0.3)	0	1 (0.3)	0
Withdrawal by parent/guardian	2 (0.6)	3 (0.8)	5 (1.4)	4 (1.1)
Withdrawal by subject	21 (5.9)	15 (4.2)	30 (8.1)	37 (10.2)

Intent-to-treat population: All randomized subjects.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)

The demographics and baseline disease characteristics for study CB-03-01/25 and study CB-03-01/26 are presented in Table 13. The demographics were generally balanced across the treatment groups within each trial and were similar in terms of age and sex between the two trials. Study CB-03-01/26 had a slightly higher proportion of subjects identify as white compared to study CB-03-01/25. The baseline disease characteristics were generally balanced across the treatment groups within each trial and were similar between the two trials.

Table 13. Demographics and Baseline Disease Characteristics

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=353)	Vehicle (N=355)	WINLEVI (N=369)	Vehicle (N=363)
Age (years)				
Mean (SD)	20.0 (6.7)	19.9 (6.8)	19.3 (5.6)	19.0 (5.4)
Median	18.0	18.0	18.0	18.0
Range	10 to 58	9 to 50	10 to 50	11 to 42
Categories, n (%)				
9 to 11	11 (3.1)	5 (1.4)	2 (0.5)	1 (0.3)
12 to 17	146 (41.4)	154 (43.4)	170 (46.1)	171 (47.1)
≥18	196 (55.5)	196 (55.2)	197 (53.4)	191 (52.6)
Sex, n (%)				
Male	132 (37.4)	140 (39.4)	126 (34.1)	142 (39.1)
Female	221 (62.6)	215 (60.6)	243 (65.9)	221 (60.9)
Race, n (%)				
White	298 (84.4)	297 (83.7)	357 (96.7)	348 (95.9)
Black or African American	31 (8.8)	38 (10.7)	7 (1.9)	6 (1.7)
Asian	9 (2.5)	10 (2.8)	0	4 (1.1)
Multiple	9 (2.5)	7 (2.0)	0	1 (0.3)
Other	6 (1.7)	3 (0.8)	5 (1.4)	4 (1.1)
IGA score, n (%)				
3 – Moderate	292 (82.7)	291 (82.0)	305 (82.7)	313 (86.2)
4 – Severe	61 (17.3)	64 (18.0)	64 (17.3)	50 (13.8)
Inflammatory lesion counts				
Mean (SD)	42.4 (11.8)	42.9 (12.3)	42.9 (12.2)	41.3 (11.0)
Median	38.0	39.0	39.0	37.0
Range	30 to 83	30 to 75	30 to 75	30 to 74

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=353)	Vehicle (N=355)	WINLEVI (N=369)	Vehicle (N=363)
Noninflammatory lesion counts				
Mean (SD)	59.1 (22.2)	60.7 (22.1)	62.8 (21.4)	63.3 (20.5)
Median	53.0	57.0	61.0	63.0
Range	30 to 100	30 to 144	30 to 177	30 to 100

Intent-to-treat population: All randomized subjects
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)

8.1.4. Results of Coprimary Efficacy Endpoints

Table 14 presents the results of the coprimary efficacy endpoints for the ITT population. For both trials, WINLEVI cream was statistically superior to vehicle cream on all coprimary endpoints (p-values ≤0.003). The treatment effect was larger in study CB-03-01/26 compared to study CB-03-01/25. The results in the PP population (not shown) were similar to those in the ITT population.

Table 14. Results of the Coprimary Efficacy Endpoints at Week 12 (ITT[1])

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=353)	Vehicle (N=355)	WINLEVI (N=369)	Vehicle (N=363)
IGA success[2]				
Proportion	17.7%	8.6%	20.4%	6.5%
Adjusted proportion[3]	18.8%	8.9%	20.8%	6.5%
Difference (95% CI)	9.9% (4.0%, 15.7%)		14.3% (8.9%, 19.7%)	
P-value[3]	<0.001		<0.001	
Absolute change from baseline in inflammatory lesion counts				
Mean	-19.7	-15.9	-20.2	-12.0
LS mean[4]	-19.4	-15.5	-20.0	-12.6
Difference (95% CI)	-3.9 (-6.5, -1.3)		-7.4 (-9.8, -5.0)	
P-value[4]	0.003		<0.001	
Absolute change from baseline in noninflammatory lesion counts				
Mean	-19.3	-13.4	-19.8	-11.3
LS mean[4]	-19.4	-13.1	-19.4	-10.9
Difference (95% CI)	-6.3 (-10.2, -2.4)		-8.4 (-12.4, -4.5)	
P-value[4]	0.002		<0.001	

Abbreviations: ITT = intent-to-treat; IGA = Investigator's Global Assessment; CI = confidence interval; LS = least square
[1] ITT population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Success is defined as an Investigator's Global Assessment score of 0 or 1 and at least a 2-grade reduction from baseline.
[3] Adjusted proportion and p-value are based on a logistic regression model with treatment and analysis center as fixed effects.
[4] Least square mean and p-value are based on analysis of covariance with treatment and analysis center as fixed effects, and baseline value as a covariate.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)

Table 15 presents the number of subjects with missing data for the coprimary endpoints along with the results of the coprimary endpoints across the various prespecified imputation methods for the handling of missing data. For IGA success, the results were generally similar across the various methods except under the worst-case scenario, which had the response rate in the

placebo group being greater than the WINLEVI group in both trials. However, as the placebo response rate for completers was 8.5% in study CB-03-01/25 and 5.4% in study CB-03-01/26, it is not reasonable to assume all subjects who discontinued placebo would have been successes if they did not discontinue.

For absolute change in inflammatory and noninflammatory lesion counts, the results were generally similar across the various methods except under the worst value and worst-case scenarios. The worst value for inflammatory lesion counts at week 12 was 161 for study CB-03-01/25 and 99 for study CB-03-01/26. The worst value for noninflammatory lesion counts at week 12 was 213 for study CB-03-01/25 and 261 for study CB-03-01/26. Using these worst values, all subjects in the WINLEVI group with missing week 12 data are assumed to have increased from baseline in inflammatory lesions (i.e., increase of ≥78 for study CB-03-01/25 and ≥24 for study CB-03-01/26) and increased from baseline in noninflammatory lesions (i.e., increase of ≥69 for study CB-03-01/25 and ≥84 for study CB-03-01/26). Given the mean changes for the placebo completers, it is not reasonable to assume that all subjects in the WINLEVI group with missing data increased in lesion counts and increased by such large values.

Table 15. Results of the Coprimary Efficacy Endpoints at Week 12 With Different Approaches for Handling Missing Data

	Study CB-03-01/25			Study CB-03-01/26		
	WINLEVI (N=353)	Vehicle (N=355)	Difference (P-Value)	WINLEVI (N=369)	Vehicle (N=363)	Difference (P-Value)
Subjects With Missing Data	51 (14.4%)	45 (12.7%)		41 (11.1%)	53 (14.6%)	
IGA success[1, 2]						
MI (primary)	18.8%	8.9%	9.9% (<0.001)	20.8%	6.5%	14.3% (<0.001)
Observed	20.5%	8.5%	12.0% (<0.001)	21.3%	5.4%	15.8% (<0.001)
LOCF	17.0%	7.2%	9.8% (<0.001)	18.5%	4.6%	13.9% (<0.001)
BOCF	17.0%	7.2%	9.8% (<0.001)	18.5%	4.6%	13.9% (<0.001)
Worst value	17.0%	7.2%	9.8% (<0.001)	18.5%	4.6%	13.9% (<0.001)
Worst case	17.3%	21.2%	-3.9% (0.2159)	19.7%	20.4%	-0.7% (0.8295)
Absolute change in inflammatory lesion counts[3]						
MI (primary)	-19.4	-15.5	-3.9 (0.0029)	-20.0	-12.6	-7.4 (<0.001)
Observed	-19.8	-15.0	-4.8 (<0.001)	-20.8	-12.5	-8.3 (<0.001)
LOCF	-18.2	-14.4	-3.9 (0.0018)	-19.8	-11.1	-8.7 (<0.001)
BOCF	-17.0	-13.3	-3.7 (0.0037)	-18.6	-10.7	-7.9 (<0.001)
Worst value	-1.2	0.4	-1.6 (0.6508)	-12.1	-2.7	-9.4 (<0.001)
Worst case	-0.8	-19.4	18.6 (<0.001)	-11.9	-17.1	5.3 (0.0033)
Absolute change in noninflammatory lesion counts[3]						
MI (primary)	-19.4	-13.1	-6.3 (0.0016)	-19.4	-10.9	-8.4 (<0.001)
Observed	-20.0	-13.2	-6.8 (<0.001)	-20.4	-10.9	-9.5 (<0.001)
LOCF	-18.6	-12.1	-6.5 (<0.001)	-19.0	-9.8	-9.2 (<0.001)
BOCF	-17.4	-11.6	-5.8 (0.0016)	-18.2	-8.9	-9.3 (<0.001)
Worst value	3.5	6.4	-3.0 (0.5227)	3.2	18.9	-15.7 (0.0049)
Worst case	4.2	-19.7	23.9 (<0.001)	3.9	-19.0	22.9 (<0.001)

Abbreviations: IGA = Investigator's Global Assessment; MI = multiple imputation; LOCF = last observation carried forward; BOCF = baseline observation carried forward
[1] Success is defined as an Investigator's Global Assessment (IGA) score of 0 or 1 and at least a 2-grade reduction from baseline.
[2] Proportions and p-values are based on a logistic regression model with treatment and analysis center as fixed effects.
[3] Least square means and p-values are based on analysis of covariance with treatment and analysis center as fixed effects, and baseline value as a covariate.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)

8.1.5. Results of Secondary Efficacy Endpoints

Table 16 presents the results of the secondary efficacy endpoints for the ITT population. For both trials, WINLEVI cream was statistically superior to vehicle cream on all secondary efficacy endpoints (p-values ≤0.014). The results in the PP population (not shown) were similar to those in the ITT population.

Table 16. Results of the Secondary Efficacy Endpoints at Week 12 (ITT[1])

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=353)	Vehicle (N=355)	WINLEVI (N=369)	Vehicle (N=363)
Absolute change from baseline in total lesion counts				
Mean	-39.2	-29.4	-40.8	-23.6
LS mean[2]	-39.2	-28.9	-40.3	-23.7
Difference (95% CI)	-10.3 (-15.7, -5.0)		-16.6 (-22.0, -11.1)	
P-value[2]	<0.001		<0.001	
Percent change from baseline in total lesion counts				
Mean	-37.5%	-28.6%	-38.2%	-22.1%
LS mean[2]	-37.1%	-28.5%	-37.7%	-22.2%
Difference (95% CI)	-8.7% (-14.0%, -3.3%)		-15.6% (-20.9%, -10.3%)	
P-value[2]	0.002		<0.001	
Percent change from baseline in inflammatory lesion counts				
Mean	-45.7%	-37.0%	-46.7%	-29.0%
LS mean[2]	-44.8%	-36.6%	-47.0%	-29.8%
Difference (95% CI)	-8.3% (-14.3%, -2.3%)		-17.2% (-22.9%, -11.5%)	
P-value[2]	0.007		<0.001	
Percent change from baseline in noninflammatory lesion counts				
Mean	-30.9%	-21.8%	-30.2%	-16.2%
LS mean[2]	-30.7%	-21.9%	-29.3%	-15.8%
Difference (95% CI)	-8.8% (-15.9%, -1.8%)		-13.5% (-19.8%, -7.1%)	
P-value[2]	0.014		<0.001	

Abbreviations: ITT = intent to treat; LS = least square; CI = confidence interval
[1] ITT population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Least square mean and p-value are based on analysis of covariance with treatment and analysis center as fixed effects, and baseline value as a covariate.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis)

8.1.6. Efficacy Results in Subjects ≥12 Years of Age

The results of the coprimary and secondary efficacy endpoints at week 12 for subjects ≥12 years of age are presented in Table 17 and Table 18, respectively. These results are very similar to those in the overall population (see Table 14 and Table 16) as the number of excluded subjects is small (16 subjects in study CB-03-01/25 and 3 subjects in study CB-03-01/26).

Table 17. Results of the Coprimary Efficacy Endpoints at Week 12 in Subjects ≥12 Years of Age (ITT[1])

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=342)	Vehicle (N=350)	WINLEVI (N=367)	Vehicle (N=362)
IGA success[2]				
Proportion	17.7%	8.5%	20.5%	6.5%
Adjusted proportion[3]	18.8%	8.7%	20.9%	6.6%
Difference (95% CI)	10.1% (4.1%, 16.0%)		14.3% (8.9%, 19.7%)	
P-value[3]	<0.001		<0.001	
Absolute change from baseline in inflammatory lesion counts				
Mean	-19.6	-15.7	-20.3	-12.0
LS Mean[4]	-19.3	-15.4	-20.1	-12.6
Difference (95% CI)	-3.9 (-6.5, -1.3)		-7.5 (-9.9, -5.2)	
P-Value[4]	0.003		<0.001	
Absolute change from baseline in noninflammatory lesion counts				
Mean	-20.2	-13.3	-19.9	-11.1
LS mean[4]	-20.4	-13.0	-19.5	-10.8
Difference (95% CI)	-7.3 (-11.1, -3.5)		-8.7 (-12.6, -4.7)	
P-value[4]	<0.001		<0.001	

Abbreviations: ITT = intent to treat; IGA = Investigator's Global Assessment; CI = confidence interval; LS = least square
[1] ITT population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Success is defined as an Investigator's Global Assessment score of 0 or 1 and at least a 2-grade reduction from baseline.
[3] Adjusted proportion and p-value are based on a logistic regression model with treatment and analysis center as fixed effects.
[4] Least square mean and p-value are based on analysis of covariance with treatment and analysis center as fixed effects, and baseline value as a covariate.
Source: Statistical Reviewer's Analysis

Table 18. Results of the Secondary Efficacy Endpoints at Week 12 in Subjects ≥12 Years of Age (ITT[1])

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=342)	Vehicle (N=350)	WINLEVI (N=367)	Vehicle (N=362)
Absolute change from baseline in total lesion counts				
Mean	-40.0	-29.1	-41.0	-23.4
LS mean[2]	-40.0	-28.6	-40.5	-23.6
Difference (95% CI)	-11.4 (-16.8, -6.0)		-16.9 (-22.4, -11.4)	
P-value[2]	<0.001		<0.001	
Percent change from baseline in total lesion counts				
Mean	-38.5%	-28.3%	-38.4%	-22.0%
LS Mean[2]	-38.1%	-28.3%	-38.0%	-22.1%
Difference (95% CI)	-9.8% (-15.2%, -4.4%)		-15.9% (-21.2%, -10.6%)	
P-value[2]	<0.001		<0.001	

	Study CB-03-01/25		Study CB-03-01/26	
	WINLEVI (N=342)	Vehicle (N=350)	WINLEVI (N=367)	Vehicle (N=362)
Percent change from baseline in inflammatory lesion counts				
Mean	-45.5%	-36.7%	-46.9%	-28.9%
LS mean[2]	-44.6%	-36.3%	-47.1%	-29.7%
Difference (95% CI)	-8.3% (-14.4%, -2.2%)		-17.5% (-23.1%, 11.8%)	
P-value[2]	0.008		<0.001	
Percent change from baseline in noninflammatory lesion counts				
Mean	-32.6%	-21.6%	-30.4%	-16.1%
LS mean[2]	-32.6%	-21.8%	-29.6%	-15.7%
Difference (95% CI)	-10.8% (-17.6%, -3.9%)		-13.8% (-20.2%, -7.5%)	
P-value[2]	0.002		<0.001	

Abbreviations: ITT = intent to treat; LS = least square; CI = confidence interval
[1] ITT population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Least square mean and p-value are based on analysis of covariance with treatment and analysis center as fixed effects, and baseline value as a covariate
Source: Statistical Reviewer's Analysis

8.1.7. Findings in Special/Subgroup Populations

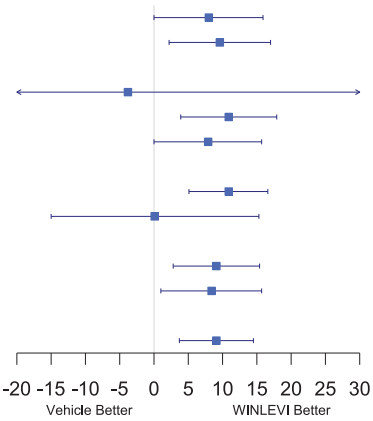
8.1.7.1. Sex, Age, Race, and Baseline IGA Score

The results for IGA success at week 12 by sex, age, race, and baseline IGA score for study CB-03-01/25 and study CB-03-01/26 are presented in Table 19 and Table 20, respectively. The results for absolute change in inflammatory and noninflammatory lesion counts at week 12 by sex, age, race, and baseline IGA score for study CB-03-01/25 and study CB-03-01/26 are presented in Table 21, Table 22, Table 23, and Table 24, respectively.

In both trials, a beneficial treatment effect was not observed in the youngest subgroup (subjects 9 years to 11 years of age); however, this may be attributed to the very small size of this subgroup (16 subjects in study CB-03-01/25, 3 subjects in study CB-03-01/26). In study CB-03-01/25, non-white subjects in the vehicle group had a larger decrease in inflammatory lesions than the non-white subjects in the WINLEVI group. In study CB-03-01/26, non-white subjects in the vehicle group had a higher IGA success rate than non-white subjects in the WINLEVI group; however, this effect was not observed in inflammatory and noninflammatory lesions. The observation of reversed treatment effect on IGA success for non-white subjects in study CB-03-01/26 may be attributed to chance due to the small size of the subgroup (27 subjects).

Table 19. IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA Score for Study CB-03-01/25 [ITT[1]]

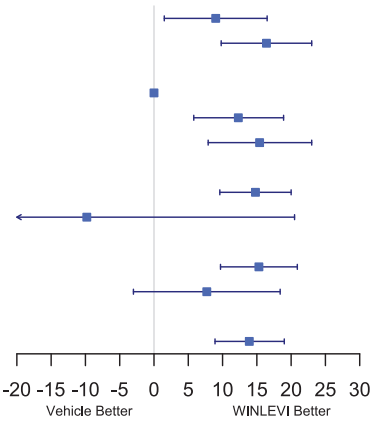
Subgroups (n[W], n[V])	WINLEVI (N=353)	Vehicle (N=355)	Difference	Difference (95% CI)
Sex				
Males (132, 140)	13.6%	5.6%	8.0%	
Females (221, 215)	20.2%	10.6%	9.6%	
Age (years)				
9-11 (11, 5)	18.2%	22.0%	-3.8%	
12-17 (146, 154)	14.8%	3.9%	10.9%	
18+ (196, 196)	19.9%	12.0%	7.9%	
Race				
White (298, 297)	17.4%	6.6%	10.9%	
Non-White (55, 58)	19.5%	19.3%	0.1%	
Baseline IGA				
3 - Moderate (292, 291)	19.7%	10.5%	9.1%	
4 - Severe (61, 64)	8.5%	0.2%	8.4%	
Overall	17.7%	8.6%	9.1%	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.

Table 20. IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA Score for Study CB-03-01/26 [ITT[1]]

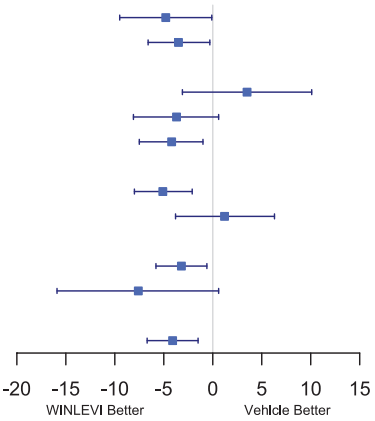
Subgroups (n[W], n[V])	WINLEVI (N=369)	Vehicle (N=363)	Difference	Difference (95% CI)
Sex				
Males (126, 142)	14.8%	5.8%	9.0%	
Females (243, 221)	23.3%	6.9%	16.4%	
Age (years)				
9-11 (2, 1)	0%	0%	0%	
12-17 (170, 171)	17.0%	4.7%	12.3%	
18+ (197, 191)	23.6%	8.1%	15.4%	
Race				
White (357, 348)	20.8%	6.0%	14.8%	
Non-White (12, 15)	7.5%	17.3%	-9.8%	
Baseline IGA				
3 - Moderate (305, 313)	22.0%	6.7%	15.3%	
4 - Severe (64, 50)	12.7%	5.0%	7.7%	
Overall	20.4%	6.5%	13.9%	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.

Table 21. Absolute Change From Baseline in Inflammatory Lesion Counts at Week 12 by Sex, Age, Race, and Baseline IGA Score for Study CB-03-01/25 [ITT[1]]

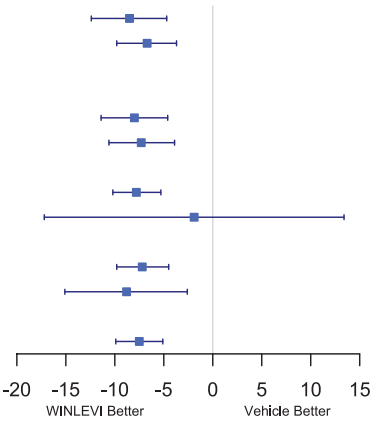
Subgroups (n[W], n[V])	WINLEVI (N=353)	Vehicle (N=355)	Difference	Difference (95% CI)
Sex				
Males (132, 140)	-18.4	-13.6	-4.8	
Females (221, 215)	-20.6	-17.1	-3.5	
Age (years)				
9-11 (11, 5)	-22.4	-25.9	3.5	
12-17 (146, 154)	-18.3	-14.6	-3.7	
18+ (196, 196)	-20.7	-16.4	-4.2	
Race				
White (298, 297)	-19.3	-14.2	-5.1	
Non-White (55, 58)	-22.3	-23.5	1.2	
Baseline IGA				
3 - Moderate (292, 291)	-20.3	-17.2	-3.2	
4 - Severe (61, 64)	-17.0	-9.4	-7.6	
Overall	-19.8	-15.7	-4.1	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as a fixed effect, and baseline value as a covariate.

Table 22. Absolute Change From Baseline in Inflammatory Lesion Counts at Week 12 by Sex, Age, Race, and Baseline IGA Score for Study CB-03-01/26 [ITT[1]]

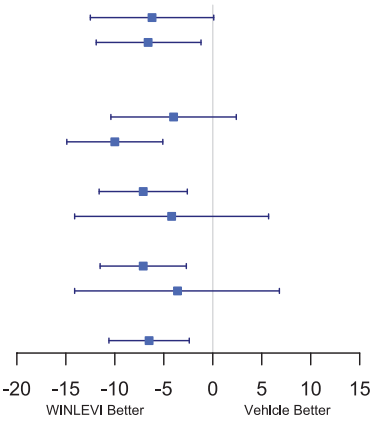
Subgroups (n[W], n[V])	WINLEVI (N=369)	Vehicle (N=363)	Difference	Difference (95% CI)
Sex				
Males (126, 142)	-19.9	-11.3	-8.5	
Females (243, 221)	-19.9	-13.1	-6.7	
Age (years)				
9-11 (2, 1)	-10.5	-33.1	22.6	
12-17 (170, 171)	-18.3	-10.4	-8.0	
18+ (197, 191)	-21.4	-14.1	-7.3	
Race				
White (357, 348)	-20.0	-12.2	-7.8	
Non-White (12, 15)	-17.5	-15.6	-1.9	
Baseline IGA				
3 - Moderate (305, 313)	-19.4	-12.2	-7.2	
4 - Severe (64, 50)	-22.4	-13.6	-8.8	
Overall	-19.9	-12.4	-7.5	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as a fixed effect, and baseline value as a covariate.

Table 23. Absolute Change From Baseline in Noninflammatory Lesion Counts at Week 12 by Sex, Age, Race, and Baseline IGA Score for Study CB-03-01/25 [ITT[1]]

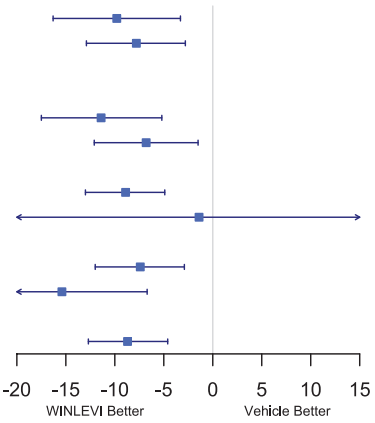
Subgroups (n[W], n[V])	WINLEVI (N=353)	Vehicle (N=355)	Difference	Difference (95% CI)
Sex				
Males (132, 140)	-16.2	-10.0	-6.2	
Females (221, 215)	-21.6	-15.1	-6.6	
Age (years)				
9-11 (11, 5)	8.0	-18.8	26.8	
12-17 (146, 154)	-15.5	-11.5	-4.0	
18+ (196, 196)	-24.2	-14.2	-10.0	
Race				
White (298, 297)	-19.3	-12.2	-7.1	
Non-White (55, 58)	-21.7	-17.5	-4.2	
Baseline IGA				
3 - Moderate (292, 291)	-21.2	-14.2	-7.1	
4 - Severe (61, 64)	-11.8	-8.2	-3.6	
Overall	-19.6	-13.1	-6.5	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as a fixed effect, and baseline value as a covariate.

