Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris

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Background: Androgens foster acnegenic pathways.

Objective: To assess the long-term safety of an androgen receptor inhibitor, clascoterone cream, 1%, in patients who participated in phase 3 studies.

Methods: Clascoterone cream was applied twice daily for up to 9 months to the face or trunk, or both. Treatment-emergent adverse events (TEAEs) and local skin reactions were evaluated at months 1, 3, 6, and 9, and at any unscheduled visit(s). The statistical analysis was performed using SAS Windows 9.3 software (SAS Institute Inc, Cary, NC).

Results: The study screened and enrolled 609 individuals (n = 317 clascoterone, n = 292 vehicle from original studies), and 347 completed the study (n = 179 clascoterone, n = 168 vehicle). Overall, 110 patients (18.1%) experienced 191 TEAEs. The most frequently reported TEAE was nasopharyngitis (n = 20). A total of 19 test article—related TEAEs occurred in 14 patients; of these, 9 experienced 9 TEAEs leading to discontinuation. There were 7 serious TEAEs in 6 individuals, but none were treatment related. One serious TEAE led to study discontinuation. Overall, treatment-emergent local skin reactions occurred in 18.1% (110 of 607). The most frequent local skin reactions on the face and trunk were erythema, scaling/dryness, and pruritus, and most were trace/minimal or mild in severity.

Limitations: Long-term efficacy was not a primary end point.

Conclusion: A low frequency of TEAEs over 9 months of clascoterone treatment was observed. (J Am Acad Dermatol 2020;83:477-85.)

Key words: acne; androgen receptor inhibitor; antiandrogen; clascoterone; cream; long-term safety; topical.

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Funding sources: This study was funded by Cassiopea S.p.A., Italy.

Conflicts of interest: Drs Eichenfield, Hebert, and Stein Gold served as study investigators and as consultants to Cassiopea and have received honoraria and fees. Dr Eichenfield has served as an investigator, advisor, or consultant for Allergan, Almirall, Foamix Pharmaceuticals, Galderma Laboratories, L'Oréal, and Ortho Dermatologics. Dr Hebert received research funds from Cassiopea and Novan that were paid to the UTHealth McGovern Medical School-Houston and is an advisor or consultant for Allergan, Almirall, Galderma, and Ortho Dermatologics. Dr Stein Gold has served as an advisor and investigator for Foamix Pharmaceuticals, GlaxoSmithKline, LEO Pharma, and Valeant, as an investigator for Janssen, and as an advisor for Novartis. Dr Cartwright is an employee of Cassiopea Inc and holds stock options. Mr Fragasso and Drs Moro and Mazzetti are employees of Cassiopea S.p.A. and hold stock options.

IRB approval status: Reviewed and approved by individual study sites.

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Accepted for publication April 15, 2020.

Reprints are not available from the authors.

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Published online April 26, 2020.

0190-9622

https://doi.org/10.1016/j.jaad.2020.04.087

Acne vulgaris is a common, inflammatory skin disease characterized by increased sebum production, inflammation, colonization with *Cutibacterium acnes*, and hyperkeratinization.[1] Acne is largely driven by androgens,[2] and onset typically coincides with adrenarche in both males and females.[3] Flares associated with hormonal fluctuations are also observed in adults.[4]

Androgens, such as dihydrotestosterone, modulate physiologic activity via binding to androgen receptors, which are abundant in keratinocytes, dermal papilla cells, sebaceous glands, and dermal fibroblasts.[5] Upon binding, the androgen receptor-dihydrotestosterone complex translocates from the cytoplasm to cell nucleus, where it interacts with promoter regions of androgen-regulated genes, thereby affecting signaling cascades that foster sebaceous gland proliferation, sebum production, and inflammatory pathways.[6] Oral androgen receptor inhibitors and blockers show efficacy in the treatment of female acne; indeed, certain oral contraceptives are United Sates Food and Drug Administration approved, and spironolactone, an aldosterone inhibitor and androgen receptor blocker, is used off label.[7,8] Owing to adverse effects (AE), such as gynecomastia, erectile dysfunction, and feminization, these medications are not recommended for males and are contraindicated in pregnancy.[7,8]

Topical androgen receptor inhibition poses an attractive therapeutic target for acne vulgaris.[5] Clascoterone cream 1% (Cassiopea S.p.A., Milan Italy), an investigative treatment for acne, is a novel topical androgen receptor inhibitor. In vitro studies suggest that clascoterone limits dihydrotestosterone binding to androgen receptors and has downstream effects on dihydrotestosterone-driven acnegenic pathways.[9] Clascoterone penetrates the skin and is rapidly metabolized to cortexolone, thus limiting systemic exposure to active androgen inhibition and potential off-target AEs.[10-12]

Two pivotal phase 3, 12-week vehicle-controlled studies (CB-03-01/25, NCT02608450; CB-03-01/26, NCT02608476) revealed that clascoterone cream significantly improved Investigator's Global Assessment (IGA) scores and lesion counts in patients aged ≥9 years with moderate to severe acne. The 12 weeks of treatment did not result in any serious treatment-related AEs, and most AEs were mild to moderate and unrelated to the study drug.[13]

Here we discuss the long-term safety of clascoterone cream 1%. Clascoterone- and vehicle-treated individuals from the phase 3 trials were enrolled in an open-label, single-arm, 9-month extension study (CB-03-01/27). The extent of drug exposure and AEs were assessed in persons aged 9 years and older with moderate to severe acne vulgaris on the face or trunk, or both.

CAPSULE SUMMARY

- Mechanistically, novel acne vulgaris treatments with favorable safety profiles for both females and males have been elusive.
- A 9-month phase 3 safety study of clascoterone cream, a topical androgen receptor inhibitor, revealed a low frequency of treatment-related adverse events.
- Clascoterone cream represents a potential long-term topical acne vulgaris treatment.

METHODS

Study design and oversight

Study CB-03-01/27 (NCT 02682264) was multicenter, open-label, long-term safety study of clascoterone cream conducted from March 2016 to August 2018. This study was conducted at 75 sites, including 40 in the United States and 35 outside the United States (Poland, Romania, Bulgaria, Ukraine, Serbia, and Republic of Georgia) over 9 months in individuals who initially had moderate to severe acne and completed a 12-week phase 3 pivotal study (CB-03-01/25 and CB-03-01/26) (Fig 1).

Institutional Review Board approval was obtained for the protocol, informed consent/assent forms, and all relevant supporting data. The study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice and all country-specific regulatory requirements. In accordance with the International Council on Harmonization technical requirements for the registration of pharmaceuticals for human use guidelines for the assessment of clinical safety for long-term treatment, the enrolled patient population size was large enough to ensure that a minimum of 300 and 100 patients completed 6 and 12 months of follow-up, respectively.

Patients

Eligible patients must have completed 1 of the phase 3 pivotal studies and enrolled within 3 days of visit 4 of the pivotal studies.

Clascoterone cream 1% treatment

Patients were treated twice daily with clascoterone cream 1% applied to the face or trunk, or both. IGA was assessed using an IGA 5-point scale

Abbreviations used:

AE: adverse event
IGA: Investigator's Global Assessment
ITT: intention to treat
LSR: local skin reaction
PP: per protocol
TEAE: treatment-emergent adverse event

from clear to severe. If the patient's IGA score was more than mild at evaluation, the clascoterone twice-daily regimen was continued. If the IGA score was clear or almost clear, an off-treatment period was initiated (Fig 1).

Assessments

Scheduled patient visits occurred at months 1, 3, 6, and 9. Disease severity, medications use, vital signs, AEs, including treatment-emergent AEs (TEAEs), and serious AEs were assessed in all patients. Urine pregnancy tests were administered to female patients at baseline, 6 months, and at the end of the study.