Table 24. Absolute Change From Baseline in Noninflammatory Lesion Counts at Week 12 by Sex, Age, Race, and Baseline IGA Score for Study CB-03-01/26 [ITT[1]]

Subgroups (n[W], n[V])	WINLEVI (N=369)	Vehicle (N=363)	Difference	Difference (95% CI)
Sex				
Males (126, 142)	-17.7	-7.9	-9.8	
Females (243, 221)	-21.1	-13.3	-7.8	
Age (years)				
9-11 (2, 1)	5.3	-60.6	65.9	
12-17 (170, 171)	-18.6	-7.2	-11.4	
18+ (197, 191)	-21.3	-14.4	-6.8	
Race				
White (357, 348)	-19.9	-10.9	-8.9	
Non-White (12, 15)	-19.1	-17.7	-1.4	
Baseline IGA				
3 - Moderate (305, 313)	-19.2	-11.8	-7.4	
4 - Severe (64, 50)	-22.9	-7.4	-15.4	
Overall	-19.9	-11.2	-8.7	

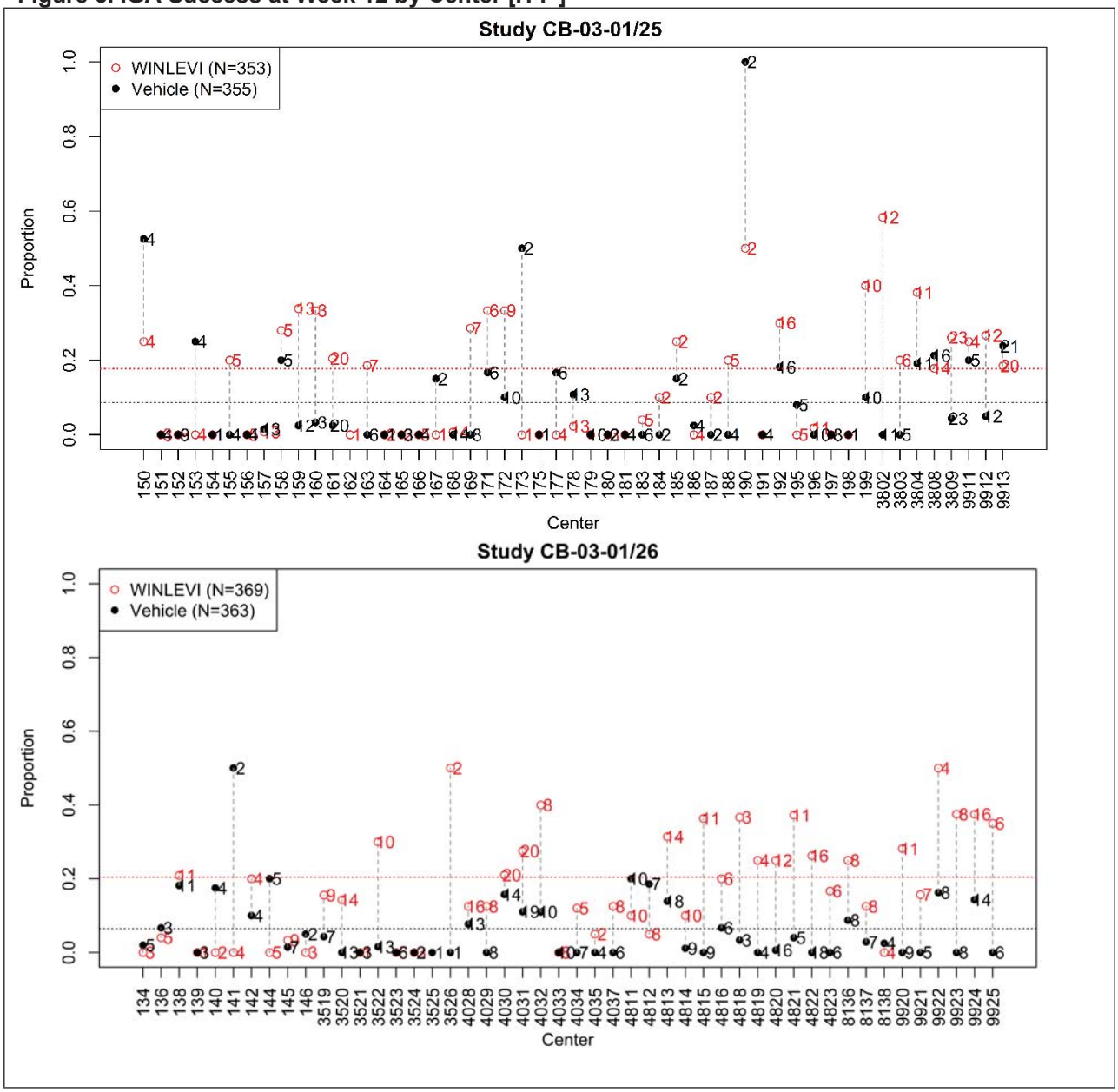


Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as a fixed effect, and baseline value as a covariate.

8.1.7.2. Center and Country

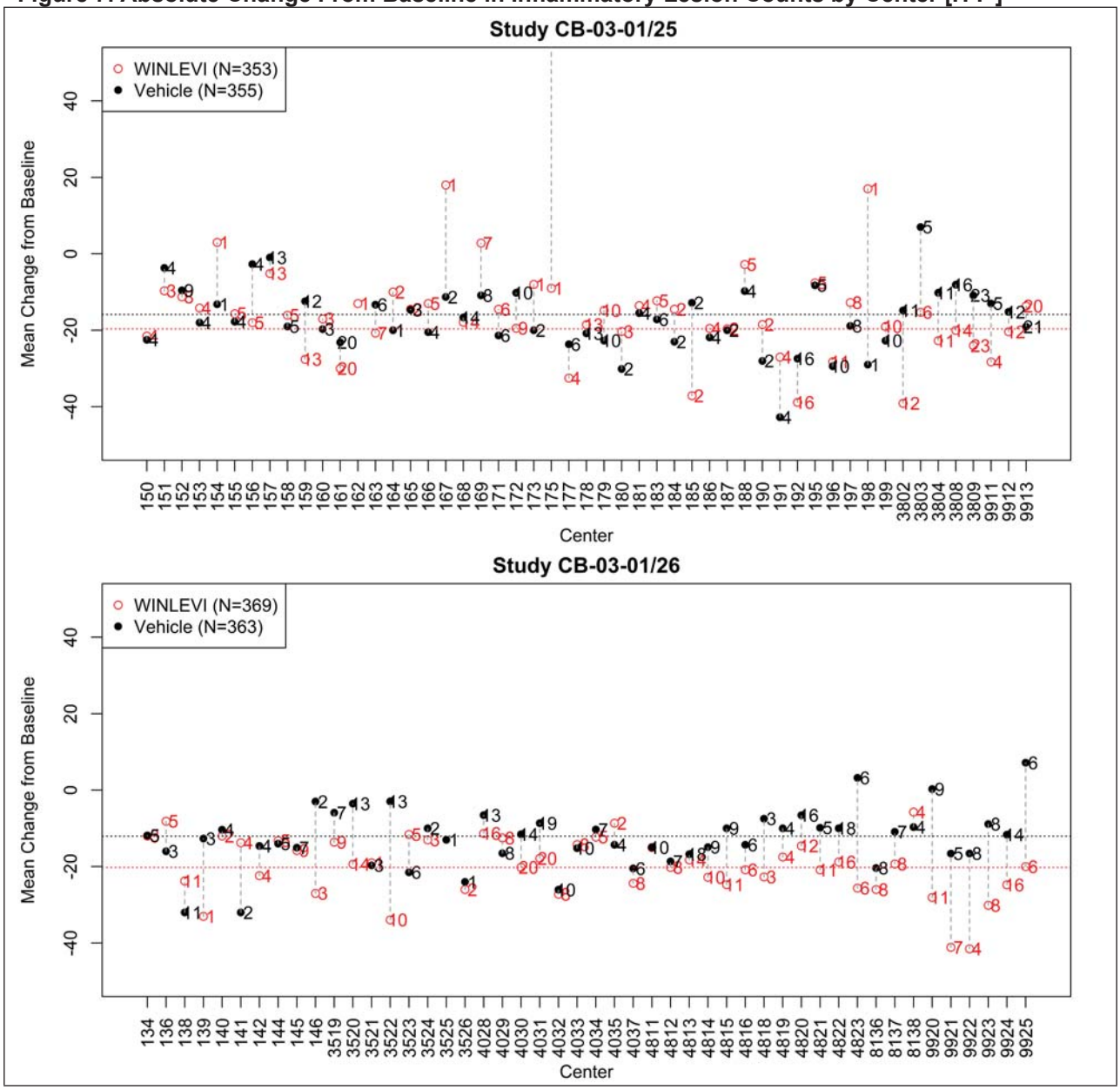
Study CB-03-01/25 enrolled and randomized 708 subjects from 55 centers (45 in United States, 7 in Ukraine, and 3 in Republic of Georgia). Study CB-03-01/26 enrolled and randomized 732 subjects from 48 centers (10 in United States, 12 in Poland, 9 in Romania, 8 in Bulgaria, 6 in Republic of Georgia, and 3 in Serbia). The results for the coprimary efficacy endpoints for both trials are presented in Figure 6, Figure 7, and Figure 8. In both trials, efficacy results varied across centers. Some centers had higher efficacy with vehicle than with WINLEVI. It does not appear that any single center drove the overall efficacy results.

Figure 6. IGA Success at Week 12 by Center [ITT[1]]



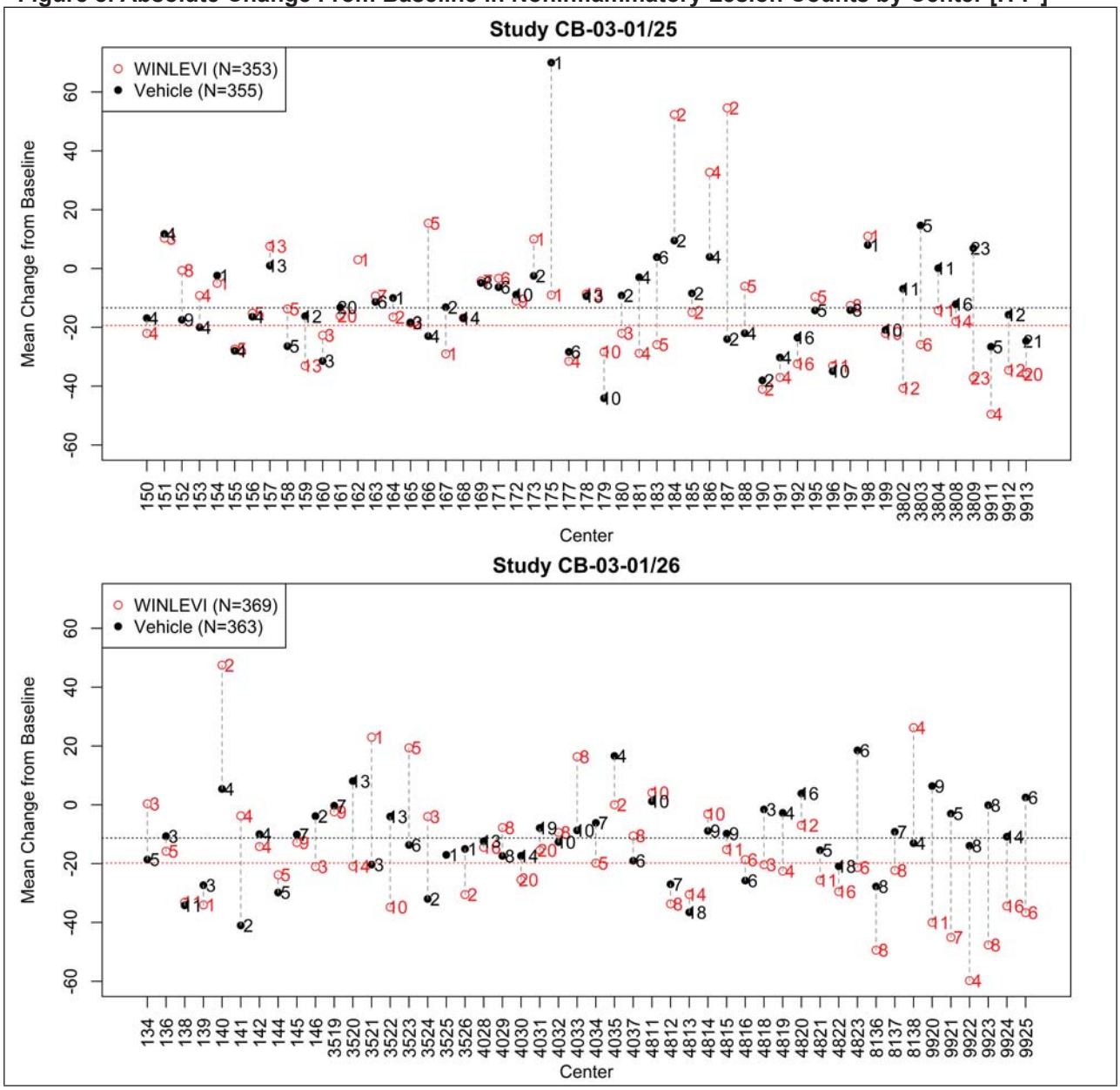
Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Dotted horizontal line denotes the overall result for each treatment group (red for WINLEVI and black for vehicle)

Figure 7. Absolute Change From Baseline in Inflammatory Lesion Counts by Center [ITT[1]]



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Dotted horizontal line denotes the overall result for each treatment group (red for WINLEVI and black for vehicle).
[3] For study CB-03-01/25, one subject in Center #175 is outside the bounds of the figure. This subject was treated with vehicle and had an increase of 122 inflammatory lesions.

Figure 8. Absolute Change From Baseline in Noninflammatory Lesion Counts by Center [ITT[1]]



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Dotted horizontal line denotes the overall result for each treatment group (red for WINLEVI and black for vehicle).

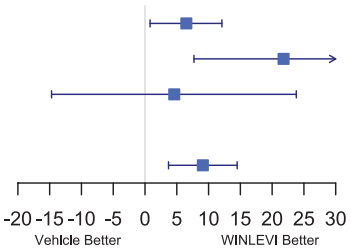
Table 25, Table 26, and Table 27 present the results of the coprimary efficacy endpoints by country for study CB-03-01/25. Table 28, Table 29, and Table 30 present the results of the coprimary efficacy endpoints by country for study CB-03-01/26. Approximately 71% and 13% of the subjects were from the United States in study CB-03-01/25 and study CB-03-01/26, respectively.

In study CB-03-01/25, the treatment effect in the United States trended in the correct direction (WINLEVI better than vehicle) for IGA success and inflammatory lesion counts; however, the

mean change in noninflammatory lesions was slightly higher in the vehicle group than in the WINLEVI group. In study CB-03-01/26, the treatment effect in the United States trended in the incorrect direction (vehicle better than WINLEVI) on all three coprimary efficacy endpoints. The size of the United States population in study CB-03-01/26 is 93 subjects compared to 502 subjects in study CB-03-01/25.

Table 25. IGA Success at Week 12 by Country for Study CB-03-01/25 [ITT[1]]

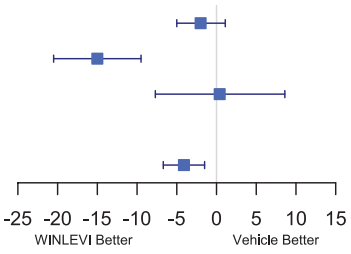
Subgroups (n[W], n[V])	WINLEVI (N=353)	Vehicle (N=355)	Difference	Difference (95% CI)
Country				
United States (251, 251)	13.5%	7.0%	6.5%	
Ukraine (66, 66)	31.7%	9.8%	21.8%	
Republic of Georgia (36, 38)	21.9%	17.4%	4.6%	
Overall	17.7%	8.6%	9.1%	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.

Table 26. Absolute Change From Baseline in Inflammatory Lesion Counts at Week 12 by Country for Study CB-03-01/25 [ITT[1]]

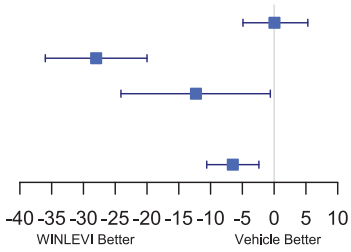
Subgroups (n[W], n[V])	WINLEVI (N=353)	Vehicle (N=355)	Difference	Difference (95% CI)
Country				
United States (251, 251)	-19.0	-17.0	-2.0	
Ukraine (66, 66)	-24.6	-9.6	-15.0	
Republic of Georgia (36, 38)	-17.1	-17.5	0.4	
Overall	-19.9	-12.4	-7.5	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as fixed effects, and baseline value as a covariate.

Table 27. Absolute Change From Baseline in Noninflammatory Lesion Counts at Week 12 by Country for Study CB-03-01/25 [ITT[1]]

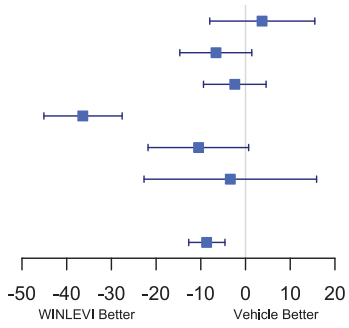
Subgroups (n[W], n[V])	WINLEVI (N=353)	Vehicle (N=355)	Difference	Difference (95% CI)
Country				
United States (251, 251)	-14.8	-14.9	0.05	
Ukraine (66, 66)	-28.7	-0.7	-28.0	
Republic of Georgia (36, 38)	-35.7	-23.3	-12.3	
Overall	-19.6	-13.1	-6.5	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as a fixed effect, and baseline value as a covariate.

Table 28. IGA Success at Week 12 by Country for Study CB-03-01/26 [ITT[1]]

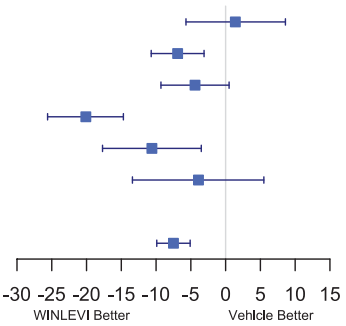
Subgroups (n[W], n[V])	WINLEVI (N=369)	Vehicle (N=363)	Difference	Difference (95% CI)
Country				
United States (47, 46)	-16.0	-19.7	3.7	
Poland (111, 111)	-19.2	-12.6	-6.6	
Romania (95, 91)	-13.2	-10.8	-2.4	
Republic of Georgia (52, 50)	-40.9	-4.5	-36.4	
Bulgaria (44, 46)	-14.3	-3.8	-10.5	
Serbia (20, 19)	-22.3	-18.9	-3.4	
Overall	-19.9	-11.2	-8.7	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.

Table 29. Absolute Change From Baseline in Inflammatory Lesion Counts at Week 12 by Country for Study CB-03-01/26 [ITT[1]]

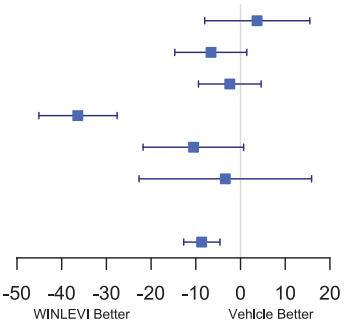
Subgroups (n[W], n[V])	WINLEVI (N=369)	Vehicle (N=363)	Difference	Difference (95% CI)
Country				
United States (47, 46)	-17.3	-18.7	1.4	
Poland (111, 111)	-19.0	-12.1	-6.9	
Romania (95, 91)	-17.5	-13.1	-4.4	
Republic of Georgia (52, 50)	-28.7	-8.6	-20.1	
Bulgaria (44, 46)	-19.6	-8.9	-10.6	
Serbia (20, 19)	-18.9	-15.0	-3.9	
Overall	-19.9	-12.4	-7.5	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as a fixed effect, and baseline value as a covariate.

Table 30. Absolute Change From Baseline in Noninflammatory Lesion Counts at Week 12 by Country for Study CB-03-01/26 [ITT[1]]

Subgroups (n[W], n[V])	WINLEVI (N=369)	Vehicle (N=363)	Difference	Difference (95% CI)
Country				
United States (47, 46)	-16.0	-19.7	3.7	
Poland (111, 111)	-19.2	-12.6	-6.6	
Romania (95, 91)	-13.2	-10.8	-2.4	
Republic of Georgia (52, 50)	-40.9	-4.5	-36.4	
Bulgaria (44, 46)	-14.3	-3.8	-10.5	
Serbia (20, 19)	-22.3	-18.9	-3.4	
Overall	-19.9	-11.2	-8.7	



Source: Statistical Reviewer's Analysis
[1] Intent-to-treat (ITT) population: All randomized subjects. Missing data were imputed using multiple imputation.
[2] Values displayed are the least square means based on analysis of covariance with treatment as a fixed effect, and baseline value as a covariate.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for clascoterone cream, 1%, for the treatment of acne vulgaris focuses on pooled data from two phase 3 trials CB-03-01/25 and CB-03-01/26 and the long-term open-label follow-up phase 3 study CB-03-01/27.

Study CB-03-01/25 and study CB-03-01/26 were multicenter, randomized, double-blind, vehicle-controlled studies to evaluate the safety and efficacy of cortexolone 17α-propionate (CB-03-01) cream, 1%, applied twice daily for *12* weeks in subjects with facial acne vulgaris.

Study CB-03-01/27 was an open-label, long-term follow-up extension study to evaluate the safety of cortexolone 17α-Propionate (CB-03-01) cream, 1%, applied twice-daily in subjects with acne vulgaris. The primary objective of this long-term study was to determine the long-term safety of CB-03-01 cream, 1%, applied BID on the face and, if applicable, the trunk for an additional 9 months in subjects with acne vulgaris who participated in the phase 3 pivotal studies for a total treatment of up to 12 months.

The phase 3 studies were the two pivotal double-blind, vehicle-controlled, multicenter studies of clascoterone cream, 1%, of identical design that included 1,440 subjects with acne vulgaris (722 clascoterone, 718 vehicle, henceforth is pool A) who applied study drug BID to the entire face for 12 weeks and the open-label follow-up safety study in which 607 of the subjects in the pivotal studies applied clascoterone BID to both the face and trunk (as applicable) for 9 additional months, providing total exposure for up to 12 months for facial acne. A total of 416 subjects have been exposed to clascoterone cream, 1%, for at least 6 months and 123 for 12 months.

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

- Male or female, 9 years of age or older
- IGA score of 3 (moderate) or 4 (severe), see Table 11 for details on the IGA scale
- 30 to 75 inflammatory lesions (papules, pustules, and nodules)
- 30 to 100 noninflammatory lesions (open and closed comedones)
- No more than two facial nodules

Approximately 700 subjects in each trial were randomized in a 1:1 ratio to either WINLEVI cream (n=350) or vehicle cream (n=350). Subjects were scheduled to be evaluated at the following four visits: baseline (day 1), and week 4, week 8, and week 12.

The Applicant also submitted supportive safety data from a phase 2 dose-finding trial, two PK/Bioavailability studies conducted under conditions of maximal use [one in adults (≥18 years, cohort 1) and adolescents (12 to <18 years, cohort 2) and one in pediatric subjects age 9 to <12 years], and an active-controlled study in subjects with acne vulgaris.

To determine the safety profile of clascoterone cream, 1%, the review team analyzed the following types of pooled data: exposure, demographics, baseline characteristics, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory results, vital signs and findings from physical examinations.

A TEAE was defined as an AE with an onset date on or after the first study product administration date; regardless of the type of the study drug, and on-treatment or off-treatment period. All reported terms (investigator descriptions) for AEs were recoded for the integrated summary of safety (ISS) using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0).

Pregnancy outcomes will be discussed in more detail in section 8.2.4 of this review.

At the end of phase 2 meeting, the Agency informed the Applicant that the potential for QT/QTc prolongation from its product should be addressed. In the Summary of Clinical Safety, the Applicant provided a risk assessment of the proarrhythmic potential of clascoterone. This is discussed in more detail in section 8.2.4 of this review.

8.2.2. Review of Safety Database

Overall Exposure

A total of 2,318 subjects were exposed to at least one application of study drug across all of the studies (Table 31). This includes 1,757 subjects exposed to CB-03-01 at any concentration and regimen, including 352 healthy subjects and 1,405 subjects with acne. Across vehicle-controlled studies 171-7151-201, CB-03-01/25, and CB-03-01/26, 792 subjects with acne were treated with CB-03-01 cream, 1%, BID for 12 weeks. Duration of exposure is summarized in Table 42 for these three studies and in ISS Table 2 by study and treatment for all studies. Exposure to CB-03-01 cream, 1%, BID was up to 12 months (including treatment period of the parent studies) for 123 subjects (Table 37).

In study CB-03-01/25, there were 47 subjects who were excluded from PPl population set by hardcoding based on blind review meeting result: 25 subjects due to lack of compliance (<80% study drug compliance), three subjects due to failure to satisfy the inclusion/exclusion criteria, and 19 subjects due to intake of prohibited medications.

Table 31. Safety Population, Size, and Denominators (Total Number of Subjects in Safety Population by Study)

	Study ID (Type)	CB-03-01 N=1757	Placebo/ Vehicle N=821	Retin-A 0.05% N=30	Total N=2318
All other than controlled trials conducted for this indication[3]	Healthy subjects				
	CB-03-01/02 (single ascending dose)	18	6	0	24
	CB-03-01/04 (multiple ascending dose)	24	0	0	24
	CB-03-01/33 (TQT)	24	8	0	32
	CB-03-01/05 (skin irritation)	36	0	0	36
	CB-03-01/32 (repeat insult patch test)	250	0	0	250
	Total healthy subjects	*352*	*14*	*0*	*366*
	Subjects with acne				
	171-7151-203 (steady-state PK)	8	0	0	8
	171-7151-202 (maximum use HPA/PK)	42	0	0	42
	CB-03-01/28 (maximum use HPA/PK)	27	0	0	27
	CB-03-01/03	28	14	30	72
	171-7151-201	288	75	0	363
(Pool A) Controlled trials conducted for this indication[2]	CB-03-01/25	353	355	0	708
	CB-03-01/26	369	363	0	732
Open-label, long-term follow-up extension study	CB-03-01/27[a]	290 [607[a]]	0	0	[607[a]]
	Total subjects with acne	*1405*	*807*	*30*	*1952*

Source: ISS Table 1
[a] Of the 607 subjects, all of whom were included in previous studies, 290 had received vehicle and 317 had received CB-03-01 in the previous controlled study, CB-03-01/25 or CB-03-01/26.
[1] nsidered for approval.
[2] (b) (4)
[3] If placebo arm patients switch to study drug in open-label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
Abbreviations: HPA = hypothalamic pituitary axis; PK = pharmacokinetic; TQT = thorough QT

In the phase 3 clinical trials CB-03-01/25 and CB-03-01/26 subjects treated with clascoterone cream, 1%, had overall mean treatment compliance of 95.4%. Subjects treated with vehicle cream had mean treatment compliance of 95% (see Table 32). There were no significant differences in the daily amount (g), days of treatment, number of actual applications, number of scheduled applications and total amount (g) between the treatment and placebo groups.

Table 32. Summary of Treatment Compliance, Safety Pool A

		Compliance [%]	Daily Amount [g]	Days of Treatment	Number of Actual Applications	Number of Scheduled Applications	Total Amount [g]
CB-03-01	Mean	95.4	2.0	80.8	156.6	162.3	159.5
	Std Dev	11.4	0.6	18.8	40.2	37.3	56.8
	Min	0	0.17	5	0	10	3.8
	Max	108.5	4.8	124.0	237.0	248.0	328.6
	Range	108.5	4.6	119.0	237.0	238.0	324.8
	Median	98.9	1.96	85	167.5	170	165
Vehicle	Mean	95.1	2.0	81.1	156.9	163.3	161.6
	Std Dev	10.8	0.5	18.7	40.1	37.4	57.4
	Min	12	0.09	8	2	2	1.4
	Max	102	4	146	247	294	317
	Range	90	4	138	245	292	316
	Median	98.8	2.0	85.0	167.0	171.0	167.6

Source Data: Reviewer Analysis of ADDA Database

There were 607 subjects who were enrolled in the long-term safety trial, CB-03-01/27. Of those,123 completed 12 months of active treatment. The mean treatment compliance for clascoterone cream, 1%, was approximately 92.8% for face and 86.1% for the trunk (see Table 33).

Table 33. Summary of Treatment Compliance in Long-Term Safety Study

	N	Mean	SD	Min	Max	Range	Median
Compliance [%] - face	581	92.8	15.1	0	114.7	114.7	99.3
Compliance [%] - trunk	241	86.1	24.4	0	102.4	102.4	97.6
Daily amount [g]	583	2.3	1.3	0.22	12.9	12.7	1.9
Days of treatment	583	184.5	96.8	19	435	416	196.0
Number of actual applications - face	581	348.6	192.9	0	801	801	377.0
Number of actual applications - trunk	241	278.1	205.7	0	1138	1138	208.0
Number of scheduled applications - face	581	370.0	193.2	33	871	838	393.0
Number of scheduled applications - trunk	241	313.4	206.5	33	1164	1131	290.0
Total amount [g]	583	415.6	323.8	8	2368.4	2360.4	373.5

Source Data: Reviewer Analysis of ADDA Database
Abbreviation: SD = standard deviation

Adequacy of Safety Database

The safety database for clascoterone cream, 1%, was adequate and consisted of the two phase 3 pivotal trial populations that totaled 1.440 subjects and a long-term safety trial in which 416 (68.5%) of 607 enrolled subjects were treated actively for 6 months, 303 (49.9%) for 9 months and 123 (20.3%) for 12 months (see Table 34 and Table 35 for subject disposition).