Primary end points included AEs and serious AEs. All AEs were based on investigator assessments and were recorded and classified by using the Medical Dictionary for Regulatory Activities. From these assessments, AEs were considered treatment related if they were definitely, possibly, or probably related to clascoterone application. Possibly or probably related AEs followed a reasonable temporal sequence and known or expected responses but could not have been reasonably explained by the patient's clinical state for possibly related AEs, and probably related AEs could have been caused by many other factors.

Statistical analysis

All statistical analysis was performed using SAS for Windows 9.3 (SAS Institute Inc, Cary, NC) otherwise stated. Summary tables (descriptive statistics or frequency tables) were provided for baseline variables, efficacy variables, and safety variables. Continuous variables are described by descriptive statistics (number, mean, SD, compliance value percentage, minimum, median, and maximum). Frequency counts and the percentage of individuals within each category are provided for categorical data.

Participants who completed 6 months or 12 months on-study in CB-03-01/27 and the pivotal study (CB-03-01/25 or CB-03-01/26) without material noncompliance with the test article (CB-03-01 cream, 1%) dosing per protocol were counted toward the desired 300 participants at 6 months and 100 participants at 12 months. Approximately 600 participants had to be enrolled to have 300 participants on-study at 6 months and 100 on-study at 12 months. These treatment durations included the 0 or 3 months of active treatment in the phase 3 pivotal studies.

The intent-to-treat (ITT) set included all enrolled individuals and was used for efficacy analyses. The per-protocol (PP) set, a subset of the ITT group, included those completing the study without significant protocol deviations and was used for efficacy analyses. The safety set was used for safety analysis and included all participants who received at least 1 application of the test article. PP exclusions included failure to satisfy any inclusion/exclusion criteria, use of prohibited medications, did not complete the study, lack of compliance, or individual was not treated with clascoterone.

All the medical history findings were coded using the Medical Dictionary for Regulatory Activities 18.1. All prior and concomitant medications were coded using the World Health Organization Drug Dictionary Enhanced version B2 of September 2015. Prior and concomitant medications were listed and summarized.

Compliance to the test article was evaluated at each visit and overall according to the following formula: 100 × number of applications/number of scheduled applications. Noncompliance was defined as a compliance value of less than 80%.

Extent of exposure

Descriptive statistics were used to summarize exposure to the test article at each visit. The date and time of the first and last application, the total amount of the test article used (calculated as number of grams applied for each subject from the weights of the returned test articles), and the mean daily amount of the test article applied (calculated as the total amount of the test article used/number of days of treatment) were listed.

Adverse events

All AEs were coded using Medical Dictionary for Regulatory Activities 18.1. Individual TEAEs (ie, all the AEs occurring or worsening after the first dose of the test article) were listed, documenting course, severity, relationship to the test article, and outcome, with the number and percentage tabulated. Missing data were not replaced.

RESULTS

Patients and enrollment

The study screened and enrolled 609 patients, of whom 317 were originally randomized to treatment with clascoterone and 292 to vehicle. The safety