Table 34. Subject Disposition by Treatment in Phase 3 Pivotal Studies (Pool A)

	Study CB-03-01/25		Study CB-03-01/26		Total	
Subject Disposition, n (%)	**CB-03-01 (N=353)**	**Placebo (N=355)**	**CB-03-01 (N=369)**	**Placebo (N=363)**	**CB-03-01 (N=722)**	**Placebo (N=718)**
Completed						
Completed	287 (81.3)	290 (81.7)	302 (81.8)	282 (77.7)	589 (81.6)	572 (79.7)
Withdrew	66 (18.7)	65 (18.3)	67 (18.2)	81 (22.3)	133 (18.4)	146 (20.3)
Reason for WD						
WD by subject	23 (6.5)	18 (5.1)	35 (9.5)	41 (11.3)	58 (8.0)	59 (8.2)
Lost to f/u	39 (11.0)	32 (9.0)	24 (6.5)	24 (6.6)	63 (8.7)	56 (7.8)
Physician decision	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Study terminated by Applicant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance with study drug	0 (0.0)	2 (0.6)	1 (0.3)	5 (1.4)	1 (0.1)	7 (1.0)
Adverse event	4 (1.1)	6 (1.7)	3 (0.8)	8 (2.2)	7 (1.0)	14 (1.9)
Pregnancy	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.3)
Lack of efficacy	0 (0.0)	3 (0.8)	3 (0.8)	1 (0.3)	3 (0.4)	4 (0.6)
Others	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.4)

Source data: ADSL; Applicant ISS Table 3.1.
Abbreviations: f/u = follow-up; WD = withdrawal

Table 35. Summary of Subject Disposition, All Subjects, Long-Term Safety

	Clascoterone Cream, 1%
Subjects in safety population	607
Completed subjects, n (%)	348 (57.3)
Subjects discontinued from study, n (%)	261 (43.0)
Primary reason for discontinuation, n (%)	
Withdrawal by subject	102 (15.2)
Lost to follow-up	90 (13.4)
Lack of efficacy	30 (4.5)
Withdrawal by parent/guardian	13 (1.9)
Adverse event	9 (1.3)
Noncompliance with study drug	5 (0.7)
Other	4 (0.6)
Pregnancy	3 (0.4)
Recovery	3 (0.4)
Progressive disease	1 (0.1)
Technical problems	1 (0.1)
All	261 (39.0)

Source: Reviewer Analysis of **Study CB-03-01/27** ADSL Database

The total subject exposure to clascoterone cream, 1%, applied daily for 12 weeks provides adequate data for the evaluation of safety. The total exposures for 6 months and 1 year are sufficient to characterize the safety of the product over longer treatment periods. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database submitted by the Applicant is sufficient to characterize the safety profile of clascoterone cream, 1%, for the treatment of moderate to severe acne vulgaris.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety of clascoterone cream, 1%. There were no significant deficiencies discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

For the phase 3 trials, an adverse event (AE) was defined as TEAEs when the onset or worsening was at or after the first study drug dose. The Applicant reported all investigator descriptions of AEs, recoded for the ISS using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. The coding of adverse events in this NDA submission appeared adequate to allow estimates of AE risk. However, some preferred terms (PTs), such as nasopharyngitis and upper respiratory infection, were pooled during analyses to capture the incidence of the AEs more effectively.

The safety assessments for phase 3 and long-term studies were presented in Table 36. Clinical laboratory tests and vital signs were not collected during the phase 3 trials.

Table 36. Safety Assessments for Vehicle-Controlled and Open-Label Long-Term Studies in Subjects With Acne Vulgaris

Vehicle-controlled studies in subjects with acne vulgaris	
171-7151-201	AEs, LSRs, clinical laboratory tests, physical examinations, vital signs, and ECGs
CB-03-01/25, CB-03-01/26	AEs, LSRs, and ECGs
Open-label study in subjects with acne vulgaris	
CB-03-01/27	AEs and LSRs

Abbreviations: AE = adverse event; ECG = electrocardiogram; HPA = hypothalamic-pituitary-adrenal; LSR = local skin reaction (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus)

Safety endpoints for CB-03-01/25, CB-03-01/26 study:

- Local and systemic adverse events (AEs) at every visit (baseline, week 4, week 8, and week 12).
- Local skin reactions (LSRs): telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus scored by frequency and severity at every visit (baseline, week 4, week 8, and week 12).
- Urine pregnancy tests (UPTs) in all women of childbearing potential (WOCBP) at every visit (baseline, week 4, week 8, and week 12).
- Material changes from baseline in ECGs at week 12.

Safety endpoints for the long-term CB-03-01/27 study:

- Incidence of any local and systemic TEAEs
- Number of subjects with presence (and severity) of each individual LSRs: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus)

for each treatment area as applicable, at each time point (baseline and long-term follow-up [LTF]) – month 1, month 3, month 6, month 9, and any unscheduled visits).

- UPTs in all WOCBP at baseline, LTF-month 6 and end-of-study (EOS).

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

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

Investigators recorded in the case report from the date the AE began and ended or that the AE was ongoing. Also recorded were the severity, relationship to the use of study drug, and action taken or outcome. Investigators categorized the severity of the AE according to the following criteria:

- Mild: The symptom had a negligible effect or no impairing effect on the subject's normal function.
- Moderate: The symptom impaired the subject's normal function to some extent.
- Severe: The symptom had an obvious, significantly impairing effect on the subject's normal function.

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

- Unlikely: There was no medical evidence to suggest that the AE may have been related to study drug usage, or there was another more probable medical explanation.
- Possible: There was medical evidence to suggest that there was a reasonable possibility that the AE may have been related to study drug usage. However, other medical explanations could not be excluded as a possible cause.
- Probable: There was strong medical evidence to suggest that the AE was related to study drug usage.

An SAE was defined as an AE that was:

- Fatal
- Life-threatening
- Significantly or permanently disabling
- A congenital anomaly or birth defect in the offspring of a subject
- Requiring in-patient hospitalization or prolonging a current hospitalization
- A medically important event that jeopardized the subject or required medical or surgical intervention to prevent one of the outcomes listed in this definition

Adverse events, and local skin tolerability assessment scores greater than zero, that were ongoing when a subject withdrew from or completed the study were followed until resolution or stabilization, or for 30 days, whichever was shorter. Subjects who experienced any clinically significant AE remained under medical supervision until the investigator or the Applicant's medical monitor deemed the AE resolved, stabilized, or was no longer serious enough to warrant follow-up.

Laboratory values that were abnormal and not assessed as AEs were followed at the discretion of the investigator or the Applicant's medical monitor until resolved or stabilized. Although pregnancy was not considered an AE, such subjects were withdrawn from the study and followed until the outcome of the pregnancy was known.

Routine Clinical Tests

In trial CB-03-01/25 and trial CB-03-01/26 (safety pool A), investigators and site staff conducted safety monitoring during clinic visits at baseline, week 4, week 8, and week 12. These evaluations consisted of assessment of local tolerability and adverse events at each visit, UPTs in all WOCBP at every visit and changes from baseline in ECGs at week 12.

Local safety assessments included an evaluation of signs (scaling, erythema, and dryness) and symptoms (burning/stinging) at the application site (see section 8.2.5.2 for scales). These LSRs were collected independently of adverse events (AEs). Only LSRs that required medical intervention (e.g., prescription medication) or required withholding the application of the test articles were to be documented as AEs. Any LSRs not listed above were recorded as AEs.

8.2.4. Safety Results

Deaths

There were no deaths in any of the trials.

Serious Adverse Events

In the phase 3 pivotal studies (pool A), TEAEs were reported for 11.4% of the 722 subjects treated with CB-03-01 and 12.7% of the 718 subjects treated with vehicle (Table 37).

Table 37. Overall Summary of Treatment-Emergent Adverse Events in Phase 3 Pivotal Studies (Pool A, Safety Population)

	CB-03-01/25		CB-03-01/26		Total	
Category, n (%)	CB-03-01 N=353	Vehicle N=355	CB-03-01 N=369	Vehicle N=363	CB-03-01 N=722	Vehicle N=718
All TEAEs	40 (11.3)	41 (11.5)	42 (11.4)	50 (13.8)	82 (11.4)	91 (12.7)
Serious TEAE	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
TEAE related to study drug	4 (1.1)	9 (2.5)	8 (2.2)	13 (3.6)	12 (1.7)	22 (3.1)
Serious TEAE related to study drug	0	0	0	0	0	0
TEAE leading to dose modification	3 (0.8)	3 (0.8)	3 (0.8)	4 (1.1)	6 (0.8)	7 (1.0)
TEAE leading to discontinuation of study drug	3 (0.8)	4 (1.1)	2 (0.5)	8 (2.2)	5 (0.7)	12 (1.7)
TEAE leading to death	0	0	0	0	0	0

Abbreviations: TEAE = treatment-emergent adverse event
Source: ISS Table 9.1

The incidences of treatment-emergent SAEs were similar in the CB-03-01 and placebo groups (0.0% versus 0.3%, respectively). Similarly, the incidence of TEAEs that led to patient discontinuation was similar in the CB-03-01 and placebo groups (0.7% versus 1.7%, respectively).

No serious TEAEs were considered related to study drug. The two serious TEAEs in pool A are summarized by system organ class (SOC) and PT in Table 38.

Table 38. Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment in Phase 3 Pivotal Studies (Pool A) (Safety Population)

	Phase 3 Pivotal Studies					
	Study CB-03-01/25		Study CB-03-01/26		Total	
System Organ Class, n (%) Preferred Term, n (%)	CB-03-01 (N=353)	Placebo (N=355)	CB-03-01 (N=369)	Placebo (N=363)	CB-03-01 (N=722)	Placebo (N=718)
Subjects with Treatment-Emergent Adverse Events	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.3)
Infections and infestations	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

Source: ADAE, ADSL MedDRA v21.0; Applicant ISS Table 16.2

In study CB-03-01/25, patient (b) (6) received placebo treatment and developed pneumonia on day 62. No action was taken with the study treatment and the condition resolved. This serious TEAE was considered not related to the study drug.

In study CB-03-01/26, patient (b) (6) received placebo treatment and developed hematoma of the right thigh on day 27. The drug study was interrupted, and the condition resolved.

Adverse Events

The only TEAE reported for ≥1% of subjects in either treatment group in pool A was nasopharyngitis (1.4% CB-03-01, 2.8% vehicle). No TEAEs were reported for ≥1% of CB-03-01-treated subjects and twice as many vehicle-treated subjects in pool A or pool B

The most significant adverse events are presented in Table 39. PTs, such as nasopharyngitis and upper respiratory infection, were pooled during analyses to capture the incidence of the AEs more effectively.

Table 39. Treatment-Emergent Adverse Events Reported for ≥1% of Subjects in Either Treatment Group in Phase 3 Pivotal Studies (Pool A, Safety Population)

	Study CB-03-01/25		Study CB-03-01/26		Total	
Preferred Term	CB-03-01 N=353	Vehicle N=355	CB-03-01 N=369	Vehicle N=363	CB-03-01 N=722	Vehicle N=718
Nasopharyngitis	7 (2.0)	14 (3.9)	5 (1.4)	11 (3)	12 (1.7)	20 (3.5)

Source: Reviewer Analysis of ADAE Database

Adverse Events With Long-Term Exposure (Study CB-03-01/27)

In the LTF study, 123 subjects were treated with CB-03-01 cream, 1%, BID and on-study for 12 months. As summarized in Table 40 the results of this study demonstrated that of CB-03-01 cream, 1%, for up to 12 months is well tolerated. TEAEs were reported for 110 (18.1%) subjects.

PTs, such as nasopharyngitis and upper respiratory infection, were pooled during analyses to capture the incidence of the AEs more effectively. The only TEAEs reported for ≥1.0% of subjects were nasopharyngitis/ upper respiratory tract infection (N=25, 4.1%).

Most TEAEs were mild or moderate in severity. Seven subjects experienced events that were reported as severe: coronary artery dissection, dizziness, eosinophilic gastroenteritis, fatigue, suicide attempt, nephrolithiasis, pancreatitis, pruritus, sciatica, and toothache.

Table 40. CB-03-01/27: Overall Summary of Subjects With Treatment-Emergent Adverse Events by Treatment Sequence From Parent Study

Category	CB-03-01/ CB-03-01 N=317 n (%)	Vehicle/ CB-03-01 N=290 n (%)	Overall N=607 n (%)	Overall (12 month on study) N=123 n (%)
Any TEAE	58 (18.3)	52 (17.9)	110 (18.1)	19 (7.3%)
Any Serious TEAE	3 (0.9)	3 (1.0)	6 (1.0)	0
Any TEAE related to study drug	12 (3.8)	2 (0.7)	14 (2.3)	0
Any serious TEAE related to study drug	0	0	0	0
Any TEAE leading to discontinuation	9 (2.8)	0	9 (1.5)	0
Any Serious TEAE leading to discontinuation	1 (0.3)	0	1 (0.2)	0
Any TEAE leading to death	0	0	0	0

Abbreviations: TEAE = treatment-emergent adverse event
Source: Applicant CB-03-01/27, Table 14.3.1.1

The proportion of subjects experiencing TEAEs and treatment-emergent LSRs was generally low throughout the study, and the number of subjects experiencing any TEAE was similar between subjects treated in the preceding controlled 12-week studies with CB-03-01 cream, 1%, or vehicle. Most TEAEs were mild in severity, and most LSRs and treatment-emergent LSRs were trace/minimal or mild in severity.

Six subjects experienced serious TEAEs: coronary artery dissection, depression, dizziness and suicide attempt, eosinophilic gastroenteritis, fatigue, and induced abortion. No serious TEAE was considered related to study drug. No labeling is recommended to describe these events.

Ten subjects (1.6%) discontinued study drug due to TEAEs, nine of whom discontinued the study due to the TEAEs. In seven subjects, the TEAEs that led to discontinuation that were considered at least possibly related to study drug were acne, acne conglobata, acne cystic, application site acne, application site dryness, application site swelling, and hair color changes. Application site reactions will be described in labeling.

For the 123 subjects treated with CB-03-01 cream, 1%, BID and on-study for 12 months, TEAEs were reported for 19 (15.4%) subjects. There were no serious TEAE, and no TEAE was related to study drug. No additions to labeling are recommended resulting from the analyses for the long-term safety population.

Dropouts and/or Discontinuations Due To Adverse Effects

Only a small proportion of subjects in safety pool A discontinued the treatment because of an adverse event, 5 of 722 (0.7%) in the clascoterone cream, 1% arm, and 12 of 718 (1.8%) in the vehicle cream arm. The incidence of TEAEs that led to patient discontinuation was similar in the CB-03-01 and placebo groups (0.7% versus 1.7%, respectively).

Treatment-emergent adverse events that lead to discontinuation of study drug by system organ class, preferred term, and treatment in phase 3 pivotal studies (pool A) (safety population) are presented in Table 41 and Table 42 (five in CB-03-01 arm and 12 in the vehicle).

The five TEAEs in the clascoterone cream, 1%, group that led to study discontinuation included: application site hypersensitivity (allergic reaction), oropharyngeal pain (burning/ sore throat), sebaceous hyperplasia (increased sebaceous hyperplasia), dermatitis contact (facial acute contact dermatitis), and hair color changes (depigmented hair on the nose). Two resolved, three were ongoing: sebaceous hyperplasia, dermatitis contact, and hair color changes.

The 12 TEAEs in the placebo group that led to study discontinuation included: application site pruritus, application site pain, application site dermatitis, application site acne (worsening or aggravation of acne), application site urticaria, application site erythema, cough (dry cough), application site nodule (inflammatory nodules), skin irritation. The majority of TEAEs resolved with the exception of: application site dermatitis, application site acne (worsening of acne), application site nodule (inflammatory nodules), and skin irritation.

Table 41. Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class, Preferred Term, and Treatment in Phase 3 Pivotal Studies (Pool A) (Safety Population)

	Phase 3 Pivotal Studies					
	Study CB-03-01/25		Study CB-03-01/26		Total	
System Organ Class, n (%) Preferred Term, n (%)	CB-03-01 (N=353)	Placebo (N=355)	CB-03-01 (N=369)	Placebo (N=363)	CB-03-01 (N=722)	Placebo (N=718)
Subjects with Treatment-Emergent Adverse Events	3 (0.8)	4 (1.1)	2 (0.5)	8 (2.2)	5 (0.7)	12 (1.7)
Skin and subcutaneous tissue disorders	1 (0.3)	0 (0.0)	2 (0.5)	4 (1.1)	3 (0.4)	4 (0.6)
Dermatitis contact	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Hair colour changes	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Sebaceous hyperplasia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Acne	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.4)
Skin irritation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	1 (0.3)	4 (1.1)	0 (0.0)	4 (1.1)	1 (0.1)	8 (1.1)
Application site hypersensitivity	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Application site dermatitis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Application site erythema	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.3)
Application site nodule	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Application site pain	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.4)
Application site pruritus	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	0 (0.0)	3 (0.4)
Application site urticaria	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Oropharyngeal pain	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)

Source: ADAE, ADSL MedDRA v21.0; Applicant ISS Table 18.2

Table 42. Patients Discontinued Treatment Due to TEAEs

Study	Unique Pt ID (USUBJID)	(b) (6)	AE Term (AEDECOD)	AE Grade (AETOXGRN)	AE Start Date (AESTDTC)	AE End Date (AEENDTC) (b) (6)
CB-03-01/25 Clascoterone	CB-03-01/25		application site hypersensitivity	2		
	CB-03-01/25		oropharyngeal pain	3		
	CB-03-01/25		sebaceous hyperplasia	3		
CB-03-01/25 Vehicle	CB-03-01/25		application site pain	3		
	CB-03-01/25		application site pain	3		
	CB-03-01/25		application site pruritus	3		
	CB-03-01/25		application site pain	3		
	CB-03-01/25		application site dermatitis	2		
	CB-03-01/25		application site urticaria	3		
CB-03-01/26 Clascoterone	CB-03-01/26		dermatitis contact	2		
	CB-03-01/26		hair color changes	3		
CB-03-01/26 Vehicle	CB-03-01/26		application site erythema	3		
	CB-03-01/26		acne	2		
	CB-03-01/26		acne	3		
	CB-03-01/26		application site nodule	2		
	CB-03-01/26		acne	3		
	CB-03-01/26		application site pruritus	3		
	CB-03-01/26		skin irritation	2		
	CB-03-01/26		application site erythema	3		
	CB-03-01/26		application site pruritus	3		
	CB-03-01/26		application site pain	3		

Source: Reviewer Analysis of ADAE, ADSL Databases

TEAEs Leading to Dose Modification

In the phase 3 pivotal studies, TEAEs led to dose modification, which was an interruption in dosing, for six subjects (0.8%) with CB-03-01 and seven subjects (1.0%) with vehicle summarized by SOC and PT (Table 43).

The TEAEs that led to dose interruption in the CB-03-01 group were application site dryness, bronchitis, dry skin, furuncle, oropharyngeal pain, and pyrexia.

Table 43. Treatment-Emergent Adverse Events Leading to Dose Modification by System Organ Class, Preferred Term, and Treatment in Phase 3 Pivotal Studies (Pool A) (Safety Population)

	Phase 3 Pivotal Studies					
	Study CB-03-01/25		Study CB-03-01/26		Total	
System Organ Class, n (%) Preferred Term, n (%)	CB-03-01 (N=353)	Placebo (N=355)	CB-03-01 (N=369)	Placebo (N=363)	CB-03-01 (N=722)	Placebo (N=718)
Subjects with Treatment-Emergent Adverse Events	3 (0.8)	3 (0.8)	3 (0.8)	4 (1.1)	6 (0.8)	7 (1.0)
General disorders and administration site conditions	2 (0.6)	3 (0.8)	0 (0.0)	2 (0.6)	2 (0.3)	5 (0.7)
Application site dryness	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pyrexia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Application site hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Application site pain	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Application site pruritus	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Application site rash	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.3)
Infections and infestations	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Furuncle	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	1 (0.1)
Oropharyngeal pain	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Dry skin	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Dermatitis contact	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

Source: Sponsor ISS Table 19.1, ADAE, ADSL

Significant Adverse Events

Across all studies, TEAEs led to study drug withdrawal, study discontinuation, or both for 22 subjects (1.3%) treated with CB-03-01, which included nine subjects in the LTF study. The most frequently reported events considered at least possibly related to CB-03-01 that were reported for subjects with acne were acne (worsening) and application site events.

Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Events are summarized in Table 44 by grade. Grade 1 to grade 5 (N, %), grade 3 (N, %), and grade 4 (N, %),.

Table 44. Summary of All Grade TEAEs by SOC and PT (More Than 1%)

	Study CB-03-01/25 CB-03-01 N=353						Study CB-03-01/25 Placebo N=355					
	G1-5 N	G1-5%	G3 N	G3%	G4 N	G4%	G1-5 N	G1-5%	G3 N	G3%	G4 N	G4%
ALL terms in AEDECOD	40	11.33	20	5.67	0	0	41	11.55	24	6.76	0	0
[SOC] Infections and Infestations	19	5.38	9	2.55	0	0	20	5.63	7	1.97	0	0
Nasopharyngitis	6	1.7	3	0.85	0	0	13	3.66	3	0.85	0	0
Upper respiratory tract infection	1	0.28	1	0.28	0	0	2	0.56	1	0.28	0	0
[SOC] Respiratory, Thoracic and Mediastinal Disorders	6	1.7	4	1.13	0	0	1	0.28	0	0	0	0
Oropharyngeal pain	2	0.57	1	0.28	0	0	1	0.28	0	0	0	0
Rhinorrhea	0	0	0	0	0	0	0	0	0	0	0	0
[SOC] Nervous System Disorders	2	0.57	1	0.28	0	0	1	0.28	0	0	0	0
Headache	2	0.57	1	0.28	0	0	1	0.28	0	0	0	0
	Study CB-03-01/26 CB-03-01 N=369						**Study CB-03-01/26 Placebo N=363**					
	G1-5 N	G1-5%	G3 N	G3%	G4 N	G4%	G1-5 N	G1-5%	G3 N	G3%	G4 N	G4%
ALL terms in AEDECOD	42	11.38	25	6.78	0	0	50	13.77	21	5.79	0	0
[SOC] Infections and Infestations	21	5.69	14	3.79	0	0	19	5.23	5	1.38	0	0
Nasopharyngitis	4	1.08	1	0.27	0	0	7	1.93	1	0.28	0	0
Upper respiratory tract infection	1	0.27	1	0.27	0	0	4	1.1	2	0.55	0	0
[SOC] Respiratory, Thoracic and Mediastinal Disorders	7	1.9	5	1.36	0	0	8	2.2	3	0.83	0	0
Oropharyngeal pain	4	1.08	4	1.08	0	0	4	1.1	1	0.28	0	0
Rhinorrhoea	3	0.81	1	0.27	0	0	5	1.38	1	0.28	0	0
[SOC] Nervous System Disorders	5	1.36	2	0.54	0	0	4	1.1	4	1.1	0	0
Headache	4	1.08	1	0.27	0	0	3	0.83	3	0.83	0	0

	Study CB-03-01/25 and CB-03-01/26 CB-03-0 N=722						Study CB-03-01/25 and CB-03-01/26 Placebo N=718					
	G1-5 N	G1-5%	G3 N	G3%	G4 N	G4%	G1-5 N	G1-5%	G3 N	G3%	G4 N	G4%
ALL Terms In AEDECOD	82	11.36	45	6.23	0	0	91	12.67	45	6.27	0	0
[SOC] Infections and Infestations	40	5.54	23	3.19	0	0	39	5.43	12	1.67	0	0
Nasopharyngitis	10	1.39	4	0.55	0	0	20	2.79	4	0.56	0	0
Upper respiratory tract infection	2	0.28	2	0.28	0	0	6	0.84	3	0.42	0	0
[SOC] Respiratory, Thoracic and Mediastinal Disorders	13	1.8	9	1.25	0	0	9	1.25	3	0.42	0	0
Oropharyngeal Pain	6	0.83	5	0.69	0	0	5	0.7	1	0.14	0	0
Rhinorrhoea	3	0.42	1	0.14	0	0	5	0.7	1	0.14	0	0
[SOC] Nervous System Disorders	7	0.97	3	0.42	0	0	5	0.7	4	0.56	0	0
Headache	6	0.83	2	0.28	0	0	4	0.56	3	0.42	0	0

Abbreviations: TEAE = treatment emergent adverse event; SOC = system, organ, class; PT = preferred term; G = grade

Treatment-Emergent Adverse Reactions

Adverse drug reactions were defined as TEAEs that were considered to be related to the study drug. No TEAEs were considered related to study drug in ≥1% of subjects treated with CB-03-01 cream, 1%, in pool A or pool B.

Three subjects had TEAEs identified as hypersensitivity or drug reaction:

- General disorders/application site hypersensitivity (verbatim: allergic reaction) was reported as a TEAE for subject (b) (6) who was treated with CB-03-01 cream, 1%, BID in study CB-03-01/25. The TEAE was reported as mild, probably related to study drug, and resolved. This event led to discontinuation and links to the narrative and case report form (CRF) are provided in Table 48. This subject is identified for the ISS as (b) (6).
- Immune system disorders/hypersensitivity (verbatim: allergic reaction) was reported as a TEAE in the treatment area for subject (b) (6) in study CB-03-01/27 (linked to the CRF in the clinical study report [CSR] addendum). This was a 50-year-old white female with acne who was treated with CB-03-01 cream, 1%, BID in the prior controlled study as well as CB-03-01/27. No relevant medical history or concomitant medications were reported at the onset of the event. The TEAE of allergic reaction began on study day 123 and was reported as mild and not related to study drug. No action was taken, the dose was not changed, and the event resolved on study day 132. The subject completed the study. This serves as the narrative for this event.
- Immune system disorders/hypersensitivity (verbatim: allergy) was reported as a TEAE not in the treatment area for subject (b) (6) in study CB-03-01/27 (linked to the CRF in the CSR addendum). This was a 15-year-old white female with acne who was treated with vehicle in the prior controlled study and CB-03-01 cream, 1%, BID in study CB-03-01/27. No relevant medical history or concomitant medications were reported at the onset of the event. The TEAE of allergy began on study day 156 and was reported as moderate and not related to study drug. The subject was treated with Clatra (an oral antihistamine) and Avamys (a corticosteroid nasal spray). The dose of study drug was not changed and the event resolved on study day 169. The subject completed the study. This serves as the narrative for this event.

Two additional subjects had events with preferred terms of hypersensitivity or application site reaction that, based on the verbatim reporting, had explanations unrelated to the study drug.

- General disorders/application site reaction (verbatim: tape reaction) was reported as a TEAE for healthy subject (b) (6) in the repeat insult patch test study CB-03-01/32. The TEAE was reported as mild, not related to study drug, and resolved. This event led to discontinuation and links to the narrative and CRF are provided in Table 48.
- Immune system/hypersensitivity (verbatim: allergies to fish oil) was reported as a TEAE for subject (b) (6) in study 171-7151-201 (linked to the CRF in the CSR addendum). This was a 17-year-old white male with acne who was treated with CB-03-01 cream 0.5% BID. No relevant medical history or concomitant medications were reported at the onset of the event. The TEAE of allergies to fish oil began on study day 28 and was reported as mild and

not related to study drug. The subject was treated with Benadryl. The dose of study drug was not changed and the event resoled on study day 30. The subject completed the study. This serves as the narrative for this event.