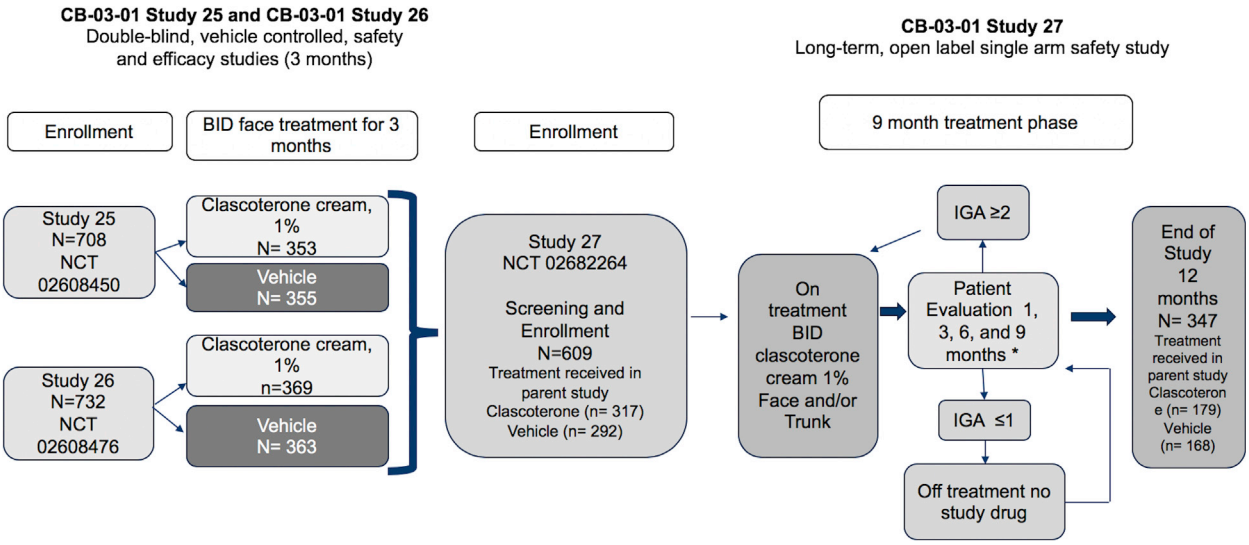

Fig 1. Study design, including the phase 3 pivotal trials (CB-03-01/25 and CB-03-01/26) and the extension study (CB-03-01/27). Pivotal trials were identically designed, 12-week, double-blind, vehicle-controlled, safety and efficacy studies. CB-03-01/27 was a long-term (9-month), open-label, single-arm safety study. *BID*, Twice daily; *IGA*, Investigator's Global Assessment.

Table I. Demographic characteristics of the intention to treat (*ITT*) and per-protocol (*PP*) populations

	Clascoterone		Vehicle		Overall	
	ITT	PP	ITT	PP	ITT	PP
Characteristic	(n = 317)	(n = 169)	(n = 292)	(n = 155)	(n = 609)	(n = 324)
Sex, No. (%)						
Female	198 (62.5)	99 (58.6)	183 (62.7)	100 (64.5)	381 (62.6)	199 (61.4)
Male	119 (37.5)	70 (41.4)	109 (37.3)	55 (35.5)	228 (37.4)	125 (38.6)
Race, No. (%)						
American Indian or Alaska Native	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)
Asian	6 (1.9)	2 (1.2)	8 (2.7)	5 (3.2)	14 (2.3)	7 (2.2)
Native Hawaiian or other Pacific Islander	2 (0.6)	1 (0.6)	1 (0.3)	1 (0.6)	3 (0.5)	2 (0.6)
Black or African American	17 (5.4)	6 (3.6)	18 (6.2)	11 (7.1)	35 (5.7)	17 (5.2)
White	283 (89.3)	158 (93.5)	258 (88.4)	135 (87.1)	541 (88.8)	293 (90.4)
Other	4 (1.3)	1 (0.6)	1 (0.3)	1 (0.6)	5 (0.8)	2 (0.6)
Multiple	4 (1.3)	0 (0.0)	6 (2.1)	2 (1.3)	10 (1.6)	2 (0.6)
Ethnicity, No. (%)						
Hispanic or Latino	27 (8.5)	10 (5.9)	15 (5.1)	7 (4.5)	42 (6.9)	17 (5.2)
Not Hispanic or Latino	290 (91.5)	159 (94.1)	277 (94.9)	148 (95.5)	567 (93.1)	307 (94.8)
Age, y						
Mean	19.2	19.6	19.2	19.7	19.2	19.7
Median	17	18	17	18	17	18
SD	5.8	6.2	6.7	7.1	6.3	6.6
Range	10-50	11-50	10-50	10-50	10-50	10-50

population included 607, excluding 2 enrolled individuals who did not receive the test article. Slightly more original clascoterone-treated patients participated. There were more females than males, and the population was predominately white (Table I).