Laboratory Findings

Changes in clinical laboratory tests were generally unremarkable in the studies in which they were evaluated. Based on the safety and PK profiles of clascoterone demonstrated in phase 1 and phase 2 studies, and as agreed upon in the Special Protocol Assessment for CB-03-01/25, clinical laboratory tests were not collected as a safety parameter in phase 3 studies. However, shift tables of hematology, chemistry, and urinalysis results were generated to summarize the normal and abnormal (abnormal high and abnormal low) status changes from the baseline to the worst postbaseline results regardless on-treatment or off-treatment. The percentages were calculated based on the number of subjects with both baseline and at least one postbaseline value (each analyte was independently evaluated). The baseline value of each variable was defined as the value recorded at the last visit on or before the first dose of study drug. Shift tables for the subjects who received CB-03-01 1% BID in study 171-7151-201 are provided in the ISS.

Five subjects experienced laboratory-related AEs during the studies, none of which were SAEs. Subject (b) (6) in study 171-7151-201 discontinued study drug due to elevated liver function tests; the subject completed the study.

In addition, seven subjects had AEs of adrenocorticotropic hormone (ACTH) stimulation test abnormal in the HPA axis suppression studies, Study 171-7151-202 and Study CB-03-01/28.

A detailed discussion about hyperkalemia is in section 8.2.5.1.

Table 45. Laboratory-Related Adverse Events

Study	Subject ID Treatment	Adverse Event (Preferred Term): Severity, Relationship, Outcome	Reported Values
CB-03-01/28	(b) (6) CB-03-01 1% BID	Leukopenia: mild, not related, resolving	Leukocytes [5.0-24.5 x 103/µL]: 11.7 (screening), 2.7 (day 14)
171-7151-201	(b) (6) CB-03-01 1% BID	Liver function test abnormal: mild, not related, drug withdrawn (subject completed the study), resolving	ALT [5-30 U/L]: 116 (BL), 31, 188, 142, 49 (EOS) AST [0-41 U/L]: 18 (BL), 42, 138, 81, 44 (EOS) AP [180-700 U/L]: 68 (BL), 69, 101, 112, 80 (EOS)
171-7151-201	(b) (6) CB-03-01 1% BID	Blood creatine phosphokinase increased: mild, not related, ongoing ALT increased; mild, not related, ongoing AST increased; mild, not related, ongoing	CK [35-232 U/L]: 5097 (EOS) ALT [5-30 U/L]: 16 (BL), 14, 19, 35 (EOS) AST [0-41 U/L]: 17 (BL), 16, 16, 90 (EOS)

Study	Subject ID Treatment	Adverse Event (Preferred Term): Severity, Relationship, Outcome	Reported Values
171-7151-201	(b) (6) CB-03-01 0.5% BID	WBC count increased: moderate, not related, resolving Neutrophil count increased; moderate, not related, resolved	WBC [3.5-10.5 x 103/µL]: 11.0 (BL), 8.8, 13.7, 11.3, 11.1 (EOS) Neutrophils [2.1-7.8 x 103/µL]: 5.9 (BL), 4.6, 10.2, 7.5, 7.8 (EOS)
CB-03-01/27	(b) (6) CB-03-01 1% BID	Anemia: mild, not related, ongoing	Laboratory values not reported

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BL = baseline; CK = creatine kinase; EOS = end of study; WBC = white blood cell
Source: Applicant Summary of Clinical Safety Table 39

Human Reproduction and Pregnancy

During the development program, females of childbearing potential were required to have a negative pregnancy test at screening and to use effective forms of contraception. In addition, UPTs were performed at week 4, week 8, week 12, and final visit or when a subject prematurely withdrew from the study.

Five pregnancies were reported during the phase 3 trials and one during a phase 2 trial. The pregnancy outcomes and study treatment received are shown in the table below.

Table 46. Pregnancy Outcomes and Study Treatment

USUBJID	SUBJID	AGE	ARM	Outcome
(b) (6)		≥18	Vehicle cream	Lost to follow-up
		≥18	Vehicle cream	Preterm delivery, week 35
		≥18	CB-03-01 cream 1%	Induced abortion
		≥18	CB-03-01 cream 1%	Full term, C-section
		12–<18	CB-03-01 cream 1%	Intrahepatic cholestasis of pregnancy associated with extreme pruritus; oligohydramnios
(b) (6)	(b) (6)	≥18	CB-03-01 cream containing 0.5% cortexolone 17a-propionate (BID)	Abortion spontaneous

Source: Clinical Reviewer Analysis of ISS database

Polycystic Ovaries/Amenorrhoea

In the long-term safety study CB-03-01/27, three patients developed polycystic ovaries and one amenorrhoea. These AEs were not observed during the phase 3 trials.

Table 47. Long-Term Safety Study CB-03-01/27

STUDYID	USUBJID	TRT01A	AGE	SEX	AEDECOD
CB-03-01/27	(b) (6)	CB-03-01	15	F	Polycystic ovaries
CB-03-01/27		CB-03-01	16	F	Amenorrhoea
CB-03-01/27		CB-03-01	29	F	Polycystic ovaries
CB-03-01/27		CB-03-01	13	F	Polycystic ovaries

Source: Clinical Reviewer Analysis of ISS database

Vital Signs

For this program, the Applicant defined hypertension categories as: systolic blood pressure (SBP) >140 mm Hg and increase from baseline >20 mm Hg (composite; measurements from the same visit), SBP >180 mm Hg, diastolic blood pressure (DBP) >90 mm Hg and increase from baseline >20 mm Hg (composite; measurements from the same visit), and DBP >105 mm Hg. The hypotension categories were: SBP <90 mm Hg and decrease from baseline >10 mm Hg and DBP <60 mm Hg and decrease from baseline >10 mm Hg.

Studies CB-03-01/25 and CB-03-01/26 did not have any postbaseline vital sign records; therefore, the vital sign shift table was only provided for study 171-7151-201, phase 2, double-blind, parallel-group, vehicle-controlled, dose-response in subjects ≥12 years old with mild to severe facial acne vulgaris (IGA grade 2 to 4)). The potentially clinically important vital signs were provided in Table 48, only for patients receiving BID clascoterone cream, 1%. Five subjects (7.6%) developed hypotension in the 1% BID clascoterone group, and three subjects (5.7%) developed hypotension in the placebo group.

Table 48. Proportion of Subjects With Clinically Important Vital Sign Values at Postbaseline Visits by Treatment in Study 171-7151-201, BID, Clascoterone Cream, 1%

Category	CB-03-01 Cream 1% BID (N=70)	Placebo BID (N=55)
Subjects with any clinically important values	6 (8.6)	5 (9.1)
Hypertension		
SBP >140 mm Hg and increase from baseline >20 mm Hg	1 (1.4)	1 (1.8)
SBP >180 mm Hg	0 (0.0)	0 (0.0)
DBP >90 mm Hg and increase from baseline >20 mm Hg	0 (0.0)	0 (0.0)
DBP >105 mm Hg	0 (0.0)	0 (0.0)
Hypotension		
SBP <90 mm Hg and decrease from baseline >10 mm Hg	1 (1.4)	1 (1.8)
DBP <60 mm Hg and decrease from baseline >10 mm Hg	5 (7.1)	3 (5.5)

Abbreviations: BID = twice daily; SBP = systolic blood pressure; DBP = diastolic blood pressure
*n1 = Number of subjects in category. n2 = Total number of subjects with vital signs collected. % = n1/n2*100%.
Includes subjects from 171-7151-201 in the placebo BID and CB-03-01 Cream 1% BID treatment groups.
Source Data: ADVS, ADSL; Applicant Table 28.1

Changes in vital signs were generally unremarkable in the studies in which they were evaluated; vital signs were not measured in the phase 3 studies. The results for subjects who received CB-03-01 1% BID or placebo in study 171-7151-201, who had potentially clinically important blood pressure results, are summarized in Table 48 (showing TEAEs of hypertension or hypotension).

- One subject in each treatment group had SBP >140 mm Hg and an increase from baseline >20 mm Hg. In these subjects the change was from 119 mm Hg to 141 mm Hg and from 120 mm Hg to 141 mm Hg.
- One subject in each treatment group had SBP <90 mm Hg and a decrease from baseline >10 mm Hg. In these subjects the change was from 102 mm Hg to 83 mm Hg and from 110 mm Hg to 79 mm Hg.
- Five CB-03-01-treated and three vehicle-treated subjects had DBP <60 mm Hg and a decrease from baseline >10 mm Hg. In the CB-03-01 group the changes were from 70 mm

Hg to 50 and 55 mm Hg (at separate visits), 68 mm Hg to 50 mm Hg, 72 mm Hg to 54 mm Hg, 78 to 52 mm Hg, and 72 mm Hg to 49 mm Hg. In the vehicle group the changes were from 70 mm Hg to 59 mm Hg, 58 mm Hg to 44 mm Hg, and 69 mm Hg to 56 mm Hg.

ECGs

Shift tables for ECG clinical interpretation (normal, abnormal-not clinically significant, and abnormal- clinically significant) were provided to analyze the change from baseline to the worst postbaseline values (if multiple postbaseline readings were available). The percentages were calculated based on number of subjects with both baseline and at least one postbaseline value. Baseline was defined as the value recorded at the last visit on or before the first dose of study drug was administered.

In study CB-03-01/25 ECG results were similar between the treatment groups with few shifts from normal to abnormal. Only one abnormal ECG result during the study was deemed clinically significant based on review by the investigator; subject (b) (6) in the CB-03-01 group had sinus rhythm first-degree atrioventricular block at baseline.

In study CB-03-01/26 ECG results were similar between the treatment groups with few shifts from normal to abnormal. Three subjects (one CB-03-01 and two vehicle) had ECG results considered not clinically significant abnormal at baseline and results considered clinically significant at day 85:

- Subject (b) (6) (CB-03-1-01) had an abnormal ECG result at day 85 that was considered clinically significant (sinus rhythm with left and right atrial enlargement, right axis deviation, poor precordial R wave progression considered a normal variant RSR' with normal QRS duration considered a normal variant first-degree atrioventricular block). Although the ECG results at baseline were considered not clinically significant, the subject presented a “technically poor tracing - 50/60 cycle electrical interference sinus rhythm left atrial enlargement right atrial enlargement poor precordial R wave progression right axis deviation incomplete right” that actually made the tracings not comparable.
- Subject (b) (6) (vehicle) had an abnormal ECG result at day 85 (sinus rhythm first-degree atrioventricular block) that was considered clinically significant. The same abnormality was present at baseline but not considered clinically significant.
- Subject (b) (6) (vehicle) had an abnormal ECG result at day 85 (sinus rhythm complete right bundle branch block early repolarization considered normal variant) that was considered clinically significant. The baseline ECG, “ectopic atrial rhythm left anterior fascicular block; inverted T wave early repolarization considered a normal variant, incomplete right bundle branch block short PR interval,” was not considered clinically significant.

QT

The Division of Cardiovascular and Renal Products Thorough QT (TQT) team reviewed the TQT study performed by the Applicant. The review was done on September 4, 2019. From the review:

No significant QTc prolongation effect of cortexolone 17a-propionate was detected in this QT assessment. The effect of cortexolone 17a-propionate was evaluated in randomized, double-blind, placebo-controlled study in healthy subjects (study # CB-03-01/33). Subjects (n=32; eight subjects, four4 groups) received a morning and evening dose (12 hours apart) of cortexolone 17α- propionate as topical application of a 7.5% solution (75 mg/mL; 225 mg in 3 mL per subjects; a total daily dose of 450 mg in 6 mL) on day 1 to day 2 and once on day 4.

The dose evaluated was 450 mg (as topical application of a 7.5% solution; 225 mg in 3 mL twice daily on day 1 to day 3 and once on day 4), which covers two times the worst-case exposure scenario. The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that cortexolone 17a-propionate is associated with significant QTc prolonging effect—see Table 49 for overall results.

Table 49. Point Estimates and 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Cortexolone 17α-propionate†	2.3	0.6	(-3.1 to 4.3)
QTc	Cortexolone 17α-propionate‡	6.7	0.3	(-3.4 to 3.9)

Abbreviations: CI = confidence interval; ECG = electrocardiogram
Topical application of a 7.5% solution (225 mg in 3 mL) twice daily on day 1† to day 3 and once on day 4‡. For further details on the FDA analysis, see section 4.

The findings of this analysis are further supported by the available nonclinical data and by time analysis and categorical analysis.

Exposure margin was used to waive the requirement for a positive control for assay sensitivity. In addition, the QT-IRT's analysis did not suggest the presence of significant negative treatment bias . The Applicant used solution formulation (7.5% solution instead of 1% cream) to achieve higher systemic exposures. The peak concentrations observed in this QT study cover the exposures observed in the maximal use study. Moreover, concentrations of metabolites (cortexolone-21-propionate and cortexolone) were lower in plasma.

Thirty-one subjects completed the study as per protocol. One subject withdrew from the study. There were no deaths, SAEs and no AEs that led to a subject's withdrawal from the study. There were no cardiac-related AEs.

One episode of ECG PR prolongation occurred in a subject with known PR prolongation at screening, ranging between 208 ms and 214 ms. The subject was cleared for inclusion in the study following cardiology review of their 12-lead and Holter ECGs. About 6 hours following the first dose on day 1, the subject's PR interval increased to 314 ms, and the day 1 evening dose was omitted to observe the subject. The PR interval returned to baseline on the morning of day 2. After discussion with the principal investigator, the PR interval increase was considered unrelated to the study medication, as it occurred too soon following the start of dosing. In addition, PR prolongation is not a known feature of the study medication. As a result, a

physiological fluctuation of the PR interval from this subject's baseline was considered the most likely explanation. The principal investigator cleared the subject to continue dosing on day 2 under close observation; however, the subject withdrew consent before receiving any further doses.

None of the events identified to be of clinical importance per the International Conference for Harmonisation E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

Immunogenicity

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

8.2.5. Analysis of Submission-Specific Safety Issues

Although systemic exposure following topical administration of clascoterone cream, 1%, appears to be very low, we considered the potential for systemic toxicity as well as local safety. Local tolerability hyperkalemia and HPA suppression are discussed below.

8.2.5.1. Hyperkalemia

Hyperkalemia is an elevated level of potassium (K+) in the blood serum. Normal potassium levels are between 3.5 mmol/L and 5.0 mmol/L. CB-03-01 is structurally similar to the steroidal antiandrogen spironolactone; chronic treatment with spironolactone can produce side effects such as hyperkalemia, gynecomastia and, menstrual irregularities. The pathogenesis of these side effects is not completely understood, but spironolactone is also able to directly block the synthesis of both adrenal and gonadal steroids (Armanini et al. 2014).

The potassium shift was evaluated across all studies due to the biological plausibility for the class of drugs. Thirty-three subjects (6.7%) had a shift to high from normal, low, or not done in the clascoterone group and only four (3.9%) had a shift in the vehicle group.

Table 50. Proportion of Subjects Who Shifted to High (From Normal, Low or Not Done)

Category	CB-03-01 (N=495)	Placebo (N=103)
Shifted to high	33 (6.7%)	4 (3.9%)
Risk difference (95% CI)	2.8% (-1.6%, 7.1%)	

Source: Clinical and Statistical Reviewer Analysis of ISS ADLB

Table 51 presents the results of the potassium shifts by age group. About 30% of pediatric patients 9 years to 11 years of age saw a shift from normal to high potassium in 14 days, based on data from phase 2 dose-ranging pediatric study in subjects with acne vulgaris (study CB-03-01/28: a maximal use PK study to evaluate HPA axis suppression potential in patients aged ≥9 to <12).

Table 51. Proportion of Subjects Who Shift to High (From Normal, Low or Not Done) by Age

Age Group	CB-03-01	Placebo	Retin-A
Overall	33/495 (6.7%)	4/103 (3.9%)	0/30 (0%)
By age (years)			
9–11	9/27 (33.3%)	-	-
12–17	5/150 (3.3%)	2/37 (5.4%)	-
18+	19/318 (6.0%)	2/66 (3.0%)	0/30 (0%)

Source: Clinical and Statistical Reviewer Analysis of ISS ADLB

Table 52 presents the results of the maximum percent change from baseline in potassium level. The clascoterone group range was up to 90.2%, whereas in the placebo group there was up to a 31.7% change from baseline.

Table 52. Maximum Percent Change From Baseline in Potassium Level

	CB-03-01 (N=495)	Placebo (N=103)
Baseline		
N	469	95
Mean (SD)	4.22 (0.42)	4.23 (0.42)
Median	4.20	4.20
Range	3.1 to 6.3	3.4 to 6.1
Maximum percent change from baseline		
N	451	90
Mean (SD)	1.1% (13.6)	0.3% (10.3)
Median	-2.1%	0%
Range	-31.0% to 90.2%	-22.4% to 31.7%
LS mean A[1]	0.99%	-0.04%
Difference (95% CI)	1.03% (-1.63%, 3.69%)	
LS mean B[2]	0.92%	0.33%
Difference (95% CI)	0.59% (-2.06%, 3.25%)	

Abbreviations: LS = least square; CI = confidence interval
[1] LS means and difference are based on analysis of covariance with treatment and baseline value in the model.
[2] LS means and difference are based on analysis of covariance with treatment, baseline value, and age in the model.
Source: Clinical and Statistical Reviewer Analysis of ISS ADLB

A detailed evaluation of the potassium laboratory findings identified nine samples that may be driving these shift tables. An Information Request to the Applicant was submitted regarding levels of potassium over 5.9. The Applicant identified that the following subjects had hemolyzed samples: CB-03-01 (b) (6), CB-03-01 (b) (6), CB-03-01 (b) (6), CB-03-01/ (b) (6) CB-03-01/ (b) (6) CB-03-01 (b) (6) and CB-03-01/ (b) (6) All were healthy adults and were treated with CB-03-01. These subjects were removed, and the shift table analysis repeated. The results, not including hemolyzed samples, are presented in the tables below.

Table 53. Proportion of Subjects Who Shift to High (From Normal, Low or Not Done)*

	CB-03-01 (N=488)	Placebo (N=103)
Shifted to High	26 (5.3%)	4 (3.9%)
Risk Difference (95% CI)	1.4% (-2.8%, 5.7%)	

Source Source Clinical and Statistical Reviewer Analysis of ISS ADLB
*Excluding hemolyzed samples

Table 54. Proportion of Subjects Who Shift to High (From Normal, Low or Not Done) By Age*

	CB-03-01	Placebo
Overall	26/488 (5.3%)	4/103 (3.9%)
By Age (years)		
9-11	9/27 (33.3%)	-
12-17	5/150 (3.3%)	2/37 (5.4%)
18+	12/311 (3.9%)	2/66 (3.0%)

Source Clinical and Statistical Reviewer Analysis of ISS ADLB
* Excluding hemolyzed samples

Table 55. Maximum Percent Change From Baseline in Potassium Level

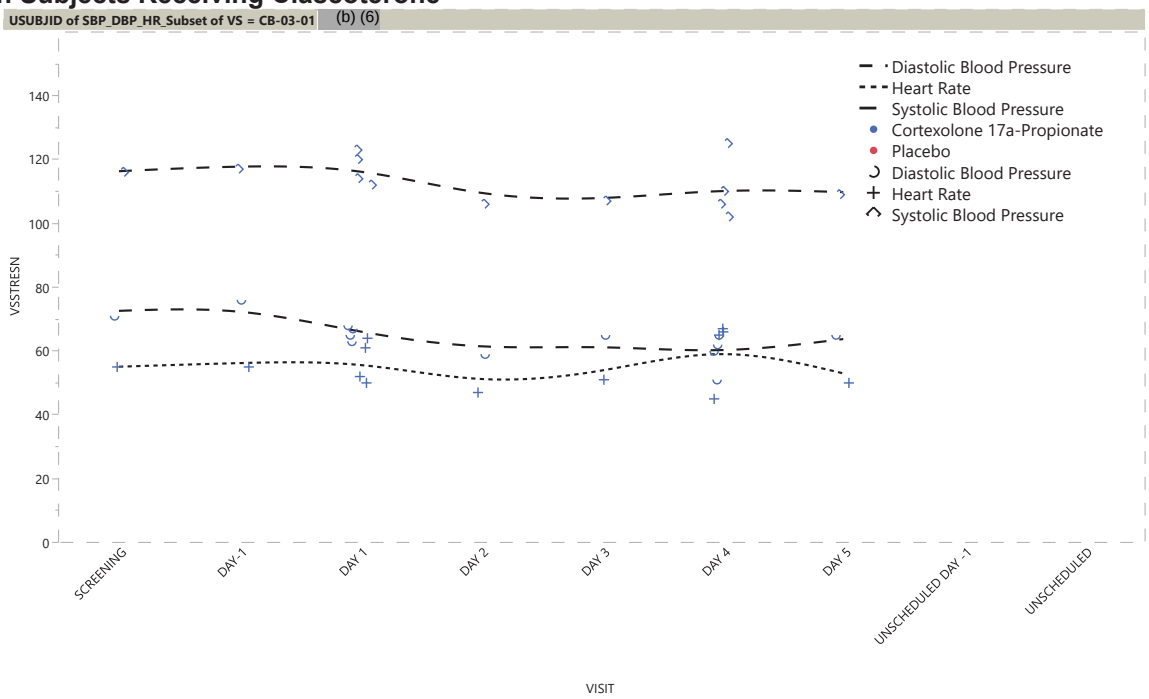
	CB-03-01 (N=495)	Placebo (N=103)
Baseline		
N	462	95
Mean (SD)	4.22 (0.41)	4.23 (0.42)
Median	4.20	4.20
Range	3.1 to 6.3	3.4 to 6.1
Maximum percent change from baseline		
N	444	90
Mean (SD)	0.2% (11.5)	0.3% (10.3)
Median	-2.2%	0%
Range	-31.0% to 63.6%	-22.4% to 31.7%
LS Mean A[1]	0.12%	-0.04%
Difference (95% CI)	0.16% (-2.06%, 2.38%)	
LS Mean B[2]	0.10%	0.06%
Difference (95% CI)	0.03% (-2.20%, 2.27%)	

[1] LS means and difference based on ANCOVA with treatment and baseline value in the model.
[2] LS means and difference based on ANCOVA with treatment, baseline value, and age in the model.
Source: Clinical and Statistical Reviewer Analysis of ISS ADLB

Overall, about 30% of pediatric patients ages 9 years to 11 years saw a shift from normal to high potassium after 14 days of treatment. The clascoterone group range was up to 63.6%, whereas in the placebo group, the range was up to 31.7% change from baseline.

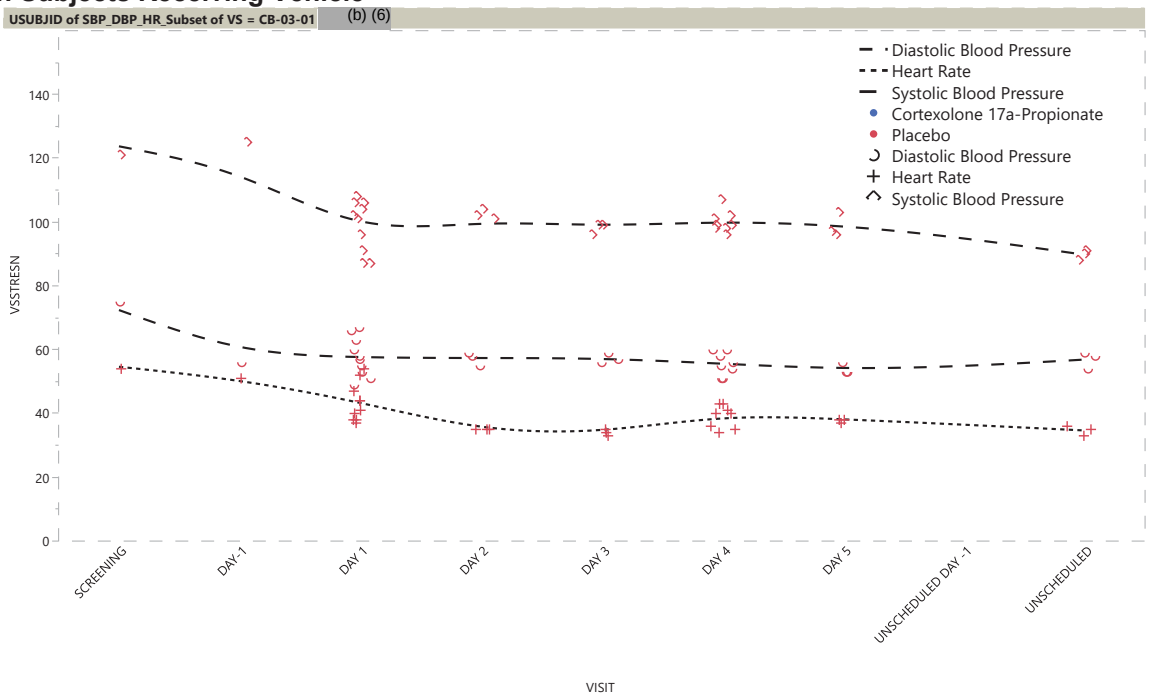
Additionally, the effect of increased potassium on vital signs such as blood pressure was evaluated. Study CB-03-01/33 in 1 site in the United Kingdom (June 2018) was designed to evaluate CB-03- 01 on QT prolongation, phase 1, randomized, double-blind, placebo-controlled in healthy adults (18 to 40 years). The treatment was with CB-03-01 solution 7.5% (3 mL) in 23 adults and eight with the vehicle, BID on day 1 to day 3, QD on day 4. There was no significant impact on diastolic or systolic blood pressure throughout the study in both subjects receiving the clascoterone (Figure 9) or vehicle (Figure 10).

Figure 9. Representative Example of Diastolic BP, Heart Rate, and Systolic Blood Pressure Over Visits in Subjects Receiving Clascoterone



Source: Clinical Reviewer Analysis

Figure 10. Representative Example of Diastolic BP, Heart Rate, and Systolic Blood Pressure Over Visits in Subjects Receiving Vehicle



Source: Clinical Reviewer Analysis

Reviewer's comment: *Hyperkalemia should be included in section 6 of the prescribing information..*

8.2.5.2. Local Tolerability: Telangiectasia, Skin Atrophy, and Striae Rubrae, Erythema, Edema, and Scaling/Dryness

As with other topical products, local tolerability in regard to cutaneous adverse events are adverse events of special interest. Telangiectasia, skin atrophy, striae rubrae, erythema, edema, and scaling/dryness, among others can occur. These parameters were evaluated at each visit during the pivotal trials, safety pool A, and during the long-term safety trial, trial CB-03-01/27, which lasted 12 months.

LSRs were collected independently of adverse events (AEs). Only LSRs that required medical intervention (e.g., prescription medication) or required withholding the application of the test articles were to be documented as AEs. Any LSRs not listed above were to be recorded as AEs. For Local Tolerability Assessments, data were pooled across the two phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26), in which 722 subjects were treated with clascoterone and 718 were treated with vehicle (designated pool A).