Of the 609 enrolled in the ITT population, 285 (n = 148 clascoterone and n = 137 vehicle) were excluded from the PP set (n = 324), mostly because the patient did not complete the study (n = 261).

The number of patients who completed the study and discontinuation rates and reasons are summarized in Table II. The most frequent reasons for early discontinuation were patient withdrawal (101 [16.6%]) and lost to follow-up (90 [14.8%]).

Table II. Patient participation and discontinuation rates and reasons in the safety population*

Variable, No. (%)	Clascoterone (n = 317)	Vehicle (n = 290)	Total (N = 607)
Individuals who completed the study	179 (56.5)	168 (57.9)	347 (57.2)
Individuals who discontinued	138 (43.5)	122 (42.1)	260 (42.8)
Reasons for discontinuation			
Withdrawal by individual	56 (17.7)	45 (15.5)	101 (16.6)
Lost to follow-up	49 (15.5)	41 (14.1)	90 (14.8)
Lack of efficacy	14 (4.4)	16 (5.5)	30 (4.9)
Withdrawal by parent/guardian	6 (1.9)	7 (2.4)	13 (2.1)
Adverse event	9 (2.8)	0 (0.0)	9 (1.5)
Noncompliance with study drug	1 (0.3)	4 (1.4)	5 (0.8)
Other†	0	4 (1.4)	4 (0.7)
Pregnancy	1 (0.3)	2 (0.7)	3 (0.5)
Recovery‡	1 (0.3)	2 (0.7)	3 (0.5)
Technical problems§	0	1 (0.3)	1 (0.2)
Progressive disease	1 (0.3)	0 (0.0)	1 (0.2)

*Study participants are summarized according to the original test article they actually received in the phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26).
†Other reasons for discontinuation included participant moved 2 hours away for school/inconvenient to continue in study, did not want to continue test article application, the participant left the country for study abroad, and the participant went abroad.
‡Participants whose lesions cleared and opted out from the study.
§Participant did not complete the treatment period because of lack of test article; owing to repeated temperature excursions, all of the test article was put in quarantine.

Overall, 250 individuals were treated for truncal acne (n = 130 from the original clascoterone group and n = 120 from the vehicle group).

Baseline IGA scores for the ITT and PP sets were similar. Most facial scores were moderate (ITT: 262 of 609 [43.0%]; PP: 133 of 324 [41.0%]) or mild (ITT: 244 of 609 [40.1%]; PP: 131 of 324 [40.4%]) and for the trunk were moderate (ITT: 93 of 251 [37.1%]; PP: 42 of 126 [33.3%]) or mild (ITT: 136 of 251 [54.2%]; PP: 72 of 126 [57.1%]). Twice as many original clascoterone participants were almost clear on the face at baseline vs original vehicle participants.

Treatment exposure and compliance

Patients on-study at 3, 6, 9, and 12 months for the safety set and PP populations were 538 of 607 (88.6%) and 324 of 324 (100%); 416 of 607 (68.5%) and 324 of 324 (100%); 303 of 607 (49.9%) and 274 of 324 (84.6%); and 123 of 607 (20.3%) and 119 of 324 (36.7%).

In the safety set, the mean total amount of test article used was 415.6 g (range, 8.0-2368.40 g), with a mean of 2.28 g/d (range, 0.22-12.95 g/d). Most participants were compliant with both face and trunk treatments (ITT, 85.4% and 76.9%; PP, 95.4% and 86.5%, respectively).

Adverse events

Overall, 110 participants (18.1%) experienced 191 TEAEs. The number of participants experiencing any TEAE was similar between those originally assigned to clascoterone (n = 58 [18.3%]) vs vehicle (n = 52 [17.9%]). A higher number of TEAEs were observed in participants originally assigned to treatment with clascoterone (n = 106) than vehicle (n = 85). TEAEs are reported in Table III. Overall, 72 participants (11.9%) experienced 110 TEAEs that were mild, 51 (8.4%) had 71 TEAEs that were moderate, and 7 (1.2%) had 10 TEAEs that were severe. The 10 severe TEAEs included eosinophilic gastroenteritis, nephrolithiasis, pancreatitis, sciatica, pruritus, dizziness, suicide attempt, coronary artery dissection, toothache, and fatigue. There were 6 participants who experienced 7 serious TEAEs, and these included moderate depression, severe eosinophilic gastroenteritis, severe dizziness, severe suicide attempt, moderate medical abortion induced, severe coronary artery dissection, and severe fatigue, none related to the test article. One serious TEAE led to study discontinuation (severe suicide attempt). There were no deaths.

Nine participants experienced 9 TEAEs that led to study discontinuation: moderate application site swelling, moderate application site dryness, moderate acne cystic, moderate application site acne, moderate acne conglobata, moderate acne, mild polycystic ovaries, severe suicide attempt, and moderate hair color changes.

The 19 TEAEs related to the test article included mild sunburn, moderate application site swelling, moderate application site pruritus, moderate application site erythema (n = 2), application site

Table III. Treatment-emergent adverse events (*TEAEs*) in the safety population

Variable	Clascoterone (n = 317	Vehicle (n = 290	Overall (N = 607)
Participants with any TEAE	58 (18.3)	52 (17.9)	110 (18.1)
Mild	36 (11.4)	36 (12.4)	72 (11.9)
Moderate	28 (8.8)	23 (7.9)	51 (8.4)
Severe	4 (1.3)	3 (1.0)	7 (1.2)
Any test article-related TEAE*	12 (3.8)	2 (0.7)	14 (2.3)
Any TEAE leading to discontinuation	9 (2.8)	0	9 (1.5)
Any serious TEAE	3 (0.9)	3 (1.0)	6 (1.0)
Any test article-related serious TEAE*	0	0	0
Any serious TEAE leading to discontinuation	1 (0.3)	0	1 (0.2)
Any TEAE leading to death	0	0	0
No. of TEAEs	106	85	191
Related to test article	17	2	19
Not related to test article	89	83	172
Mild	57	53	110
Moderate	42	29	71
Severe	7	3	10
No, of TEAEs leading to discontinuation	9	0	9
No. of serious TEAEs	4	3	7
Related to test article	0	0	0
Not related to test article	4	3	7
No. of serious TEAEs leading to			
Discontinuation	1	0	1
Death	0	0	0

	Events (n = 106)		Events (N = 85)		Events (N = 191)	
	No.	N (%)	No.	N (%)	No.	N (%)
Most frequent TEAEs		58 (18.3)		52 (17.9)		110 (18.1)
Nasopharyngitis	7	6 (1.9)	13	10 (3.4)	20	16 (2.6)
Upper respiratory tract infection	8	7 (2.2)	1	1 (0.3)	9	8 (1.3)
Respiratory tract infection viral	1	1 (0.3)	4	4 (1.4)	5	5 (0.8)
Sinusitis	3	3 (0.9)	2	2 (0.7)	5	5 (0.8)
Application site acne	4	4 (1.3)	0	0	4	4 (0.7)

dryness (n = 1 mild, n = 1 moderate), application site acne (n = 1 mild, n = 1 moderate), moderate cystic acne, application site pain (n = 1 mild, n = 1 moderate), moderate acne conglobata, mild dysgeusia, moderate acne (n = 2), mild contact dermatitis, severe pruritus, and moderate hair color changes. The latter finding occurred on study day 113 in a 23-year-old white woman who experienced depigmented hair within the facial treatment area. This TEAE was considered possibly related to the test article, led to discontinuation from the study, and was ongoing at the last visit. There was no additional follow-up, and the participant did not experience any other TEAEs or local skin reactions (LSRs). She reported no concomitant medications and did not receive truncal treatment with the test article.