The investigator or designee rated the severity of telangiectasia, skin atrophy, and striae rubrae on a 5-point scale from 0 = none to 4 = severe, and rated erythema, edema, and scaling/dryness on the scales shown in Table 56. Subjects rated stinging/burning and pruritus (itching) on the scales shown in Table 57. These LSRs were collected independently of adverse events (AEs). Only LSRs that required medical intervention

Table 56. Investigator Rating Scales for Erythema, Edema, and Scaling/Dryness

Score/LSR	Assessment
Erythema	
0	None
1	Minimal – barely perceptible erythema
2	Mild – predominantly minimal erythema (pink) in the treated area with or without a few isolated areas of more intense erythema
3	Moderate – predominantly moderate erythema (red) in the treated area with or without a few isolated areas of intense erythema (bright red)
4	Severe – predominantly intense erythema (bright red) in the treated area with or without a few isolated areas of very intense (fiery red) erythema
Edema	
0	None
1	Minimal – scant, rare edema
2	Mild – easily seen edema, minimally palpable, involving up to 1/3 of the treatment area
3	Moderate – easily seen edema and typically palpable, involving between 1/3 to 2/3 of the treatment area
4	Severe – easily seen edema, indurated in some areas, involving over 2/3 of the treatment area

Score/LSR	Assessment
Erythema	
Scaling/dryness	
0	None
1	Minimal – barely perceptible desquamation
2	Mild – limited areas of fine desquamation in up to 1/3 of the treatment area
3	Moderate – fine desquamation involving 1/3 to 2/3 of the treatment area or limited areas of coarser scaling
4	Severe – coarser scaling involving more than 2/3 of the treatment area or limited areas of very coarse scaling

Abbreviation: LSR = local skin reaction
Source: Applicant submission

Table 57. Subject Rating Scales for Stinging/Burning and Pruritus

Score/LSR	Assessment
Stinging/burning	
0	None
1	Minimal, barely perceptible – tolerable and little discomfort
2	Moderate – tolerable, but causes some discomfort
3	Severe – very uncomfortable or intolerable
Pruritus (itching)	
0	None – no evidence of itching
1	Mild – only aware of itching at times, only present when relaxing, not present when focused on other activities
2	Moderate – often aware of itching, annoying, sometimes disturbs sleep and daytime activities
3	Severe – constant itching, distressing; frequent sleep disturbance, interferes with activities

Abbreviation: LSR = local skin reaction
Source: Applicant submission

In the phase 3 pivotal studies, in which only the face was treated, the proportion of subjects experiencing each LSR was similar between the treatment groups. The most severe intensity of each LSR during the studies was no or trace for most subjects (Table 59). The most frequent treatment-emergent LSRs were erythema (12.2% CB-03-01, 15.3% vehicle) and scaling/dryness (10.5% CB-03-01, 10.3% vehicle) (Table 60). Most of the treatment-emergent LSRs were trace or mild in severity. Subjects applied first dose of study product at the baseline visit.

There were two assessments of local skin reactions, one before application of first dose and on after application of first dose. Table 58 presents the immediate and long-term LSR. The proportion of subjects experiencing each LSR was similar between the treatment groups. The most frequent treatment-emergent LSRs were erythema and scaling/dryness. Analysis of ADSR database reveals that about 10% of the local evaluations were not completed.

Table 58. Number (Percentage) of Subjects With Immediate and Long-Term Local Skin Reactions in Pooled Phase 3 Pivotal Studies (Safety Population)

	Immediate		Long-Term	
Reaction	WINLEVI Cream 1% (N=722)	Vehicle Cream (N=718)	WINLEVI Cream 1% (N=687[a])	Vehicle Cream (N=662[a])
Edema	4 (0.6%)	2 (0.3%)	25 (3.6%)	23 (3.5%)
Erythema/reddening	18 (2.5%)	21 (2.9%)	84 (12.2%)	101 (15.3%)
Pruritus	18 (2.5%)	21 (2.9%)	52 (7.6%)	55 (8.3%)
Scaling/ dryness	1 (0.1%)	3 (0.4%)	72 (10.5%)	68 (10.3%)
Skin atrophy	0	0	11 (1.6%)	17 (2.6%)
Stinging/burning	24 (3.3%)	32 (4.5%)	28 (4.1%)	28 (4.2%)
Striae rubrae	1 (0.1%)	0	17 (2.5%)	10 (1.5%)
Telangiectasia	4 (0.6%)	1 (0.1%)	8 (1.2%)	12 (1.8%)

Source: Statistical Reviewer Analysis

Table 59. Number (Percentage) of Subjects With Local Skin Reactions by Severity in Pooled Phase 3 Pivotal Studies (Safety Population)

	CB-03-01 Cream 1% (N=722)				Vehicle (N=718)			
Reaction	**Trace/Mild[a]**	**Moderate**	**Severe**	**Total**	**Trace/Milda**	**Moderate**	**Severe**	**Total**
Edema	64 (8.9)	6 (0.8)	0	70 (9.7)	65 (9.1)	2 (0.3)	0	67 (9.3)
Erythema/reddening	233 (32.3)	30 (4.2)	2 (0.3)	265 (36.7)	240 (33.4)	26 (3.6)	2 (0.3)	268 (37.3)
Pruritus	76 (10.5)	23 (3.2)	2 (0.3)	101 (14.0)	81 (11.3)	23 (3.2)	3 (0.4)	107 (14.9)
Scaling/dryness	128 (17.7)	2 (0.3)	0	130 (18.0)	135 (18.8)	3 (0.4)	0	138 (19.2)
Skin atrophy	68 (9.4)	7 (1.0)	2 (0.3)	77 (10.7)	58 (8.1)	5 (0.7)	4 (0.6)	67 (9.3)
Stinging/burning	68 (9.4)	6 (0.8)	3 (0.4)	77 (10.7)	63 (8.8)	7 (1.0)	2 (0.3)	72 (10.0)
Striae rubrae	39 (5.4)	1 (0.1)	0	40 (5.5)	36 (5.0)	2 (0.3)	0	38 (5.3)
Telangiectasia	44 (6.1)	2 (0.3)	0	46 (6.4)	45 (6.3)	4 (0.6)	0	49 (6.8)

Source: ISS Table 31.1
[a] Minimal or mild for erythema, edema, and scaling/dryness; minimal for stinging/burning; and mild for pruritus

Table 60. Number (Percentage) of Subjects With Treatment-Emergent (New or Worsening) Local Skin Reactions After Day 1 by Severity in Pooled Phase 3 Pivotal Studies (Safety Population)

	CB-03-01 Cream 1% (N=687)[a]				Vehicle (N=662)[a]			
Reaction	**Trace/Mild[b]**	**Moderate**	**Severe**	**Total**	**Trace/Mild[b]**	**Moderate**	**Severe**	**Total**
Edema	22 (3.2)	3 (0.4)	0	25 (3.6)	22 (3.3)	1 (0.2)	0	23 (3.5)
Erythema/reddening	73 (10.6)	11 (1.6)	0	84 (12.2)	88 (13.3)	12 (1.8)	1 (0.2)	101 (15.3)
Pruritus	36 (5.2)	14 (2.0)	2 (0.3)	52 (7.6)	37 (5.6)	15 (2.3)	3 (0.5)	55 (8.3)
Scaling/dryness	70 (10.2)	2 (0.3)	0	72 (10.5)	67 (10.1)	1 (0.2)	0	68 (10.3)
Skin atrophy	10 (1.5)	1 (0.1)	0	11 (1.6)	16 (2.4)	1 (0.2)	0	17 (2.6)
Stinging/burning	23 (3.3)	3 (0.4)	2 (0.3)	28 (4.1)	23 (3.5)	3 (0.5)	2 (0.3)	28 (4.2)
Striae rubrae	17 (2.5)	0	0	17 (2.5)	10 (1.5)	0	0	10 (1.5)
Telangiectasia	8 (1.2)	0	0	8 (1.2)	10 (1.5)	2 (0.3)	0	12 (1.8)

Source: ISS Table 31.1a
[a] The denominators for calculating the percentages were the 687 of 722 patients treated with WINLEVI cream and 662 of 718 patients treated with vehicle in these studies who had local skin reaction results reported after day 1.
[b] Minimal or mild for edema, erythema, and scaling/dryness; minimal for stinging/burning; and mild for pruritus

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The phase 3 protocols did not include patient-reported outcome.

8.2.7. Safety Analyses by Demographic Subgroups

Overall summaries of TEAEs for subjects who received CB-03-01 by the subgroups of age, gender, and race are shown in Table 61 for pool A.

In the pooled phase 3 pivotal studies, a higher proportion of subjects age 9 years to <12 years experienced TEAEs (23.1%) compared to those 12 years to <18 years (10.8%) or 18 years to <65 years (11.5%). This trend is difficult to interpret due to the small number of subjects in the youngest age group (13 compared to 316 and 393 in the older groups). The proportion of subjects who experienced TEAEs was similar between genders, race categories, and whether subjects had moderate or severe disease at baseline (IGA score). There were no notable differences among the subgroups in the nature of the TEAEs.

Table 61. Overall Summary of Treatment-Emergent Adverse Events by Subgroups of Age, Gender, Race, for CB-03-01 1% Cream, BID Group in Phase 3 Pivotal Studies (Pool A)

	Age			Gender		Race		Total
Category, n (%)	9-<12 (n=13)	12-<18 (n=316)	≥18 (n=393)	Male (n=258)	Female (n=464)	White (n=655)	Non-White (n=67)	All (n=722)
All TEAEs	3 (23.1)	34 (10.8)	45 (11.5)	27 (10.5)	55 (11.9)	77 (11.8)	5 (7.5)	82 (11.4)
Serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs related to study drug	0 (0.0)	5 (1.6)	7 (1.8)	4 (1.6)	8 (1.7)	11 (1.7)	1 (1.5)	12 (1.7)
Serious TEAEs related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to dose modification	1 (7.7)	1 (0.3)	4 (1.0)	0 (0.0)	6 (1.3)	6 (0.9)	0 (0.0)	6 (0.8)
TEAEs leading to discontinuation of study drug	0 (0.0)	2 (0.6)	3 (0.8)	2 (0.8)	3 (0.6)	5 (0.8)	0 (0.0)	5 (0.7)
TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BID = twice daily; TEAE = treatment-emergent adverse event
Source Data: Applicant ISS Table 20.1 ADAE, ADSL

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant submitted supportive safety data from one phase 2 dose-ranging trial and two PK studies conducted under conditions of maximal use. Safety results from these studies will be summarized briefly below.

- Study 171-7151-201 phase 2, double-blind, parallel-group, vehicle-controlled, dose response vehicle-controlled studies in subjects with acne vulgaris subjects ≥12 years old with mild to severe facial acne vulgaris (IGA Grade 2 to 4)

Safety Results

AEs

Overall, 123 AEs were reported by 93 subjects. The percentage was similar across the five treatment groups with no difference between the treated groups and vehicle; however, a higher proportion of subjects had AEs in the CB-03-01 0.5% BID group, 38.2% versus 18.6% to 25.0% in the other groups . The AEs reported by four or more subjects (≥5% incidence of any AE in any treatment group) are shown in Table 20. Only two AEs were deemed probably (application site pain) or possibly (nasopharyngitis) related to study drug (CB-03-01 1% QD) and both events were mild in severity and observed in the same subject. All AEs were mild or moderate in severity except for three that were severe (miscarriage, right ankle fracture, and right arm fracture). The majority of AEs had recovered/resolved without sequelae at the end of the study.

Two SAEs were reported, miscarriage and right ankle fracture, which were both considered unrelated to study drug. One AE (urinary tract infection; deemed unrelated to study drug) led to the subject's discontinuation from the study.

Local Tolerability

All CB-03-01 cream regimens were well-tolerated locally. The incidence of LSRs was similar across treatment groups and low throughout the study. Telangiectasia, skin atrophy, striae rubrae, edema, scaling/dryness, stinging/burning, and pruritus were absent for the majority of subjects (>82%). Erythema was the most prevalent LSR with 36.8% of subjects having at least minimal erythema at some time. The CB-03-01 0.5% BID group had more subjects with at least minimal erythema over the duration of the study compared to the other treatment groups. Overall, relative to baseline, no clinically relevant signs of the typical LSRs associated with corticosteroid use (e.g., telangiectasia, atrophy, striae) were observed in any treatment group.

- Study CB-03-01/28 maximum use HPA/PK study to evaluate adrenal suppression potential and PK in pediatric subjects with acne vulgaris pediatric subjects (9 years to <12 years)

Objectives

To evaluate the adrenal suppression potential and PK in pediatric subjects with acne vulgaris

Design

In this maximum use HPA/PK study, 27 subjects applied open-label CB-03-01 cream, 1%, to the face and trunk BID for 2 weeks. Subjects were instructed to apply 2 grams per application (1 gram on the face and 1 gram on the trunk) for a total of 4 grams daily. Subjects had a CST at the screening visit and day 14/EOS. PK samples were collected prior to the first application of CB-03-01 at day 1 and at specified times at day 7 and day 14. Study drug was applied by the subject or in the clinic under supervision on day 1 and day 7 and at home for all other applications.

Subjects

Males and females 9 years to <12 years old with moderate to severe facial acne vulgaris (IGA score 3 or 4) and obvious acne on the trunk (shoulder, upper chest, and/or back)

Safety Results

HPA Axis Suppression

See Clinical Pharmacology section 6.

AEs

Five subjects reported five TEAEs. The four TEAEs of ACTH stimulation test abnormal were deemed to be related to CB-03-01 cream, 1%, and had resolved by the end of the study. The TEAE of leukopenia, which was not considered related to CB-03-01, was resolving at the EOS.

No SAEs were reported and no subject discontinued due to an AE.

Local Tolerability

Skin atrophy and striae rubrae were absent for all subjects at all visits. The majority of LSRs were absent for all subjects at all visits: telangiectasia (≥96.3%), stinging/burning (≥96.3%), scaling/dryness (≥88.9%), pruritus (≥85.2%), edema (≥85.2%), and erythema (≥70.4%). Except for four cases of moderate LSRs in three subjects (moderate erythema pre- and postapplication at day 1, moderate stinging/burning at day 7, and moderate erythema at day 14), all other LSRs were trace, minimal, or mild in severity. There were no severe LSRs. Erythema was the most commonly occurring LSR with eight subjects (8/27, 29.6%) having minimal/mild/moderate erythema pre- and postapplication on day 1 and on day 14/EOS.

- Study 171-7151-202 maximum use HPA/PK study to evaluate adrenal suppression potential and PK in adults and adolescents with acne vulgaris adults (≥18 years, cohort 1) and adolescents (12 years to <18 years, cohort 2)

Objectives

To evaluate the adrenal suppression potential and PK in adults and adolescents with acne vulgaris

Design

In this maximum use HPA/PK study, subjects applied open-label CB-03-01 cream, 1%, to the face and trunk BID for 2 weeks. Subjects were instructed to apply 6 grams (subjects who were >18 years old or <18 with a body surface area [BSA] >1.6 m2) or 4 grams (subjects who were <18 years old with a BSA <1.6 m2) of the cream per application. Subjects had a CST at the screening visit and day 14/EOS. PK blood samples were collected prior to the first application of CB-03-01 at day 1 and at specified times at day 5, day 10, and day 14. At the completion of cohort 1 in adults (>18 years of age), and after an interim safety review by the medical monitor to confirm there were no material safety issues in cohort 1, cohort 2 was enrolled in adolescents (≥12 years to <18 years).

Subjects

Males and females ≥12 years old with moderate to severe facial acne vulgaris (IGA score 3 or 4) and obvious acne on the chest and/or back

Safety Results

HPA Axis Suppression

See Clinical Pharmacology section 6.

AEs

Nine AEs were reported among eight subjects. Four AEs were considered by the investigator probably (one abnormal CST result and one application site folliculitis) or definitely (two abnormal CST results) related to study drug. All other AEs were considered unlikely related or not related. The AEs were mild except for diarrhea, which was moderate in severity.

No SAEs were reported and no subject discontinued due to an AE.

Local Tolerability

The LSRs were trace, mild, or minimal except for one moderate case of pruritus in cohort 2. Pruritus was reported in seven subjects, erythema and stinging/burning were each reported in four subjects, scaling/dryness was reported in three subjects, and telangiectasia (trace) was reported in one subject. Skin atrophy, striae rubrae, and edema were not reported for any subject.

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 program, the trial designs did not include specific assessments to evaluate for carcinogenicity or screen for safety signals related to malignancy. However, no malignant neoplasms were reported during the phase 3 trials. The Applicant intends to rely on nonclinical information related to carcinogenicity.

Human Reproduction and Pregnancy

This was discussed in section 8.2.4 in the Significant Adverse Events subsection.

Pediatrics and Assessment of Effects on Growth

HPA Axis Suppression

Patients experienced an abnormal ACTH stimulation test.

Table 62. Abnormal ACTH Stimulation Tests in Pediatric Patients

USUBJID	Age	Sex	Arm	AESEV	AEREL
171-7151-202 (b) (6)	14	F	CB-03-01 cream, 1% - 6g	Mild	Probably related
171-7151-202	14	F	CB-03-01 cream, 1% - 4g	Mild	Definitely related
CB-03-01 (b) (6)	11	M	CB-03-01 cream, 1%	Mild	Definitely related
CB-03-01	10	F	CB-03-01 cream, 1%	Mild	Probably related
CB-03-01	11	F	CB-03-01 cream, 1%	Moderate	Definitely related
CB-03-01	10	F	CB-03-01 cream, 1%	Moderate	Probably related

Source: Clinical Reviewer Analysis
Abbreviations: AESEV = adverse event severity; AEREL = adverse event related

Reviewer's comment: *All abnormal ACTH stimulation tests are considered to be related to the treatment. For details on HPA suppression, see the Clinical Pharmacology section.*

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

There have been no instances of CB-03-01 overdose in the clinical studies.

Drug Abuse Potential, Withdrawal, and Rebound

Clascoterone (CB-03-01, cortexolone 17α propionate) acts as an androgen receptor inhibitor and is not a central nervous system-active new molecular entity.

In a nonclinical safety pharmacology study, the potential neurobehavioral effects of CB-03-01 were evaluated in rats following single SC administration (Report CB 03 01/13). The GLP compliant study design consisted of five groups of eight male Wistar rats, dosed by SC injection with vehicle control, positive control chlorpromazine at 10 mg/kg, or CB 03-01 at 10, 50, or 250 mg/kg.

On the study day, animals were first scored by the Irwin standardized observation battery. Subsequently, they were dosed with CB-03-01 or its vehicle in a volume of 5 mL/kg or chlorpromazine in a volume of 1 mL/kg. The Irwin scores were performed again at 0.5 hours, 1 hour, 2 hours, 4 hours, and 8 hours after administration. Dose formulation analyses revealed concentrations ranging from 88% to 106% of target.

CB-03-01 did not affect behavior at any dose or timepoint while the positive control produced the anticipated depressive effects.

Clinically, the two pivotal phase 3 studies were double-blind, vehicle-controlled, multicenter studies of CB 03 01 cream, 1%, and included 1440 subjects with acne vulgaris (722 CB-03-01, 718 vehicle); subjects applied study drug twice daily to their face for 12 weeks. Results of those studies were pooled for the integrated analysis of safety (pool A). Nervous system and psychiatric TEAEs were infrequent (ISS Table 10.1):

Nervous System Disorders

- Headache: 6/722 (0.8%) with CB-03-01, 4/718 (0.6%) with placebo
- Sciatica: 1/722 (0.1%) with CB-03-01, 0/718 with placebo
- Neuralgia: 0/722 with CB-03-01, 1/718 (0.1%) with placebo

Psychiatric Disorders

- Depression: 1/722 (0.1%) with CB-03-01, 0/718 with placebo
- Libido decreased: 1/722 (0.1%) with CB-03-01, 0/718 with placebo
- Mood swings: 1/722 (0.1%) with CB-03-01, 0/718 with placebo
- Insomnia: 0/722 with CB-03-01, 1/718 (0.1%) with placebo

Only two of these TEAEs were considered by the investigator to be possibly related to study drug, one case of headache with CB-03-01 and one case of headache with vehicle.

Based on the nonclinical and clinical data demonstrating the lack of central nervous system activity with topically applied clascoterone formulations, and consistent with FDA's Guidance for Industry on Assessment of Abuse Potential of Drugs, the review team concludes that there is no liability for abuse potential with the clascoterone drug product.

Withdrawal and Rebound

No studies of CB-03-01 have been designed to evaluate withdrawal and/or rebound. However, in the LTF Study CB-03-01/27 treatment on the face and/or trunk may have been discontinued if/when acne cleared and restarted if/when acne worsened, according to the assessment of the investigator for each treatment area (face and trunk).No safety issues were identified in that study.

Suicide Attempt

One study subject in study CB-03-01/27 (phase 3) ID = CB-03-01 (b) (6) age 14, had a suicide attempt. She was in the CB-03-01 study group.

Subject (b) (6), a 14-year-old Caucasian female, experienced a serious TEAE of severe dizziness on day 145 (b) (6) of the study that required hospitalization, and a second serious TEAE of severe suicide attempt on day 172 (b) (6) of the study that also required hospitalization. Both serious TEAEs were considered not related to test article. The dizziness did not lead to study discontinuation and recovered/resolved on day 172 (b) (6) of the study. The suicide attempt led to study discontinuation and recovered/resolved on day 172 (b) (6) of the study. The subject enrolled into the study on (b) (6), and discontinued from the study on (b) (6) due to the serious TEAE of suicide attempt.

In the long-term safety study CB-03-01/27, one patient had a suicide attempt. Nothing in the patient medical history or medication reflects an increased risk for suicide. (b) (6)

(b) (6)

It is not possible to conclude if this suicide attempt is related to the drug.

Reviewer's comment: *Labeling for depression/suicidality is not recommended given the background rate in this age group in general and for acne patients in particular.*

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Clascoterone cream, 1%, is not marketed in any jurisdiction. There are no ongoing nonclinical or clinical trials that could provide additional data to inform the current or anticipated safety evaluation for this product. Therefore, no postmarketing safety data are available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the safety data for clascoterone cream, 1%, identified no safety signals. There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of clascoterone cream, 1%, in the postmarket setting. Reporting of local application site events is the primary expectation in the postmarketing environment.

8.2.11. Integrated Assessment of Safety

The safety profile for clascoterone cream, 1%, was adequately characterized during the drug development program. The primary safety database consisted of 1,440 subjects from phase 3 clinical trials CB-03-01/25 and CB-03-01/26 (pool A). All randomized subjects who were included in the safety analysis set used the study drug at least once and provided at least one postbaseline evaluation. Long-term safety up to 12 months of treatment came from clinical trial CB-03-01/27.

Review of the safety data, including the long-term safety data, did not reveal any contraindications to treatment with clascoterone cream, 1%, to be included in product labeling (section 4 CONTRAINDICATIONS). The data continue to support advising patients about the potential for skin irritation in section 5 WARNINGS AND PRECAUTIONS of labeling. Active assessment of local tolerability indicated that the percentage of subjects who reported signs and symptoms (erythema, scaling, dryness, stinging/burning) at a postbaseline visit was similar in the clascoterone cream, 1%, group to the vehicle group.

Treatment with clascoterone cream, 1%, was not associated with an increased risk of mortality or serious adverse events. There were no deaths in the development program for clascoterone cream, 1%, and there were no serious adverse events assessed as related to either study product. In the pooled safety analysis set (pool A), serious adverse events occurred in 0% subjects in the clascoterone cream, 1%, group and 0.3% subjects in the vehicle group. Among

subjects in the clascoterone cream, 1%, group, there were no serious adverse events. Among subjects in the vehicle group, serious adverse events included pneumonia and hematoma.

There were five pregnancies throughout the development program; three on clascoterone cream, 1%, and two on vehicle. Among the four subjects on clascoterone cream, 1%, there were an induced abortion, full-term C-section and intrahepatic cholestasis of pregnancy associated with extreme pruritus; oligohydramnios. Among the subjects on vehicle, there was one lost to follow-up and one preterm delivery, week 35. The Applicant considered any congenital anomaly/birth defect, and any abortion (voluntary, spontaneous, or therapeutic) a serious adverse event. The data collected in the overall program is insufficient to ascertain the teratogenicity of clascoterone cream, 1%. However, with low systemic exposure, patients should be advised to use this topical androgenic receptor inhibitor only if the benefits outweigh the risks. The available data from the submission or a review of the literature does not indicate a clear risk for use during pregnancy or lactation, or that there is a clear risk of infertility. The review team in section 8 of labeling conveys the uncertainty regarding a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. It also includes a precaution for lactating mothers.

The currently available safety data from two 12-week phase 3 trials demonstrate that clascoterone cream, 1%, appears safe for the treatment of acne vulgaris in patients 12 years of age and older. The safety profile of long-term use of clascoterone cream, 1% (12 months) appears to be the same as short-term use. Postmarketing risk management will include professional labeling and routine pharmacovigilance. As there were no major safety issues with the use of clascoterone cream, 1%, and the safety profile, the review team recommends no other risk management tools and assessments (risk evaluation and mitigation strategy or clinical postmarketing studies) beyond product labeling.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were generally consistent across trials and endpoints. For the handling of missing data, the results were similar across the various methods investigated to impute the missing data (see Table 15), except under the worst case/value approaches; however, the assumptions for these approaches were deemed not reasonable given the observed data.

There were a large number of sites in each trial, and there were a small number of subjects per treatment group in most sites. Efficacy results varied across centers and some centers had higher efficacy with vehicle than with WINLEVI. It does not appear that any single center drove the overall efficacy results.

8.3.2. Conclusions and Recommendations

To establish the safety and efficacy of WINLEVI (clascoterone) cream, 1%, for the treatment of moderate to severe acne vulgaris the Applicant submitted data from two-identically designed, randomized, multicenter, double-blind, vehicle-controlled, phase 3 trials (CB-03-01/25 and CB-03-01/26). Both trials enrolled subject 9 years of age and older with moderate to severe acne vulgaris, defined as:

- Male or female, 9 years of age or older
- IGA score of 3 (moderate) or 4 (severe), see Table 11 for details on the IGA scale
- 30 to 75 inflammatory lesions (papules, pustules, and nodules)
- 30 to 100 noninflammatory lesions (open and closed comedones)
- No more than two facial nodules

Both were identically-designed to enroll and randomize approximately 700 subjects in a 1:1 ratio to either WINLEVI cream (n=350) or vehicle cream (n=350). Subjects applied study product to the face twice daily for 12 weeks. Subjects were scheduled to be evaluated at the following four visits: baseline (day 1), and week 4, week 8, and week 12.

The coprimary endpoints for the two trials were:

- Proportion of subjects achieving IGA success at week 12, with success defined as an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-point reduction from baseline
- Absolute change from baseline in noninflammatory lesion counts at week 12
- Absolute change from baseline in inflammatory lesion counts at week 12

The protocols specified the following secondary efficacy endpoints: 1) Absolute change from baseline in total lesion counts (inflammatory and noninflammatory) at week 12; 2) Percent change from baseline in total lesion counts (inflammatory and noninflammatory) at week 12; 3) Percent change from baseline in noninflammatory lesion counts at week 12 and 4) Percent change from baseline in inflammatory lesion counts at week 12.

In both trials, clascoterone cream, 1%, was statistically superior to vehicle for the coprimary and secondary endpoints, for subjects 12 years and older. A beneficial treatment effect was not observed in subjects 9 years to 11 years of age (see section 8.1.7); however, this may be attributed to the very small size of this subgroup (16 subjects in study CB-03-01/25 and 3 subjects in study CB-03-01/26). Refer to section 8.1.4 for discussion of the coprimary endpoints and section 8.1.5 for discussion of the secondary endpoints.

The Applicant conducted a comprehensive assessment of the safety of clascoterone cream, 1%, in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions. None of the safety issues identified in the review of the NDA would preclude market approval. Neither does it necessitate any safety mitigation strategies.

Submitted safety and efficacy data support approval of NDA 213433, WINLEVI (clascoterone) cream for the topical treatment of for the treatment of moderate to severe acne vulgaris in patients age 12 years and older.

9. Advisory Committee Meeting and Other External Consultations

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

10. Pediatrics

In the phase 3 and phase 1 trials, the Applicant established the safety and efficacy of clascoterone cream, 1%, for use in the target pediatric population age 12 years to less than 17 years for the treatment of acne vulgaris.