The number of participants with TEAEs and the number of TEAEs leading to discontinuation were both higher in participants originally assigned to treatment with clascoterone in the pivotal study.

Systemic AEs, including reduced libido and feminization in male participants, were absent in this long-term safety study. No safety signals were identified from vital signs or laboratory assessments. No differences between sexes were observed.

Local skin reactions

The frequency of any LSRs on the face or the trunk was consistent throughout the study (Table IV). The most frequently reported LSRs were erythema, scaling/dryness, and pruritus. Overall, erythema was the most frequent LSR on the face, occurring in 147 of 607 (24.2%), and trunk, occurring in 40 of 250 (16.0%). Facial and truncal scaling/dryness was observed in 101 of 607 (16.6%) and in 24 of 250 (9.6%), followed by pruritus in 53 of 607 (8.7) and in 9 of 250 (3.6%). Most participants had LSRs that were trace/minimal or mild in severity. In general, the proportion of participants who received CB-03-01 as the original product with treatment-emergent LSRs

Table IV. Local skin reactions by visit and treatment group for face and trunk

Treatment area/visit	Erythema, No. (%)		Scaling/dryness, No. (%)		Edema, No. (%)		Pruritus, No. (%)		Telangiectasia, No. (%)		Skin atrophy, No. (%)		Stinging/burning, No. (%)		Striae rubrae, No. (%)	
	Clascoterone	Vehicle	Clascoterone	Vehicle	Clascoterone	Vehicle	Clascoterone	Vehicle	Clascoterone	Vehicle	Clascoterone	Vehicle	Clascoterone	Vehicle	Clascoterone	Vehicle
Face																
Baseline, pre-treat	58 (18.3)	43 (14.8)	31 (9.8)	28 (9.6)	7 (2.2)	5 (1.7)	10 (3.2)	13 (4.5)	5 (1.5)	7 (2.4)	23 (7.3)	22 (7.6)	2 (0.6)	2 (0.7)	5 (1.6)	1 (0.3)
Baseline, post-treat	53 (16.7)	43 (14.8)	19 (6.0)	14 (4.8)	5 (1.5)	3 (1.0)	5 (1.6)	9 (3.1)	5 (1.5)	8 (2.7)	23 (7.3)	22 (7.6)	3 (0.9)	2 (0.7)	6 (1.9)	0
Month 1	49 (15.4)	34 (11.7)	21 (6.6)	24 (8.2)	7 (2.2)	1 (0.3)	8 (2.5)	7 (2.4)	6 (1.9)	6 (2.1)	21 (6.7)	22 (7.6)	10 (3.1)	7 (2.4)	4 (1.2)	0
Month 3	36 (11.3)	27 (9.3)	14 (4.4)	13 (4.4)	4 (1.2)	3 (1.0)	4 (1.3)	6 (2.1)	6 (1.9)	7 (2.4)	21 (6.5)	19 (6.6)	3 (0.9)	1 (0.3)	3 (0.9)	0
Month 6	27 (8.5)	20 (6.8)	16 (5.0)	7 (2.4)	1 (0.3)	3 (1.0)	4 (1.3)	4 (1.4)	4 (1.2)	4 (1.3)	17 (5.3)	15 (5.2)	0	1 (0.3)	3 (0.9)	0
Month 9	31 (9.8)	19 (6.5)	15 (4.7)	11 (3.8)	2 (0.6)	6 (2.0)	6 (1.9)	6 (2.1)	4 (1.2)	8 (2.7)	16 (5.0)	17 (5.9)	3 (0.9)	1 (0.3)	4 (1.2)	2 (0.6)
Trunk																
Baseline, pre-treat	13 (10.0)	14 (11.7)	6 (4.6)	6 (5.0)	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.7)	1 (0.8)	1 (0.8)	0	3 (2.5)	0	0	0	0
Baseline, post-treat	13 (10.0)	11 (9.1)	5 (3.8)	5 (4.2)	1 (0.8)	1 (0.8)	0	2 (1.7)	0	1 (0.8)	1 (0.8)	3 (2.5)	1 (0.8)	1 (0.8)	0	0
Month 1	10 (7.7)	9 (6.7)	4 (3.1)	7 (5.8)	1 (0.8)	1 (0.8)	2 (1.5)	1 (0.8)	0	0	0	3 (2.5)	0	0	1 (0.8)	0
Month 3	6 (4.6)	9 (7.5)	2 (1.5)	3 (2.5)	1 (0.8)	2 (1.7)	1 (0.8)	0	0	0	0	3 (2.5)	0	1 (0.8)	0	0
Month 6	4 (3.1)	8 (6.7)	3 (2.3)	4 (3.3)	0	3 (2.5)	1 (0.8)	1 (0.8)	0	0	0	4 (3.3)	0	0	1 (0.8)	0
Month 9	2 (1.6)	10 (8.3)	0	4 (3.3)	0	2 (1.7)	0	0	0	0	0	2 (1.6)	0	0	0	1 (0.8)