Acne vulgaris is a common skin disease with onset in adolescence, generally at or shortly after the onset of puberty. NAMCS data show more than 91% of acne visits were for adolescent patients, with the number of visits for prepuberty or midchildhood patients substantially lower (Davis et al. 2013). Therefore, the Applicant requested a partial pediatric waiver in conducting studies in children younger than 9 years old with acne vulgaris for clascoterone cream, 1%, because the necessary studies are impossible or highly impracticable (section 505B(a)(4)(A)(i) of the Act). This is supported by: 1) the limited availability of subjects <9 years of age (due to very low incidence of acne vulgaris in this age group); 2) recent FDA precedents granting a waiver from conducting studies in children with acne vulgaris under 9 years of age (Epiduo).

The Pediatric Review Committee agreed with the Division that the assessments were adequate (September 2015). Therefore, no postmarketing requirements or commitments for deferred pediatric studies are needed under the Pediatric Research Equity Act (21 CFR 314.55(b) and 601.27(b)). Refer to Pediatrics and Assessment of Effects on Growth for a discussion regarding the Pediatric Study Plan.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed prescribing information (PI) and carton/container labels for WINLEVI (clascoterone) cream, 1%. The review team provided recommendations regarding the

PI that are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, proposed patient package insert (PPI), and carton/container. These comments are reflected in final labeling. Refer to the OPDP review by Laurie Buonaccorsi, Regulatory Review Officer dated April 24, 2020. In addition, Madhuri R. Patel, PharmD, from the Division of Medication Error Prevention and Analysis provided comments regarding the proposed carton and container labels (review in DARRTs dated February 13, 2020).

Table 63. Location of Labeling Discussion for Significant High-Level Labeling Changes

Summary of Significant High level Labeling Changes	
Section	**Location of Reviewer Comments on Proposed Labeling**
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	Section 8.1
4 CONTRAINDICATIONS	Section N/A
5 WARNINGS AND PRECAUTIONS	Section 8.2.2
6 ADVERSE REACTIONS	Sections 8.2.4, 8.3.2. 8.2.1,8.2.2
7 DRUG INTERACTIONS	Section 6.3
8 USE IN SPECIFIC POPULATIONS	Sections 8.2.4, 5.5.4
12 CLINICAL PHARMACOLOGY	Section 6.3
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of product labeling (sections 1, 2, 5, 6)
13 NONCLINICAL TOXICOLOGY	Section 5

Other Prescription Drug Labeling

The Applicant submitted a PPI for WINLEVI (clascoterone) cream, 1%. The Division of Medical Policy Programs and OPDP reviewed and provided comments regarding the PPI. The final labeling will reflect their recommendations. Refer to patient labeling review by Susan Redwood in DARRTs (April 30, 2020). In summary, in the collaborative review of the PPI, the Division did the following:

- Simplified wording and clarified concepts where possible
- Ensured that the PPI is consistent with the PI
- Removed unnecessary or redundant information
- Ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- Ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

12. Risk Evaluation and Mitigation Strategies

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

13. Postmarketing Requirements and Commitment

None.

14. Division Director (OCP) Comments

None.

15. Division Director (OB) Comments

Not applicable.

16. Division Director (Clinical) Comments

I concur with the recommendation to approve NDA 213433, WINLEVI (clascoterone) cream, 1%, for the topical treatment of acne vulgaris in patients aged 12 years and older, pending completion of the review by the Office of Product Quality.

Clascoterone is a new molecular entity and an androgen receptor-inhibitor, with structural similarity to dihydrotestosterone and spironolactone. Nonclinical data suggest the presence of topical anti-androgenic activity; systemic antiandrogenic activity was not observed in animals. There is low systemic absorption with topical administration.

Clascoterone's effectiveness in the treatment of acne vulgaris was based on two identical randomized, double-blind, vehicle-controlled, 12-week phase 3 trials (708 and 732 subjects randomized for study CB-03-01/25 and study CB-03-01/26, respectively) in subjects with moderate to severe acne vulgaris. Overall results of the three coprimary endpoints in these trials (IGA success [IGA score of clear or almost clear and at least two point improvement from baseline]); absolute change from baseline in noninflammatory lesion counts; and absolute change from baseline in inflammatory lesion counts) were consistent in demonstrating a treatment benefit.

Across vehicle-controlled studies (171-7151-201, CB-03-01/25, CB-03-01/26), 792 subjects with acne were treated with clascoterone cream, 1%, BID for 12 weeks, and 123 subjects were exposed for up to 12 months. In the phase 3 trials, premature discontinuation was either similar between groups or higher in vehicle-treated subjects, suggesting that clascoterone was well-tolerated. There were no deaths in the clinical program; no serious adverse events were observed in clascoterone-treated subjects in the phase 3 trials. During the 12-week phase 3 trials, there were no observed imbalance regarding adverse events, such as gynecomastia or reduction in body hair, that would indicate a systemic anti-androgenic effect; however, any

conclusion should be interpreted with caution given the lack of events in either group. Routine postmarketing surveillance can include monitoring for such events.

The review team did not recommend approval in patients aged 9 years to 11 years old. I concur, based on the lack of benefit in this small subgroup, along with the increased proportion of TEAE and increased percentage of HPA axis suppression.

17. Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve NDA 213433 for WINLEVI (clascoterone) cream, 1%, for the topical treatment of acne vulgaris in patients 12 years of age and older. Clascoterone is an androgen receptor inhibitor and a new molecular entity.

Substantial evidence of effectiveness was demonstrated relative to vehicle in patients 12 years of age and older evaluated at 12 weeks in two randomized, controlled phase 3 trials. Topical treatment with clascoterone was well tolerated in these trials, and among 123 patients exposed to 12 months of active treatment. The risks associated with clascoterone use can be adequately mitigated by product labeling; a risk evaluation and mitigation strategy or risk evaluation and mitigation strategies will not be required.

Subgroup analysis of patients under 12 years of age did not show a beneficial treatment effect. In addition, the proportions of patients under 12 years of age that experienced HPA axis suppression or shifts from normal to high potassium levels were greater than in other age groups. For these reasons, WINLEVI is not indicated in patients under 12 years of age.

18. Appendices

18.1. References

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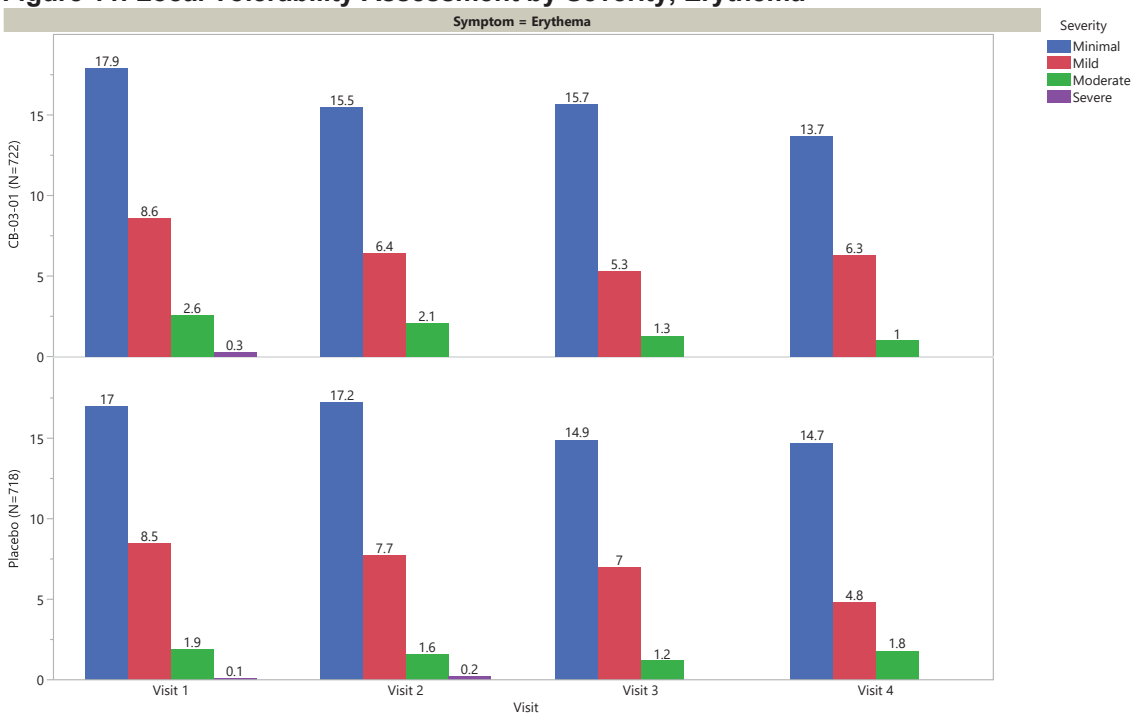
18.2. Clinical Assessments

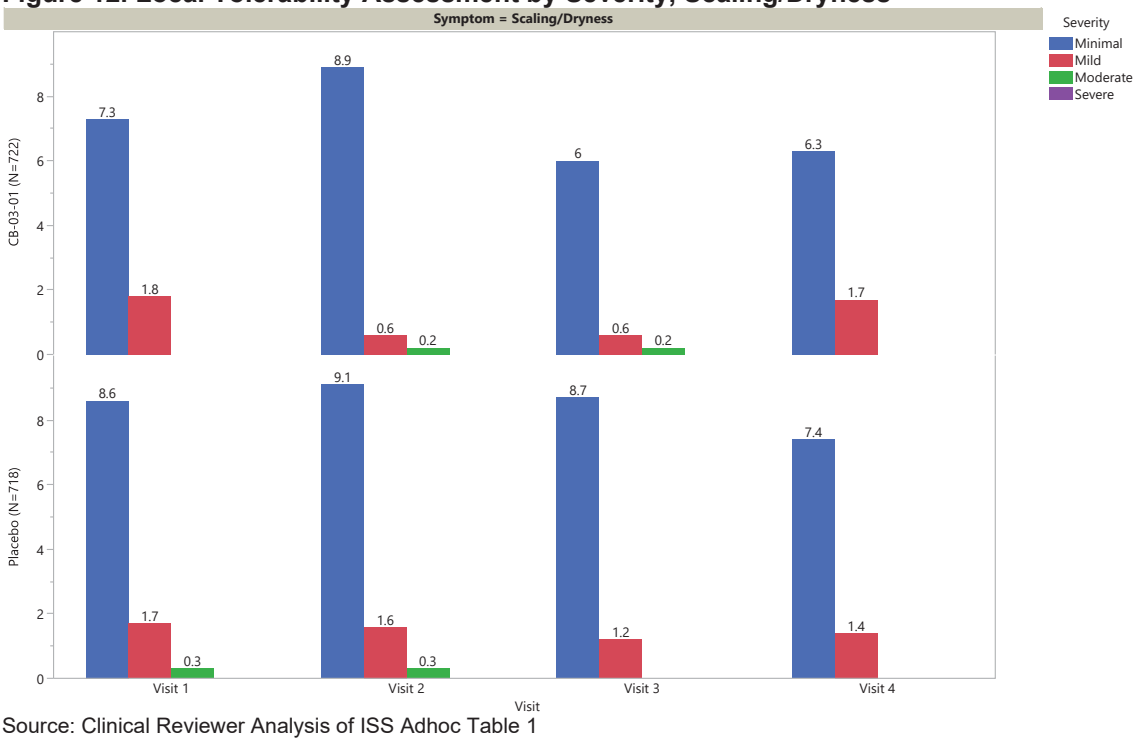
Local Tolerability Assessments by Severity

Figure 11. Local Tolerability Assessment by Severity, Erythema



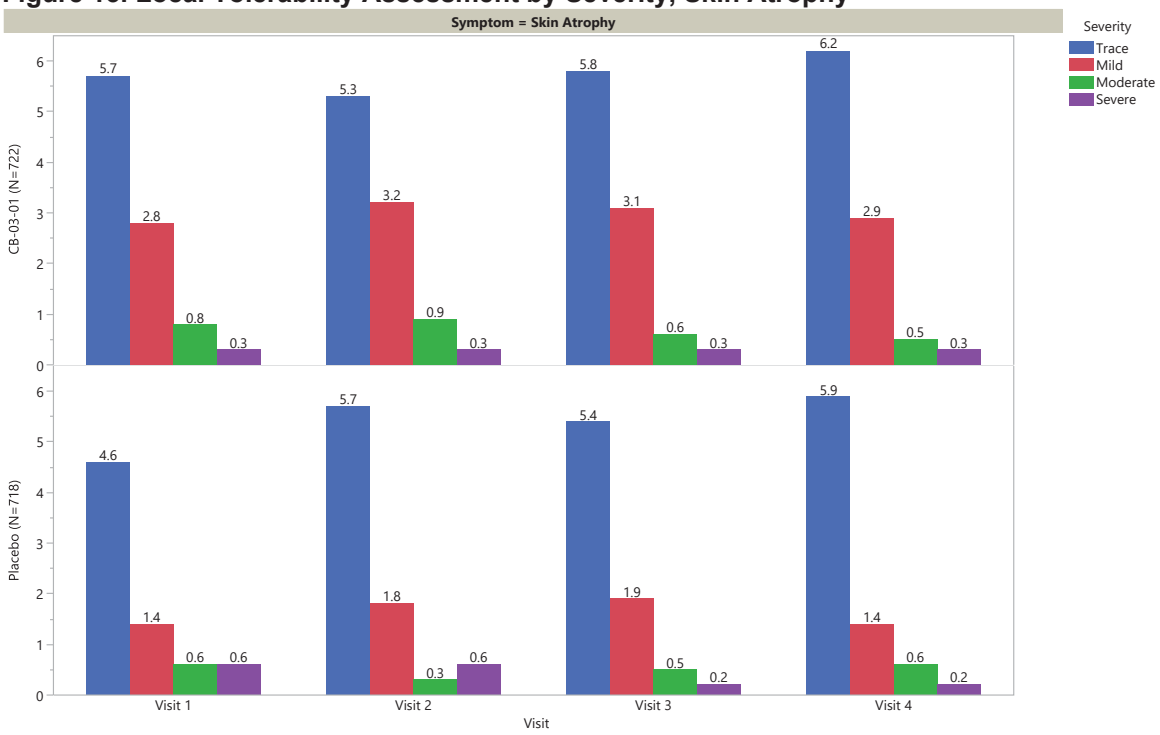
Source: Clinical Reviewer Analysis of ISS Adhoc Table 1

Figure 12. Local Tolerability Assessment by Severity, Scaling/Dryness



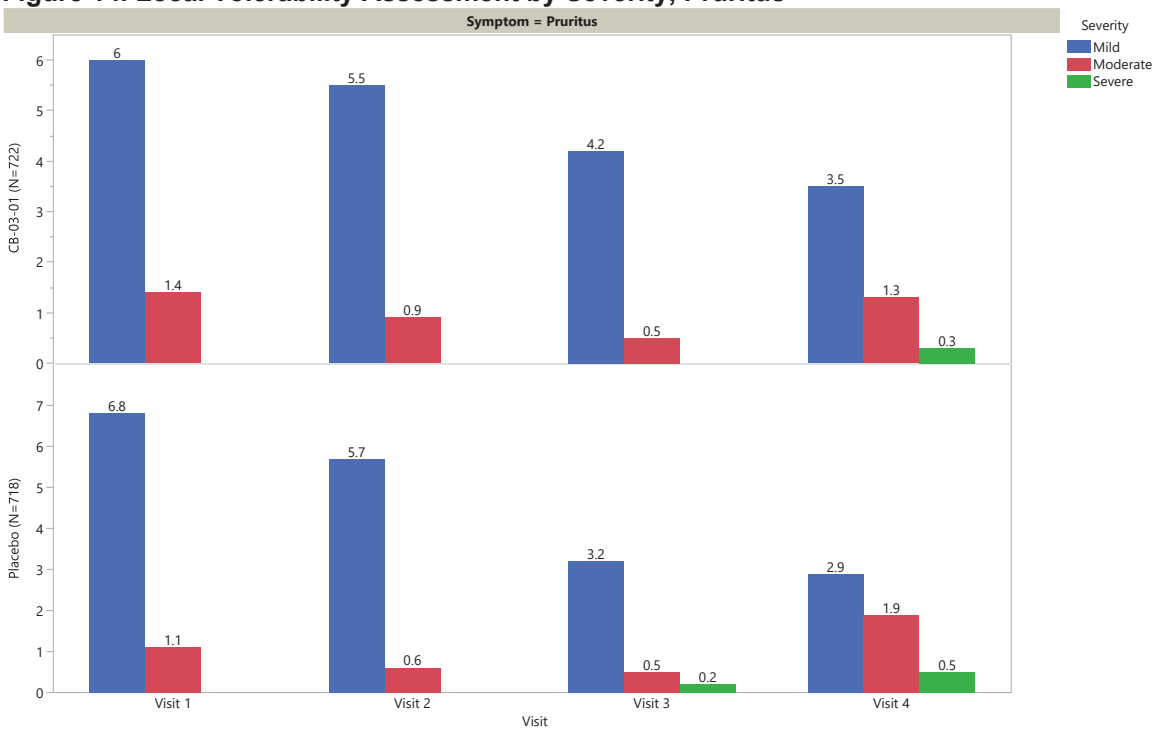
Source: Clinical Reviewer Analysis of ISS Adhoc Table 1

Figure 13. Local Tolerability Assessment by Severity, Skin Atrophy



Source: Clinical Reviewer Analysis of ISS Adhoc Table 1

Figure 14. Local Tolerability Assessment by Severity, Pruritus



Source: Clinical Reviewer Analysis of ISS Adhoc Table 1

18.3. Clinical Pharmacology Assessments

The clascoterone acne vulgaris clinical development program included 13 clinical studies in support of the proposed indication.

- Six phase 1 trials in healthy subjects and subjects with acne vulgaris
  - Study CB-03-01/02: A single ascending-dose pharmacokinetic (PK) study in healthy male subjects
  - Study CB-03-01/04: A repeat-dose PK study in healthy adult subjects
  - Study CB-03-01/05: A repeat-dose study in healthy subjects to evaluate potential cumulative skin irritation
  - Study CB-03-01/32: A repeat-dose study in healthy subjects to determine potential to induce sensitization
  - Study CB-03-01/33: A repeat-dose QT/QTc study in healthy subjects
  - Study 171-7151-203: A repeat-dose safety/PK study in subjects with acne vulgaris
- Four Phase2 dose range or maximal use trials in subjects with acne vulgaris (patients)
  - Study 171-7151-202: A maximal use PK study to evaluate hypothalamic-pituitary-adrenal (HPA) axis suppression potential in patients aged ≥12
  - Study CB-03-01/28: A maximal use PK study to evaluate HPA axis suppression potential in patients aged 9 to 11
  - Study CB-03-01/03: A comparative pilot study in adult patients
  - Study 171-7151-201: A dose-ranging study in patients aged ≥12
- Three phase 3 efficacy and safety trials in subjects ≥9 years old with acne vulgaris
  - Two identical pivotal studies
    - Study CB-03-01/25
    - Study CB-03-01/26
  - Study CB-03-01/27: An open-label long-term study up to 12 months

Of note, the PK studies (171-7151-202 and CB-03-01/28) conducted under maximal use conditions are considered as pivotal clinical pharmacology studies for this NDA.

The Applicant has also characterized the absorption, distribution, metabolism, and excretion property of clascoterone in vitro by using human biomaterials.

18.3.1. Summary of Bioanalytical Method Validation and Performance

18.3.1.1. Determination of Clascoterone and Its Metabolites Concentrations in Human Plasma

Three liquid chromatography with tandem mass spectrometry assays for determination of concentrations of clascoterone and its metabolites cortexolone-21-propionate and/or cortexolone in human plasma were developed and validated by three vendors (Table 64). The validation parameters and performance of each assay are summarized in Table 65. These

methods are applicable for quantitation of clascoterone or cortexolone-21-propionate within a nominal range of 0.25 ng/mL to 250 ng/mL with lower limit of quantitation (LLOQ) of 0.25 ng/mL, and for quantitation of cortexolone within a nominal range of 0.5 ng/mL to 500 ng/mL with LLOQ of 0.5 ng/mL.

Table 64. Bioanalytical Validation Reports and Associated Clinical Studies

Validation Report	Associated Clinical Study	Notes
(b) (4) Report 433-3/434-3	CB-03-01/02 CB-03-01/04	Exploratory data
(b) (4) Report (b) (4) 12B-0163	CB-03-01/28* 171-7151-202* 171-7151-203	*Maximal use PK study
(b) (4) Report (b) (4) 18B-0015	CB-03-01/33	QT/QTc study

18.3.1.2. Determination of Clascoterone and Its Metabolites Concentrations in Human Urine

The Applicant developed the liquid chromatography with tandem mass spectrometry assays for determination of clascoterone, cortexolone and tetrahydrocortexolone (endogenous substrates) in human urine. Briefly, the methods were validated for the determination of a total (conjugated and unconjugated) analyte concentrations of clascoterone, cortexolone and tetrahydrocortexolone in human urine after enzymatic cleavage by β-glucuronidase digestion with respect to sensitivity, specificity, reproducibility, linearity, accuracy and precision, recovery and analyte stability. These methods are applicable for quantitation of the three analytes within a nominal range of 0.5 ng/mL to 500 ng/mL.

Reviewer's comment: *The bioanalytical assays were applied to determine a total amount of unconjugated and conjugated forms of each analyte in human urine. Therefore, the PK data obtained from human urine samples is considered exploratory.*

18.3.1.3. Determination of Cortisol in Human Serum

The Applicant used ADVIA Centaur Cortisol assay for determination of serum cortisol concentrations in the two maximal use PK/pharmacodynamic (PD) studies. Briefly, ADVIA Centaur Cortisol is a competitive immunoassay using direct chemiluminescent technology. All testing was performed on ADVIA Centaur XP analyzers (b) (4)). The assay is applicable for quantitation of serum cortisol concentrations from 0.50 mcg/dL to 75 mcg/dL (13.80 nmol/L to 2069 nmol/L). The within-run precision and accuracy are summarized in Table 66. The cortisol samples are stable up to 10 days at ambient temperatures. The long-term storage stability of PK samples was adequately established.

Table 65. Bioanalytic Methods and Validation Parameters of Clascoterone and Its Metabolites in Human Plasma

Report	Analyte	Sample Volume (µL)	Linear Range (ng/mL)	LLOQ (ng/mL)	Intra Day Accuracy (%DEV)	Precision (%)
(b) (4) Report 433-3/434-3	Clascoterone	50	2.5–250	2.5	3.40–3.99	1.45 – 4.61
	Cortexolone	50	2.5–250	2.5	-7.35 – -4.96	1.37 – 5.17
(b) (4) Report (b) (4) 12B-0163*	Clascoterone	50	0.25–250	0.25	- 1.47 – 4.50	0.722 – 9.57
	Cortexolone	50	0.50–500	0.5	- 4.46 – 9.72	1.22 – 7.15
(b) (4) Report (b) (4) 18B-0015*	Clascoterone	50	0.25–250	0.25	-6.50 – 4.00	0.40 – 5.11
	Cortexolone	50	0.50–500	0.5	- 10.3 – 2.67	0.66 – 3.61
	Cortexolone-21-propionate	50	0.25–250	0.25	- 6.00 – 3.20	1.13 – 4.53

Abbreviations: DEV = relative deviations between measured mean values and nominal values, LLOQ = lower limit of quantification
*Bioanalytical method was applied in the maximal use PK studies (b) (4) 12B-0163) or QT/QTc study (b) (4) 18B-0015).
Note: Clascoterone, cortexolone and cortexolone-21-proprionate were stable in human plasma up to 99 days when stored frozen at -20°C and -70°C.
Source of data: Reviewer's summary based on Bioanalytical Reports (b) (4) 12B-0163 and (b) (4) 8B-0015) and Modul 2.7.1)

Table 66. Validation Parameters of Cortisol in Human Serum

Within-Run Precision							
Control	Level	N	Assayed Mean	SD	%CV	Verification Limit Within Run	Comment
40881	1	10	4.76	0.17	3.57	6.44 %CV	Within acceptable limits
40882	2	10	25.93	0.87	3.35	6.20 %CV	Within acceptable limits
40883	3	10	36.46	1.14	3.13	6.20 %CV	Within acceptable limits
Accuracy							
Control	Level	N	Assayed Mean	Published Control Range			Comment
40881	1	10	4.76	3.18 – 6.42			Within acceptable limits
40882	2	10	25.93	21.50 – 33.50			Within acceptable limits
40883	3	10	36.46	29.50 – 50.50			Within acceptable limits

%CV = coefficients of variation, SD = standard deviation
Source: Clinical Laboratory Analysis Report for Serum Cortisol (b) (4) C/Y2028)
Source: Module 2.7.1, Table 7

18.3.2. Clinical Pharmacology Studies

18.3.2.1. Study CB-03-01/02: Single Ascending Dose Study in Healthy Adult Males

Study CB-03-01/02 was a phase 1 randomized, double-blind, placebo-controlled, single-ascending dose first-in-human study that assessed safety, tolerability, and PK after a single-dose topical application of clascoterone cream, 1%, in healthy male subjects.

Twenty-four eligible subjects (18 years old to 48 years old) were divided into three cohorts of eight subjects. In each cohort, six subjects received on the ventral surface of one forearm 1 mL, 2 mL, or 4 mL of clascoterone cream, 1% (corresponding to approximately 10 mg, 20 mg, and 40 mg of clascoterone as active ingredient amount, respectively) and the same volume of matching placebo cream on the contralateral forearm. Two subjects received matching placebo cream on both forearms.

The assigned study drug was nonconclusively applied to the ventral surfaces of the forearms and maintained for 8 hours. Serial blood samples and cumulative urine were collected for determination of clascoterone and its metabolites cortexolone and/or tetrahydroxortexolone concentrations up to 36 hours postapplication.

Plasma Data

- Clascoterone concentrations were detectable in one and two subjects at some timepoints in the 1 mL and 2 mL treatment group (n=6), respectively, ranging from 0.75 ng/mL to 30.39 ng/mL. In the 4 mL treatment group, clascoterone was detectable in five out of six subjects at some timepoints, ranging from 0.70 ng/mL to 7.96 ng/mL.
- Cortexolone concentrations were detectable (up to 3.2 ng/mL) in only some subjects at some timepoints including predose.

Reviewer's comment: *The PK profiles of clascoterone and cortexolone were not characterized due to the low number of detected concentrations of both analytes.*

Urinary Data

- For most of the subjects, the unchanged or free clascoterone, cortexolone, and tetrahydroxortexolone were not detectable in urine samples, except for one sample of one subject receiving 4 mL of clascoterone cream, 1%, with the clascoterone concentration of 3.57 ng/mL.
- The total (free + glucuronide conjugated) clascoterone was detected in 15 of 18 subjects starting from 6 hours postapplication. The urinary excretion results (Table 67) suggest that following single topical application of clascoterone cream, 1%, for 8 hours, the excretion of free and/or glucuronide conjugated clascoterone accounted for approximately 0.1% to 0.5% of the dose and was dose-independent in healthy subjects.

Table 67. Urinary Excretion of Total Clascoterone (Mean ± SD)

Dose	N	Cumulative Excretion (µg)	Excretion Rate (µg/h)	% Dose Excreted
1 mL	6	46.08 ± 21.24	1.28 ± 0.59	0.46 ± 0.21
2 mL	6	78.06 ± 40.84	2.17 ± 1.13	0.39 ± 0.20
4 mL	6	56.19 ± 41.09	1.56 ± 1.14	0.14 ± 0.10

Source: Clinical Study Report CB-03-01/02, Table 11.4.1

- The total (free + glucuronide conjugated) cortexolone and tetrahydrocortexolone were quantifiable in all urine samples. The results (Table 68, Table 69) suggest that there was no difference in excretion of conjugated cortexolone and tetrahydroxortexolone between active and placebo treated subjects.

Table 68. Urinary Excretion of Total Cortexolone (Mean ± SD)

Dose	N	Cumulative Excretion (µg)	Excretion rate (µg/h)
1 mL	6	104.11 ± 27.40	2.89 ± 0.76
2 mL	6	112.82 ± 19.17	3.13 ± 0.53
4 mL	6	114.37 ± 38.19	3.18 ± 1.06
1, 2, and 4 mL of matching placebo cream	6	119.90 ± 24.62	3.33 ± 0.68

Source: Clinical Study Report CB-03-01/02, Table 11.4.3

Table 69. Urinary Excretion of Total Tetrahydrocortexolone (Mean ± SD)

Dose	N	Cumulative Excretion (µg)	Excretion rate (µg/h)
1 mL	6	135.10 ± 43.44	3.75 ± 1.21
2 mL	6	132.76 ± 33.91	3.69 ± 0.94
4 mL	6	133.17 ± 66.15	3.70 ± 1.84
1, 2, and 4 mL of matching placebo cream	6	134.77 ± 45.72	3.74 ± 1.27

Source: Clinical Study Report CB-03-01/02, Table 11.4.5

18.3.2.2. Study CB-03-01/04: Repeat-Dose Study in Healthy Adult Subjects

Twenty-four eligible subjects were divided into two cohorts (n=12 per cohort) and received 4 mL or 8 mL of clascoterone cream, 1% (corresponding to approximately 40 mg and 80 mg respectively of clascoterone, respectively) and placebo cream once daily (QD) for 14 consecutive days.

Clascoterone

- Plasma: Clascoterone was found in plasma of some subjects, but most samples fell below the lower limit of quantitation (BLQ: 2.5 ng/mL). Plasma concentrations of clascoterone increased after repeat applications and the interindividual variability for clascoterone was high (Table 70).
- Urine: Less than 1% of the applied dose was excreted into urine as total clascoterone (Table 71). Compared to the first application, the renal extraction rate of total clascoterone increased by threefold to fourfold after the 14th application in either dose group (Table 71).

Table 70. Plasma Concentrations of Clascoterone After Repeat Dosing

Time	CB-03-01 plasma concentrations (ng/mL)±SD					
	4 mL			8 mL		
	1st application	10th application	14th application	1st application	10th application	14th application
	N=12	N=12	N=12	N=12	N=12	N=12
Pre-dose	BLQL	BLQL	BLQL	BLQL	BLQL	BLQL
2 h	NA	BLQL	BLQL	NA	BLQL	BLQL
4 h	BLQL	0.24±0.82	1.24±1.91	BLQL	BLQL	BLQL
6 h	0.22±0.77	1.73±1.83	2.42±2.24	BLQL	BLQL	0.97±1.44
8 h	0.50±1.17	2.15±1.62	1.97±1.77	BLQL	1.01±1.50	2.13±1.63
12 h	BLQL	BLQL	BLQL	BLQL	0.23±0.78	BLQL
16 h	NA	NA	BLQL	NA	NA	BLQL
24 h	BLQL	BLQL	BLQL	BLQL	BLQL	BLQL

Source: Clinical Study Report CB-03-01/04, Table 11.4.1

Table 71. Urinary Excretion of Total Clascoterone (Mean ± SD)

Daily Dose	4 mL			8 mL		
Application	1st	10th	14th	1st	10th	14th
	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12
Collection Period	Excretion (µg)					
0-24 h	122.7 ± 83.6	248.3 ± 97.6	370.4 ± 113.1	56.4 ± 37.5	134.4 ± 59.1	250.2 ± 81.4
	Excretion Rate (µg/h)					
0-4 h	0.23 ± 0.27	3.80 ± 1.81	8.24 ± 5.75	0.08 ± 0.18	3.18 ± 0.81	4.61 ± 1.81
4-12 h	15.2 ± 10.4	29.1 ± 12.2	32.4 ± 13.6	7.01 ± 4.71	15.2 ± 0.73	19.3 ± 10.3
12-24 h	NA	NA	6.53 ± 2.55	NA	NA	6.47 ± 2.72

Source: Clinical Study Report CB-03-01/04, Table 11.4.2

Cortexolone and Tetrahydrocortexolone

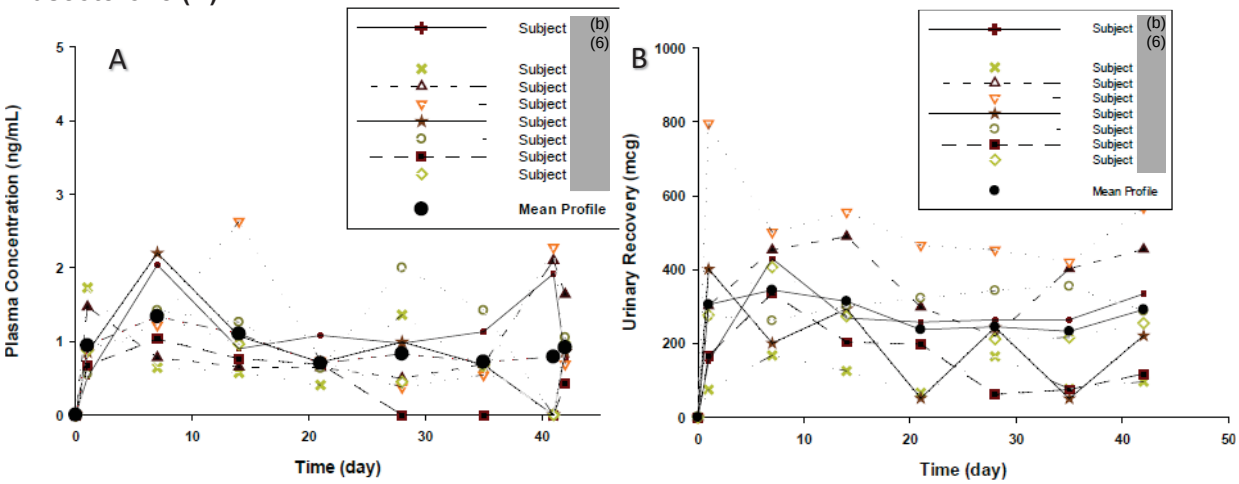
The cumulative excretion and excretion rate of the metabolite cortexolone naturally present in urine were not affected by the multiple applications of either volume of clascoterone cream 1%, while the cumulative excretion and excretion rate of tetrahydrocortexolone increased by 1.5 to 1.8 times over the baseline after the 14th application.

18.3.2.3. Study 171-7151-203: Repeat-Dose Study in Adult Subjects with Acne Vulgaris

Study 171-7151-203 was an open-label and repeat-dose study. Eight adult subjects with moderate to severe acne vulgaris on the face, chest and/or back applied approximately 6 grams of clascoterone cream, 1%, daily on the affected areas for 6 weeks.

Results based on quantifiable plasma and urine data (Figure 15) indicate that clascoterone steady-state was achieved within the first week of clascoterone cream, 1%, once daily application. The mean steady-state plasma level was 1.4 ng/mL. The results of the clascoterone PK parameters after the last application on day 42 are summarized in Table 13.

Figure 15. Trough Plasma Concentrations of Clascoterone (A) and Urinary Recovery of Total Clascoterone (B)



Source: Clinical Study Report 171-7151-203, Appendix 16.2.13, Figures 1 and 2

Table 72. Clascoterone Plasma Concentrations on Day 42

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	T_{min} (h)	C_{avg} (ng/mL)	AUC_τ (h*ng/mL)
(b) (6)	1.92	0[a]	0.77	24	1.17	28.08
	0.95	24	0[a]	0[a]	0.48	11.61
	4.42	4	1.33	16	2.3	55.22
	6.31	4	0.69	24	2.47	59.33
	3.96	4	0[a]	0[a]	2.08	49.99
	1.59	6	0[a]	0[a]	1.2	28.7
	0.5	4	0[a]	0[a]	0.38	9.12
	2.07	4	0[a]	0[a]	1.06	25.54
N	8	8	8	8	8	8
Mean	2.71	6.3	0.35	8	1.39	33.45
Median	2	4	0	0	1.18	28.39
CV%	73	118	148	141	58	58

AUC_τ = area under the plasma concentration-time profile over the dosing interval; C_{avg} = average plasma concentration over the dosing interval; C_{max} = maximum plasma concentration over the dosing interval; C_{min} = minimum plasma concentration over the dosing interval; CV = coefficient of variation; T_{max} = time C_{max} was reached; T_{min} = time when C_{min} was achieved

a The zero entries reflect pre-dose values.

Source: Clinical Study Report 171-7151-203, Appendix 16.2.13, Table 3

18.3.2.4. Study 171-7151-202: Maximal Use PK Study in Subjects Aged ≥12 with Acne Vulgaris

Study 171-7151-202 was an open-label study to determine the adrenal suppression potential and to evaluate the PK of clascoterone under maximal use conditions of clascoterone cream, 1%, in 20 adults (≥18 years of age) and 22 adolescents (12 years to 17 years of age) with moderate to severe facial acne vulgaris and acne on the chest and/or back. Eligible subjects applied approximately 6 grams of clascoterone cream, 1%, to their entire face, shoulders, upper chest and upper back (treatment area) twice daily for 2 weeks. Subjects who were 12 years to 17 years of age and had a total body surface area (BSA) ≤1.6m^2 applied approximately 4 grams of test article to the treatment area BID for 2 weeks. The PK of clascoterone was assessed after a single topical application and at steady state (after topical application BID for 14 days) in all subjects. Demographic information is summarized in Table 73.

Table 73. Demographic Information for Study 171-7151-202

CHARACTERISTIC	Cohort 1 N (%) N=20	Cohort 2 N (%) N=22
SEX		
Female	15 (75.0%)	12 (54.5%)
Male	5 (25.0%)	10 (45.5%)
ETHNICITY		
Not Hispanic or Latino	20 (100.0%)	21 (95.5%)
Hispanic or Latino	0 (0.0%)	1 (4.5%)
RACE		
White	17 (85.0%)	21 (95.5%)
Asian	1 (5.0%)	0 (0.0%)
Black or African American	1 (5.0%)	0 (0.0%)
Multiple	1 (5.0%)	1 (4.5%)
AGE (years)		
Mean	24.4	15.6
Median	23	16
Standard Deviation	5.84	1.33
Minimum to Maximum	18.0 to 40.7	12.8 to 17.6

Information obtained from Table 14.1.3.
Cohort 1 = adults, Cohort 2 = adolescents
Source: Clinical Study Report 171-7151-202, Table 11.2-1

Actual Dose Used

The adult and adolescent subjects received the mean ± SD daily dose of clascoterone cream, 1%, of 11.3±0.83 grams and 9.3±2.47 grams, respectively. The to-be-marketed formulation was used in this study.

Pharmacokinetics

The PK results of clascoterone are summarized in Table 74. The steady state concentration of clascoterone was achieved by 96 hours (day 5). Clascoterone systemic exposure associated with topical application was similar between adults and adolescents (Figure 16). On day 14, plasma

concentrations of clascoterone increased approximately twofold compared to the first dose (Table 74).

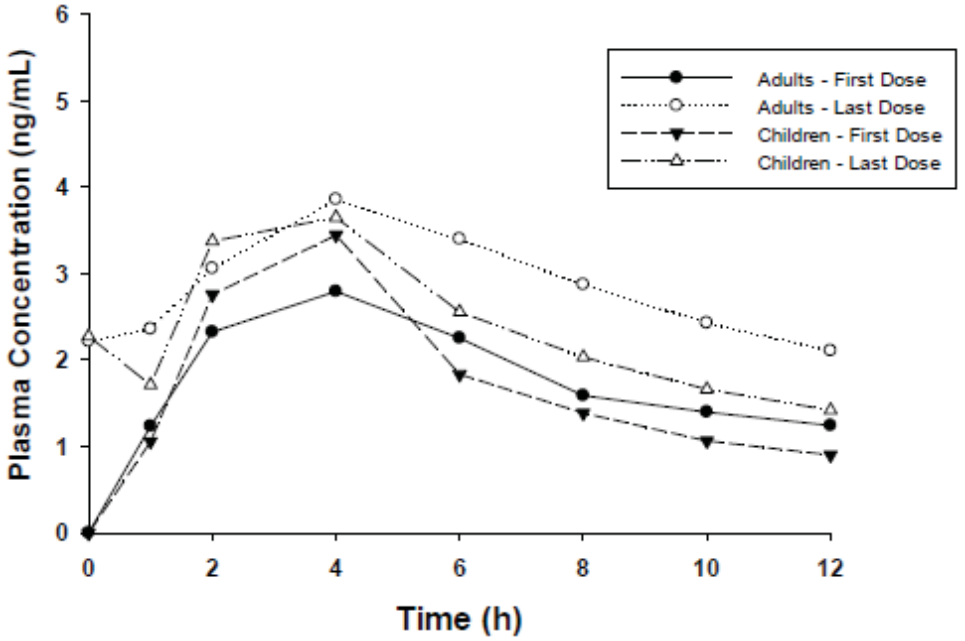
In general, the plasma concentrations of cortexolone in most samples (adults: 93% first dose, 74% last dose; adolescents: 88% first dose, 67% last dose) were below the LLOQ of 0.5 ng/mL in both adult and adolescent subjects.

Table 74. PK of Clascoterone in Adults and Adolescents Under Maximal Use Conditions

	Mean (SD)								
	C_{max} (ng/mL)			AUC_{τ} (h*ng/mL)			C_{avg} (ng/mL)		
Subjects*	**D1**	**D14**	**D14/D1**	**D1**	**D14**	**D14/D1**	**D1**	**D14**	**D14/D1**
Adults (n=20) (≥18 years)	3.23 (1.95)	4.46 (2.93)	1.4	22.02 (13.46)	37.14 (22.30)	1.7	1.84 (1.11)	3.10 (1.86)	1.7
Adolescents (n=22) (12-17 years)	3.58 (4.20)	4.61 (4.63)	1.3	22.55 (22.03)	30.97 (24.06)	1.4	1.88 (1.84)	2.58 (2.00)	1.4

Abbreviations: AUC_{τ}=area under the plasma concentration-time over the dosing interval (i.e., 0 to 12 hours), C_{avg} = the average plasma concentrations over the dosing interval, C_{max} = the maximum plasma concentration, D1 = day 1, D14 = day 14, SD = standard deviation
*Under maximal use conditions: subjects received 6 grams of WINLEVI cream per each application, except for adolescent subjects with a body surface area (BSA)<1.6m^2 who received 4 grams of WINLEVI per each application.
Source: Reviewer's summary based on Clinical Study Report 171-7151-202

Figure 16. Mean Plasma Concentrations of Clascoterone in Adult and Adolescent Subjects



Source: Clinical Study Report 171-7151-202, Appendix 16.1.13, Figure 7

Effect of Clascoterone on HPA Axis Suppression

The Applicant evaluated potential effect of clascoterone on HPA axis suppression by performing cosyntropin stimulation tests (CSTs) prior to and post clascoterone cream, 1%, topical applications. An abnormal HPA axis response (HPA suppression) or abnormal CST was defined as a 30-minute poststimulation serum cortisol level of ≤18 mcg/dL at day 14. Additional PK blood samples were collected for PK/PD analysis.

The CST results indicate that one adult (1/20; 5% in cohort 1) and two adolescents (2/22; 9% in cohort 2) demonstrated an abnormal HPA axis response on day 14/end-of-study (EOS), but cortisol levels for all three suppressed subjects returned to normal approximately 4 weeks after day 14/EOS (Table 75).

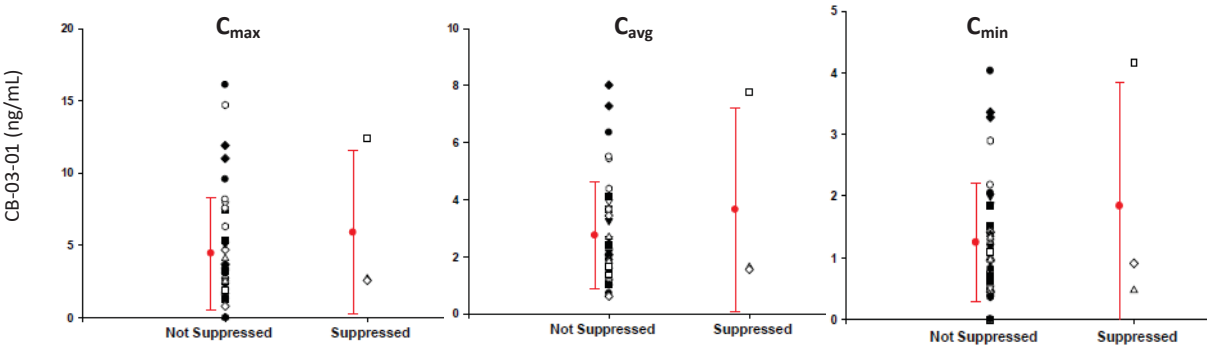
Comparisons of the mean clascoterone maximum (C_{max}), average (C_{avg}), and minimum (C_{min}) concentrations in subjects with and without adrenal suppression are summarized in Figure 17. Overall, no clear relationship between HPA axis suppression and clascoterone systemic exposure was observed due to small sample size of subjects with HPA axis suppression.

Table 75. Subjects Who Had Adrenal Suppression at Day 14/EOS

Cohort	Subject #	Total Test Article used (grams)	EOS Post-CST Cortisol (µg/dL)	Follow-Up (~4 weeks after EOS) Post-CST Cortisol (µg/dL)
Cohort 1	(b) (6)	167.9	17.7†	23.4
Cohort 2		158.6	17.0†	19.5
		105.8	14.9†	22.3

*Data from Listings 16.2.7.1 and 16.2.5.2.
†All three of these abnormal CST results were documented as AEs.
Source: Clinical Study Report 171-7151-202, Table 11.5-1

Figure 17. Clascoterone Concentrations in Subjects With or Without Adrenal Suppression



Source: Clinical Study Report 171-7151-202, Figures 11.6-3, 11.6-4, 11.6-5

18.3.2.5. Study CB-03-01/28: Maximal Use PK Study in Subjects 9 to 11 Years with Acne Vulgaris

Study CB-03-01/28 was an open-label study to determine the adrenal suppression potential and trough plasma concentrations of clascoterone under maximal use conditions of clascoterone cream, 1%, in 27 subjects 9 years to 11 years of age with at least moderate facial acne vulgaris and obvious acne on the trunk (shoulders, upper chest, and/or back). Eligible subjects applied approximately 2 grams of clascoterone cream, 1%, to the treatment area BID for 2 weeks. Demographic information is summarized in Table 76.

Table 76. Demographic Information for Study CB-03-01/28

CHARACTERISTIC	CB-03-01 Cream N=27 n (%)
SEX	
Female	22 (81.5)
Male	5 (18.5)
ETHNICITY	
Not Hispanic or Latino	20 (74.1)
Hispanic or Latino	7 (25.9)
RACE	
White	25 (92.6)
Black or African American	1 (3.7)
Asian	1 (3.7)
AGE (years)	
Mean	10.2
Median	11.0
Standard Deviation	0.9
Minimum, Maximum	(9, 11)
AGE DISTRIBUTION (years)	
9	8 (29.6)
10	5 (18.5)
11	14 (51.9)

Source: Table 14.1.2.1 and Listing 16.2.4.1.
Source: Clinical Study Report CB-03-01/28, Table 11.2.1-1

Actual Dose Used

The pediatric subjects aged 9 years to 11 years received the mean ± SD daily dose of clascoterone cream, 1%, of 4.2±0.80 grams. The to-be-marketed formulation was used in this study.

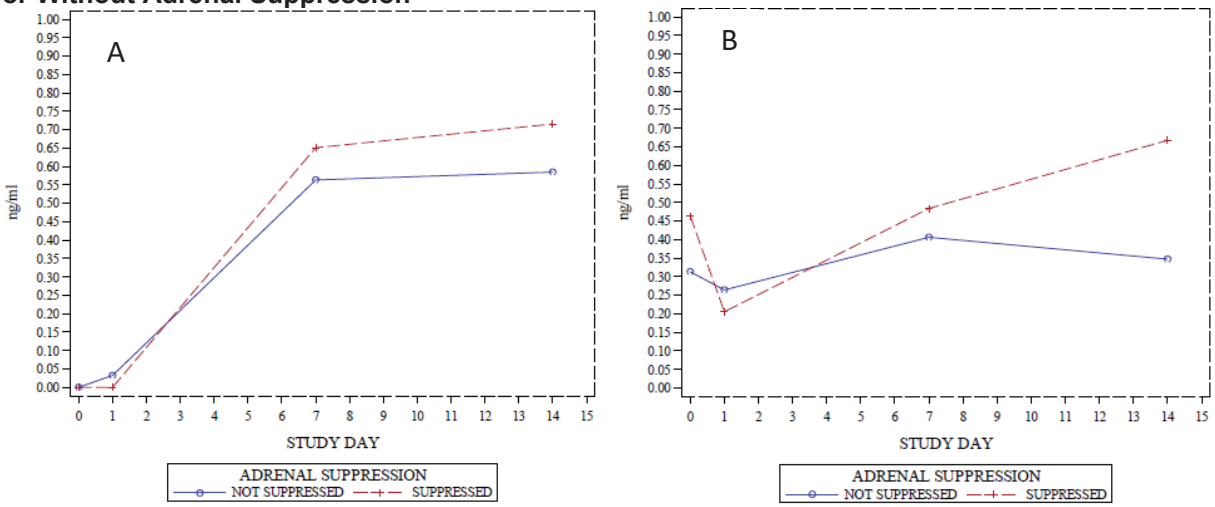
Pharmacokinetics

In most of the subjects, morning trough plasma concentrations of clascoterone and cortexolone were generally near or below the LLOQ on day 2, day 7, and day 14. On day 7 and day 14, the average trough concentrations of clascoterone were 0.58 ng/mL and 0.61 ng/mL, respectively; the average trough concentrations of cortexolone (a metabolite) were 0.42 ng/mL and 0.40 ng/mL, respectively.

Effect of Clascoterone on HPA Axis Suppression

The CST results indicate that four of 27 subjects (15%) had an abnormal HPA axis response on day 14/EOS, but cortisol levels for all four suppressed subjects returned to normal approximately 4 weeks after day 14/EOS. The average trough concentrations of clascoterone and cortexolone on day 14 in subjects with adrenal suppression were higher than those in subjects without adrenal suppression (Figure 18). However, no definitive conclusions on the relationship between HPA axis suppression and clascoterone systemic exposure could be made due to small sample size of subjects with HPA axis suppression.

Figure 18. Average Clascoterone (A) and Cortexolone (B) Trough Concentrations in Subjects With or Without Adrenal Suppression



Source: Clinical Study Report CB-03-01/28, Figures 11.5-3, 11.5-4

Reviewer's comment: *The average cortexolone trough concentration in the subjects with HPA axis suppression was ~twofold higher than those without HPA axis suppression.*

Effect of Clascoterone on Plasma Potassium Levels (Hyperkalemia)

Plasma potassium levels in nine of 27 pediatric subjects aged 9 years to 11 years (~ 33%) showed a shift from normal to high during the 14-day treatment period. As shown in Table 77, both plasma concentrations of clascoterone and cortexolone in these subjects were generally low, and there is no clear correlation (data not shown) between plasma concentrations of clascoterone or cortexolone (a metabolite) and potassium levels in the pediatric subjects who had a shift in potassium from normal to high.

Table 77. Plasma Concentrations of Clascoterone and Cortexolone in Pediatric Subjects Who Had a Shift in Potassium From Normal to High

	Clascoterone (ng/mL)				Cortexolone (ng/mL)			
Subject#	Screening	Day 1	Day 7	Day 14	Screening	Day 1	Day 7	Day 14
(b) (6)	BQL	BQL	BQL	0.378	BQL	BQL	0.749	BQL
	BQL	BQL	0.392	0.545	1.1	BQL	0.713	1.51
	BQL	BQL	1.38	0.844	BQL	BQL	0.826	BQL
	BQL	BQL	0.654	0.358	BQL	BQL	BQL	BQL
	BQL	BQL	BQL	BQL	1.02	BQL	BQL	BQL
	BQL	BQL	0.57	0.256	0.689	BQL	BQL	BQL
	BQL	BQL	1.25	2.55	BQL	BQL	BQL	0.868
	BQL	0.679	0.768	0.918	0.66	0.676	0.89	0.917
	BQL	BQL	1.02	0.986	BQL	0.821	1.23	0.972

Abbreviations: BQL = belowthe LLOQ; LLOQ = lower limit of quantitation
LLOQ:0.25 ng/mL for clascoterone, 0.5 ng/mL for cortexolone
*Subject with hypothalamic-pituitary-adrenal suppression

18.3.2.6. Study CB-03-01/33: Thorough-QT Study in Healthy Subjects

Study CB-03-01 was a randomized, double-blind, placebo-controlled phase 1 study investigating the effects of clascoterone and its metabolites on QTc interval in healthy subjects. Thirty-two eligible subjects received topically either clascoterone of 225 mg (as a 3 mL of clascoterone 7.5% solution) or matching placebo twice daily in a 3:1 ratio for 3 days, and a single morning dose on day 4.

Pharmacokinetics

The PK parameters of clascoterone and cortexolone (a metabolite) are summarized in Table 78 and Table 79, respectively. Plasma levels of cortexolone-21-propoinate (another metabolite) were only detectable in five of 24 subjects during the multiple-dose period, ranging from 0.26 to 1.58 ng/mL.

Table 78. Pharmacokinetics of Clascoterone (Mean ± SD) in Healthy Subjects

Visit	Day 1 (Hour 0-24 unless otherwise stated)	Day 4 (Hour 72-96)
C_{max} (ng/mL)	4.81 [2.64] (n=24)	7.65 [4.35] (n=22)
AUC_{0-12} (ng×h/mL)	19.96 [7.70] (n=24) (Hour 0-12)	59.86 [22.25] (n=21) (Hour 72-84)
AUC_{0-24} (ng×h/mL) (two doses on Day 1, one on Day 4)	57.28 [16.53] (n=23)	113.94 [53.63] (n=22)
AUC_{0-last} (ng×h/mL)	55.15 [19.24] (n=24)	181.87 [97.87] (n=22)
AUC_{0-Inf} (ng×h/mL)	NC	219.34 [92.03] (n=20)
T_{max} (h)	21.00 [5.70] (n=24)	6.20 [6.60] (n=22)
Half-life Lambda z (h)	NC	26.80 [14.60] (n=20)
Lambda-z (1/h)	NC	0.03 [0.01] (n=20)
MRT (h)	NC	38.30 [20.0] (n=20)

Data source: Table 14.2.4
Standard Deviation [SD]
Source: Clinical Study Report CB-03-01/33, Table 14

Table 79. Pharmacokinetics of Cortexolone (Mean ± SD) in Healthy Subjects

Visit	Day 1 (Hour 0-24 unless otherwise stated)	Day 4 (Hour 72-96)
C_{max} (ng/mL)	1.16 [0.43] (n=5)	1.27 [0.59] (n=21)
AUC_{0-12} (ng×h/mL)	NC	11.24 [3.31] (n=8)
AUC_{0-24} (ng×h/mL) (two doses on Day 1, one on Day 4)	15.52 [0.08] (n=2)	20.40 [8.19] (n=19)
AUC_{0-last} (ng×h/mL)	15.52 [0.08] (n=2)	31.65 [23.11] (n=21)
AUC_{0-Inf} (ng×h/mL)	NC	110.83 [42.64] (n=7)
T_{max} (h)	18.40 [10.30] (n=5)	10.90 [15.50] (n=21)
Half-life Lambda z (h)	NC	90.10 [53.70] (n=7)
Lambda-z (1/h)	NC	0.01 [0.01] (n=7)
MRT (h)	NC	129.50 [72.70] (n=7)

Data source: Table 14.2.6
Standard Deviation [SD]
Source: Clinical Study Report CB-03-01/33, Table 17

Pharmacodynamics

No significant QTc prolongation effect of clascoterone was detected (for details see QT Study Consultation Review in the Document Archiving, Reporting, and Regulatory Tracking System dated November 15, 2019).