on the face was higher throughout the study compared with those who received vehicle as the original product.

DISCUSSION

The safety profile of clascoterone cream 1% was favorable overall for long-term treatment of patients aged ≥9 years with moderate to severe acne vulgaris. Clascoterone demonstrated low frequency of TEAEs, a low frequency of treatment related AEs, most of which were mild or moderate, and no accumulation or increase in AEs over time. The single TEAE of depigmented hair within the facial treatment area was considered atypical because it had not been observed in previous clinical studies of clascoterone.[11-14] Together, these results indicate that clascoterone may be a potential option for long-term topical treatment of acne vulgaris.

Although clascoterone is steroidal in chemical structure, it is functionally an androgen receptor inhibitor,[9,10] and as such, AEs consistent with topical steroid use, such as new or worsening atrophy, telangiectasia, or striae, were not observed. Moreover, systemic AEs associated with oral androgen receptor inhibitors[8] were not observed in male or female participants treated with topical clascoterone in this long-term study, in previous phase 2 studies,[11,12] or in both pivotal studies.[13] Indeed, previous studies indicate low systemic exposure to clascoterone.[11,12]

Across the 9 months of safety analysis of both the pivotal[13] and long-term safety studies, most treatment-related AEs were mild. During this long-term study, new or worsening application site erythema and scaling/dryness were the most common LSRs. These results are consistent with previous trial results.[11-13]

Clascoterone represents a novel, potential first-in-class topical androgen receptor inhibitor that targets a key driver in the pathology of acne in both female and male individuals aged ≥9 years. With its proposed mechanism of action of limiting dihydrotestosterone-androgen receptor binding in sebocytes, clascoterone likely reduces downstream activation of androgen-driven lipid production and inflammation in acne lesion formation in vivo.[9-13]

The safety data presented here and data from a higher concentration of clascoterone solution undergoing investigation for treatment of androgenetic alopecia[14] suggest that a once daily higher concentration of clascoterone cream for acne is plausible; however, further studies are needed to test this hypothesis. Additional studies are also needed to elucidate the safety of concomitant use of clascoterone and other topical acne medications.

CONCLUSION

Clascoterone cream 1% boasts a consistent and favorable safety profile, thereby holding promise as alternative or adjunct to traditional acne treatments.

The authors thank the patients, investigators, and sites. This article was in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The authors thank Caridad Rosette, PhD, and Mara Gerloni, PhD, for the mechanism of action experimental studies, and Roberta Macis, MS, for data retrieval and proofreading.

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