18.3.3. Studies Using Human Biomaterials

18.3.3.1. Plasma Protein Binding

Plasma protein binding of clascoterone is 84% to 89% and is independent of concentrations, in vitro (b) (4) 11M-0048).

18.3.3.2. Metabolism

- Metabolic profile in human plasma (B37653): Incubation of clascoterone 0.1 mg/mL with human plasma generated two metabolites, cortexolone-21-propionate and cortexolone (Table 80).
- Metabolic profile in hepatocytes (b) (4) 11M-0047): The in vitro study indicated that incubation of clascoterone 10 µmol/L with cryopreserved hepatocytes from humans generated cortexolone and other unidentified metabolites (see section 18.3.3.3).

Table 80. Metabolism of Clascoterone in Human Plasma at 37.8°C

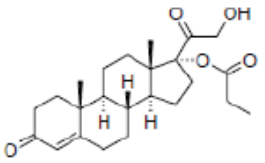
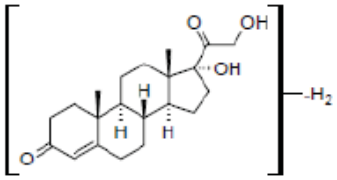
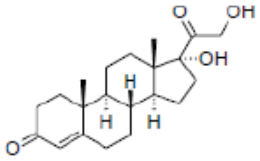
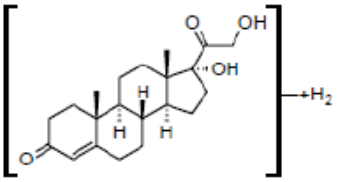
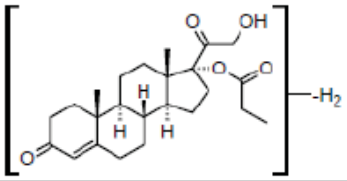
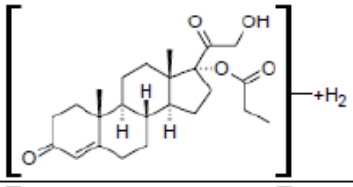
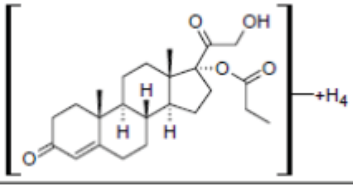
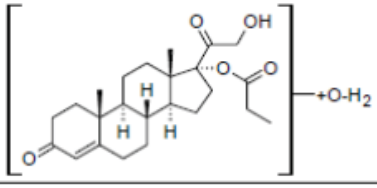
Incubation Time	CB-03-01 (%)	Cortexolone 21-propionate (%)	Cortexolone (%)
0	99.6	0.5	0.0
30 min	93.2	6.5	0.4
1 hr	85.2	13.2	1.7
2 hr	67.2	25.3	7.5
4 hr	30.3	33.8	35.9
6 hr	11.3	23.8	64.9

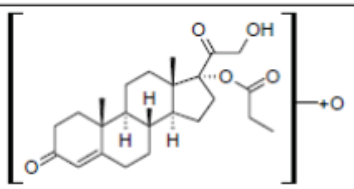
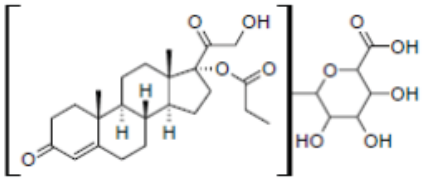
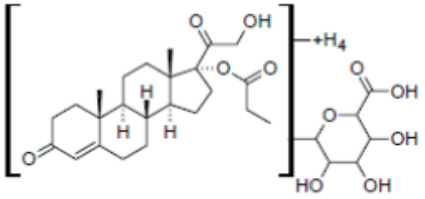
% is relative to the sum of CB-03-01, cortexolone 21-propionate, and cortexolone expressed as a mean of 4 donors
Source: B37653, Table
Source: Summary of Clinical Pharmacology Studies, Table 3

18.3.3.3. Drug-Drug Interactions

- Cytochrome P450 (CYP) induction study (CB-03-01/16): Clascoterone up to 30µM did not induce CYP 1A2, 2B6, or 3A4 (Table 82).
- CYP inhibition study (CB-03-01/18, GT050709): In vitro, clascoterone inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 with an IC50 value of >40µM (Table 83).

Table 81. Structures of Clascoterone and Proposed Metabolites in Hepatocytes

Name	Theoretical *m/z*	Structure or Proposed Structure
Parent	403.25	
M1	345.21	
M2	347.22	
M3	349.24	
M4	401.23	
M5	405.26	
M6	407.28	
M7	417.23	

M8, M9, M10, M11	419.24	
M12	579.28	
M13, M14, M15	583.31	

m/z reflects the quasi-molecular ion [M+H]+ generated during LC/MC/MS analysis. The M2 metabolite has been identified as cortexolone, an endogenous substrate.
Source: Study report of (b) (4) 11M-0047, Figure 1

Table 82. CYP Induction With Clascoterone in Human Hepatocytes (n=3)

CYP Isoenzyme	CB-03-01 (µM)	Relative Metabolite Formation (%) for Each Donor	Positive Control	Relative Metabolite Formation of Positive Control (%)	40% of Positive Control Cutoff (%)	Percentage of Positive Control (%)
1A2	1	100, 100, 66.5	50 µM Omeprazole	5135, 2663, 4633	2154, 1125, 1913	nd
	2	100, 100, 66.5				nd
	5	129, 100, 66.5				nd
	10	100, 100, 66.5				nd
	50	100, 100, 66.5				nd
3A4	1	97.1, 91.7, 95.6	25 µM Rifampicin	350, 763, 493	200, 365, 257	nd
	2	97.7, 96.0, 99.3				nd
	5	91.0, 79.6, 103				nd
	10	88.7, 81.2, 99.7				nd
	50	84.7, 93.3, 91.3				nd
2B6	1	85.4, 94.0, 103	25 µM Rifampicin	555, 280, 393	282, 172, 217	nd
	2	83.0, 96.9, 99.4				nd
	5	76.4, 81.6, 107				nd
	10	81.5, 82.4, 94.5				nd
	50	85.1, 91.6, 92.6				nd

nd = not determined in any donor (<minimal required metabolite formation as an inducer)
Source: Summary of Clinical Pharmacology Studies, Table 4

Table 83. CYP Inhibition With Clascoterone in Pooled Human Liver Microsomes

	Activity Compared to Solvent Control (Mean of 3 Replicates)			IC_{50} determination	
CB-03-01 (µM)	Determined After Co-incubation (%)	Determined After Pre-incubation (%)	Ratio of Activity Co-incubation/ Pre-incubation	Pre-incubation	Co-incubation
CYP 1A2, phenacetin as model substrate					
1	100	120	nd	No inhibition	No inhibition
2	83.3	97.8	nd		
5	94.3	90.3	nd		
10	116	108	nd		
25	106	107	nd		
50	120	108	nd		
CYP 2C8, amodiaquine as model substrate					
1	95,4	89.5	1.07	Moderate inhibition, IC_{50} ~41 µM	Slight inhibition at 50 µM, IC_{50} not determined
2	90.9	92.7	0.98		
5	65.2	95.8	0.68		
10	64.9	93.0	0.70		
25	56.7	83.1	0.61		
50	46.8	78.5	0.60		
CYP 2C9, diclofenac as model substrate					
1	109	92.1	nd	Slight inhibition at 50 µM, IC_{50} not determined	Slight inhibition at 25 and 50 µM, IC_{50} not determined
2	98.3	103	nd		
5	91.9	102	nd		
10	92.5	98.8	nd		
25	70.3	96.5	0.73		
50	56.9	71.6	0.79		
CYP 2C19, S-mephenytoin as model substrate					
1	118	105	nd	No inhibition	No inhibition
2	111	100	nd		
5	82.3	97.3	nd		
10	133	92.9	nd		
25	92.3	85.1	nd		
50	105	92.9	nd		
CYP 2D6, dextromethorphan as model substrate					
1	97.9	102	nd	No inhibition	No inhibition
2	101	98.6	nd		
5	95.0	112	nd		
10	95.7	98.0	nd		
25	91.8	100	nd		
50	90.8	89.1	nd		

CB-03-01 (µM)	Activity Compared to Solvent Control (Mean of 3 Replicates)			IC_{50} determination	
	Determined After Co-incubation (%)	Determined After Pre-incubation (%)	Ratio of Activity Co-incubation/ Pre-incubation	Pre-incubation	Co-incubation
CYP 3A4, testosterone as model substrate					
1	94.3	115	nd	No inhibition	Slight inhibition, IC_{50} not determined
2	115	93.4	nd		
5	98.6	94.7	nd		
10	94.3	90.1	nd		
25	85.4	84.5	nd		
50	87.3	73.1	> 1.15		
CYP 3A4, midazolam as model substrate					
1	99.4	87.7	nd	Slight inhibition, IC_{50} not determined	Slight inhibition, IC_{50} not determined
2	88.2	93.3	nd		
5	90.1	91.3	nd		
10	81.3	95.4	nd		
25	71.4	86.4	0.83		
50	63.8	71.5	0.89		
CYP 2B6, bupropion as model substrate					
1	114	93.5	nd	No inhibition	No inhibition
2	115	93.8	nd		
5	115	94.7	nd		
10	111	91.7	nd		
25	105	96.1	nd		
50	112	91.9	nd		
CYP 2E1, chlorzoxane as model substrate					
1	87.7	86.1	nd	No inhibition	No inhibition
2	89.4	116	nd		
5	87.4	100	nd		
10	87.3	86.9	nd		
25	109	114	nd		
50	116	121	nd		

nd = not determined because no inhibition was observed
Source: CB-03-01/18, Table 9

18.4. Financial Disclosure

The Applicant certified on FDA Form 3454 that the Applicant has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). Furthermore, none of the investigators was the recipient of significant payments of the sorts defined in 21 CFR 54.2(f).

Table 84. Clinical Investigators

Study	Number of Principal Investigators	Disclosures
CB-03-01/25	53	0
CB-03-01/26	50	0
CB-03-01/28	11	0
CB-03-01/33	1	0
171-7151-201	13	0
171-1751-202	3	0
Total	**131**	**0**

At the pre-NDA meeting, the Applicant agreed that the financial information would be included in the NDA for the investigators in study CB-03-01/25 and study CB-03-01/26 (pivotal efficacy studies), study CB-03-01/28 (HPA axis suppression), study CB-03-01/33 (thorough QT), study 171-7151-201 (dose ranging), and study 171-7151-202 (HPA axis suppression). A single Form FDA 3454 with certification by the Applicant was provided with the list of the investigators and subinvestigators for the sites that randomized subjects, all of whom had no disclosable financial interests or arrangements.

Covered Clinical Studies: CB-03-01/25 and CB-03-01/26 (Pivotal Efficacy Studies), CB-03-01/28 (HPA Axis Suppression), CB-03-01/33 (Thorough QT), 171-7151-201 (Dose Ranging), and 171-7151-202 (HPA Axis Suppression)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 131		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 131		
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
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)

18.5. Nonclinical Pharmacology/Toxicology

18.5.1. Calculations for Multiples of Exposures

After 42 days of applying 6 g/day of clascoterone cream, 1%, the mean AUC in adult subjects was 33.45 ng·hr/mL. Systemic clascoterone exposure was comparable between adults and adolescents. Because the maximum recommended human dose (MRHD) is 2 g/day, the AUC at the MRHD can be estimated as 11.15 ng·hr/mL (33.45 ng·hr/mL ÷ [6 g/day ÷ 2 g/day] = 11.15 ng·hr/mL). The following table summarizes the multiples of exposure based on AUC comparisons between the MRHD and AUC values from nonclinical studies referenced in the label.

Table 85. Multiples of Exposure Based on AUC Comparisons Between MRHD and AUC Values From Nonclinical Studies Referenced in Label

Study	Species	Dose (mg/kg/day)	Dose Note[a]	AUC (ng·hr/mL)	Multiples of exposure[a]
Embryofetal development	Rat	1	LOAEL (development)	93.6	8
		25	NOAEL (maternal)	3750	336
	Rabbit	0.4	NOAEL (development)	136	12
		1.5	NOAEL (maternal)	431	39
Prenatal and postnatal development	Rat	12.5	NOAEL	1818[c]	163
Fertility and early embryonic development	Rat	2.5	NOAEL (development)	364[c]	33
		12.5	NOAEL (fertility)	1818[b]	163

Abbreviations: LOAEL = lowest-observed-adverse-effect-level; NOAEL = no-observed-adverse-effect-level; AUC = area under curve
[a] Calculated by dividing the nonclinical AUC by the estimated AUC at the MRHD (11.15 ng·hr/mL)
[b] Estimated using the GD 17 AUC_{0-t} for the 5 mg/kg/day dose level in the rat EFD study ([12.5 mg/kg/day ÷ 5 mg/kg/day] x 727 ng·hr/mL =1818 ng·hr/mL)
[c] Estimated using the GD 17 AUC_{0-t} for the 5 mg/kg/day dose level in the rat EFD study ([2.5 mg/kg/day ÷ 5 mg/kg/day] x 727 ng·hr/mL =364 ng·hr/mL)

18.5.2. Nonclinical Labeling

Recommended changes to nonclinical information in section 8.1, section 12.1, and section 13.1 of the Applicant's proposed labeling are provided below. Substantial changes are recommended to section 12.1 because the Applicant did not provide adequate nonclinical data to support most of the claims made in that section; (b) (4) and there is inadequate evidence that the subsequent claims in section 12.1 are clinically relevant. Reviewer-recommended deletions and additions are indicated by ~~strikethrough~~ and underlined text, respectively.

The pharmacologic class for clascoterone is androgen receptor inhibitor, which is provided in the Highlights of Prescribing Information, Indications and Usage section of the label.

8.1 Pregnancy

Risk Summary

There are no available data on WINLEVI cream use in pregnant women to (b) (4) evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (b) (4). In animal reproduction studies, subcutaneous administration (b) (4) -of clascoterone- (b) (4) to pregnant rats and rabbits during organogenesis at doses 8 or 39 times the maximum recommended human dose (MRHD), respectively, (b) (4) increased malformations in rats and postimplantation loss and resorptions in rabbits (b) (4) ~~[(see Data)~~ (b) (4)

Data

Animal Data

(b) (4)

In an embryofetal development study, clascoterone was administered subcutaneously to pregnant rats at doses of 1 mg/kg/day, 5 mg/kg/day, or 25 mg/kg/day during the period of organogenesis. No clascoterone-related maternal toxicity or effects on uterine parameters were noted at doses up to 25 mg/kg/day (336 times the MRHD based on AUC comparison). Clascoterone-related malformations were noted at all dose levels, without a dose relationship. Omphalocele was noted in a single fetus at each dose level. External and visceral malformations (severe dilation of the lateral and third cerebral ventricles; thin skin, small size, and protruding tongue) were noted in two additional fetuses at 1 mg/kg/day (8 times the MRHD based on AUC comparison).

(b) (4)

In an embryofetal development study, clascoterone was administered subcutaneously to pregnant rabbits at doses of 0.1 mg/kg/day, 0.4 mg/kg/day, or 1.5 mg/kg/day during the period of organogenesis. Post-implantation loss and resorptions were increased at 1.5 mg/kg/day (39 times the MRHD based on AUC comparison). No developmental toxicity was noted at doses up to 0.4 mg/kg/day (12 times the MRHD based on AUC comparison).

No clascoterone-related maternal toxicity or fetal malformations were noted at doses up to 1.5 mg/kg/day (39 times the MRHD based on AUC comparison).

(b) (4) n a prenatal and postnatal development study, clascoterone was administered (b) (4) subcutaneously to pregnant rats (b) (4) at doses (b) (4) of 0.5 mg/kg/day, 2.5 mg/kg/day, and 12.5 mg/kg/day (b) (4) beginning on (b) (4) -gestation day 6 and continuing through lactation day 20 (b) (4) (b) (4) No significant maternal or developmental toxicity was observed at doses up to 12.5 mg/kg/day (163 times the MRHD based on AUC comparison).

12.1 Mechanism of Action

Clascoterone is an (b) (4) androgen receptor inhibitor. (b) (4) he mechanism of action of WINLEVI cream for the treatment of acne vulgaris is unknown.

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Clascoterone cream (0.1%, 1%, or 5%) was not carcinogenic after daily topical administration in a 2-year carcinogenicity study in rats. (b) (4) An increased incidence of the non-neoplastic finding of atrophy of the skin and subcutis at the application site was reported in males and females treated with (b) (4) 1% and 5% clascoterone cream.

(b) (4)

Clascoterone was not mutagenic in the Ames reverse mutation assay and was not clastogenic in the in vitro human lymphocyte chromosomal aberration assay. In rats, clascoterone administered via subcutaneous injection did not induce micronuclei in the bone marrow at 500 or 1000 mg/kg but a slight increase in micronuclei occurred in two of five rats at 2000 mg/kg. The response was considered equivocal. Overall, the weight of evidence indicates that clascoterone does not represent a genotoxic risk.

(b) (4)

In a fertility and early embryonic development study in rats, clascoterone was administered subcutaneously at doses of 0.5 mg/kg/day, 2.5 mg/kg/day, or 12.5 mg/kg/day from 2 to g4 weeks before mating through mating. Clascoterone increased pre-implantation loss at 12.5 mg/kg/day (163 times the MRHD based on AUC comparison). Clascoterone had no (b) (4) effects on mating or fertility in rats at doses up to 12.5 mg/kg/day (163 times the MRHD based on AUC comparison). No effects were noted on development at doses up to 2.5 mg/kg/day (33 times the MRHD based on AUC comparison).

Revised Nonclinical Sections Presented As Clean-Copy Text Below

8.1 Pregnancy

Risk Summary

There are no available data on WINLEVI cream use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, subcutaneous administration of clascoterone to pregnant rats and rabbits during organogenesis at doses eight or 39 times the maximum recommended human dose (MRHD), respectively, increased malformations in rats and postimplantation loss and resorptions in rabbits *(see Data)*.

Data

Animal Data

In an embryofetal development study, clascoterone was administered subcutaneously to pregnant rats at doses of 1 mg/kg/day, 5 mg/kg/day, or 25 mg/kg/day during the period of organogenesis. No clascoterone-related maternal toxicity or effects on uterine parameters were noted at doses up to 25 mg/kg/day (336 times the MRHD based on AUC comparison). Clascoterone-related malformations were noted at all dose levels, without a dose relationship. Omphalocele was noted in a single fetus at each dose level. External and visceral malformations (severe dilation of the lateral and third cerebral ventricles; thin skin, small size, and protruding tongue) were noted in two additional fetuses at 1 mg/kg/day (8 times the MRHD based on AUC comparison).

In an embryofetal development study, clascoterone was administered subcutaneously to pregnant rabbits at doses of 0.1 mg/kg/day, 0.4 mg/kg/day, or 1.5 mg/kg/day during the period of organogenesis. Post-implantation loss and resorptions were increased at 1.5 mg/kg/day (39 times the MRHD based on AUC comparison). No developmental toxicity was noted at doses up to 0.4 mg/kg/day (12 times the MRHD based on AUC comparison). No clascoterone-related maternal toxicity or fetal malformations were noted at doses up to 1.5 mg/kg/day (39 times the MRHD based on AUC comparison).

In a prenatal and postnatal development study, clascoterone was administered subcutaneously to pregnant rats at doses of 0.5 mg/kg/day, 2.5 mg/kg/day, and

12.5 mg/kg/day beginning on gestation day 6 and continuing through lactation day 20. No significant maternal or developmental toxicity was observed at doses up to 12.5 mg/kg/day (163 times the MRHD based on AUC comparison).

12.1 Mechanism of Action

Clascoterone is an androgen receptor inhibitor. The mechanism of action of WINLEVI cream for the treatment of acne vulgaris is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Clascoterone cream (0.1%, 1%, or 5%) was not carcinogenic after daily topical administration in a 2-year carcinogenicity study in rats. An increased incidence of the non-neoplastic finding of atrophy of the skin and subcutis at the application site was reported in males and females treated with 1% and 5% clascoterone cream.

Clascoterone was not mutagenic in the Ames reverse mutation assay and was not clastogenic in the in vitro human lymphocyte chromosomal aberration assay. In rats, clascoterone administered via subcutaneous injection did not induce micronuclei in the bone marrow at 500 or 1000 mg/kg but a slight increase in micronuclei occurred in two of five rats at 2000 mg/kg. The response was considered equivocal. Overall, the weight of evidence indicates that clascoterone does not represent a genotoxic risk.

In a fertility and early embryonic development study in rats, clascoterone was administered subcutaneously at doses of 0.5 mg/kg/day, 2.5 mg/kg/day, or 12.5 mg/kg/day from 2 to 4 weeks before mating through mating. Clascoterone increased pre-implantation loss at 12.5 mg/kg/day (163 times the MRHD based on AUC comparison). Clascoterone had no effects on mating or fertility in rats at doses up to 12.5 mg/kg/day (163 times the MRHD based on AUC comparison). No effects were noted on development at doses up to 2.5 mg/kg/day (33 times the MRHD based on AUC comparison).

18.5.3. Review of Carcinogenicity Study Conducted With Clascoterone

Study Title: CB-03-01 Cream: A 24-Month Dermal Carcinogenicity Study in Rats

Study no.: V01-CB01-601
Study report location: SDN 1
Study initiation date: March 13, 2015
Conducting laboratory and location: (b) (4)
GLP compliance: Y
Drug, lot #, and % purity:

- Clascoterone vehicle cream: lot #6731/1, 6732/1, 6910/1; 0% purity (no clascoterone detected)
- Clascoterone cream, 0.1%: lot #6737/1, 6738/1, 6911/1; 103%, 103.5%, 100.2% purity

- Clascoterone cream, 1%: lot #6739/1, 6740/1, 6912/1; 101.5%, 101.4%, 99.3% purity
- Clascoterone cream, 5%: lot #6733/1, 6734/1, 6914/1; 102.9%, 102.9%, 98.9% purity

Prior exec CAC dose concurrence: Y
Basis for dose selection: Maximum feasible dose
Reviewer carcinogenicity conclusion (negative/positive): Negative
ECAC carcinogenicity conclusion (negative/positive): Negative

Tumor Findings

No clascoterone cream-related tumors were observed in either sex.

Methods

- Doses: 0% (untreated), 0% (vehicle cream), 0.1%, 1%, and 5% cream (0, 0, 0.1 mg/mL, 1 mg/mL, and 5 mg/mL; 0, 0, 0.052 mg/kg/day, 0.52 mg/kg/day, and 2.6 mg/kg/day)
- Frequency of dosing: Once daily
- Number/Sex/Group: 65
- Dose volume: 0.52 mL/kg applied to 10% BSA
- Formulation/Vehicle: Propylene glycol (b) (4) cetyl alcohol (b) (4), polysorbate 80 (b) (4) edetate sodium (b) (4) (b) (4)
- Route of administration: Topical
- Species: Rat
- Strain: Sprague-Dawley
- Age: Approximately 6 weeks of age at dosing initiation
- Comment on study design and conduct: Study included an untreated control group to evaluate potential vehicle effects. The application site was gently washed with water and blotted dry to remove residue prior to dose application. No noteworthy deviations.
- Dosing comments (dose adjustments or early termination):
  - An advice letter was sent to the Applicant on October 26, 2016, conveying early termination criteria for this study, including the recommendation to terminate all groups of a sex if a control group of that sex reaches 20 animals. Because male and female controls decreased to 20 animals during week 97, all groups were terminated beginning week 97 through week 99; animals that died after the start of week 97 were considered terminal sacrifices.
  - On day 2 of week 97, the number of surviving untreated control males decreased to 20; the Applicant provided notice on February 2, 2017, that all males were being terminated. On day 6 of week 97, the number of surviving vehicle control females and HD females decreased to 20 and 15, respectively; the Applicant provided notice on February 8, 2017, that all female groups were being terminated.
  - No dose adjustments were made.
- Dosing Solution Analysis: Clascoterone and vehicle creams were used as provided by the Applicant; the testing facility did not analyze dosing formulations.

Key Study Findings

- No clascoterone cream-related tumors were noted in either sex.
- Clascoterone cream application did not increase mortality, affect body weight, or produce adverse clinical observations.
- Clascoterone cream-related microscopic findings were limited to minimal to marked dose-related atrophy at the application site in both sexes at concentrations ≥1%.

Observations and Results

Mortality

Animals were checked twice daily for health/mortality. The study was terminated early, after completing 96 weeks of treatment. As determined by the statistical reviewer, clascoterone cream did not increase overall mortality. Unscheduled deaths occurred at similar rates in all groups (range: 39 to 50); the most common causes were pituitary adenoma (both sexes), mammary tumors (females only), and progressive cardiomyopathy (primarily males).

Clinical Signs

A detailed physical examination was conducted once weekly, beginning prior to dosing initiation and continuing through study termination. Dermal evaluations and palpation for masses were conducted weekly during dosing. The skin at the application site was noted as purple and/or translucent in most MD and HD animals during week 51 to week 100. No other clascoterone cream-related effects were noted.

Body Weights

Body weights were recorded weekly during pretest and continuing through week 14; every 2 weeks from week 15 to week 28; and every 4 weeks thereafter. No clascoterone cream-related effects were noted.

Feed Consumption

Food consumption was determined by recording food weight on the same schedule as body weights (see above). No clascoterone cream-related effects were noted.

Gross Pathology

Clascoterone cream-related macroscopic findings were limited to dose-related thinning of the skin at the application site; this finding generally correlated to microscopic findings of atrophy of the skin at the application site.

Histopathology

Peer review conducted: Yes, by an independent pathologist
Historical control provided for tumor incidence: Yes

An adequate battery of tissues was reviewed by the study pathologist. Clascoterone cream-related microscopic findings were limited to minimal to marked atrophy of the skin at the application site at concentrations ≥1% in both sexes; incidence and severity was dose-related and similar between sexes. Other microscopic findings lacked a dose relationship and/or were of similar incidence and severity to controls.

Neoplastic

No clascoterone-related tumor findings were noted in female rats. A statistically significant dose relationship was noted for sebaceous cell adenoma at the topical application site in male rats, with a borderline pairwise statistical comparison in high dose males (p =0.0536); this was considered clascoterone-related by the Applicant. However, when sebaceous cell adenoma, sebaceous cell carcinoma, keratoacanthoma, and hair follicle tumors were appropriately combined for statistical analyses, there were no statistically significant drug-related tumors based on dose relationship or pairwise comparison. Therefore, the incidence of sebaceous cell adenoma in males was not considered clascoterone-related.

Non-neoplastic

At concentrations ≥1%, clascoterone cream produced minimal to marked atrophy of the skin and subcutis at the application site. Incidence and severity were dose-related and similar between sexes. Atrophy at the application site was not noted at the LD or in controls. No clascoterone cream-related microscopic findings were noted at the LD.

Toxicokinetics

Toxicokinetic assessment was not performed.

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/s/

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