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ORIGINAL ARTICLE

Long-Term Safety and Efficacy of Twice-Daily Topical Clascoterone Cream 1% in Patients ≥ 12 Years of Age With Acne Vulgaris

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ABSTRACT

Background: Clascoterone cream 1% is approved for the treatment of acne vulgaris in patients aged ≥ 12 years based on results from two 12-week Phase 3 studies in patients with moderate-to-severe acne. Safety and efficacy of clascoterone in patients aged ≥ 12 years from an open-label, long-term extension study are presented.

Methods: Enrolled patients applied clascoterone cream 1% twice daily to the entire face and, if desired by the patient and/or investigator, truncal acne, for up to 9 months. Patients achieving Investigator's Global Assessment score of 0 or 1 (IGA 0/1) could stop treatment and resume if/when acne worsened. Safety was assessed from treatment-emergent adverse events (TEAEs) and local skin reactions (LSRs [telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus]) in all treated patients. Efficacy was assessed from IGA at each visit among those completing the study per-protocol (PP); face and trunk were evaluated individually.

Results: Of 600 patients aged ≥ 12 years (original randomization: 311 clascoterone, 289 vehicle), 343 completed the extension study (177 clascoterone, 166 vehicle). There were 187 TEAEs in 108/598 clascoterone-treated patients (18.1%), including 56/311 (18.0%) and 52/287 (18.1%) patients originally randomized to clascoterone and vehicle, respectively; the most common LSRs (previous clascoterone/vehicle) were erythema (face, 8.0%/7.7%) and scaling/dryness (face, 10.0%/7.3%). The percentage of PP patients with facial and truncal IGA 0/1 increased to 48.9% (156/319) and 52.4% (65/124), respectively, at study end.

Conclusions: Clascoterone cream 1% maintained a favorable safety and efficacy profile for up to 12 months in patients aged ≥ 12 years.

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INTRODUCTION

Acne vulgaris is a chronic skin condition characterized by excess sebum production, hyperkeratinization, *Cutibacterium acnes* colonization, and inflammation.[1] Acne vulgaris affects approximately 85% of adolescents and young adults between 12 and 25 years of age, attributable in part to the influence of pubertal hormonal changes, but can also persist into adulthood.[2] Androgens such as dihydrotestosterone (DHT) play a key role in driving acne pathogenesis via expression of genes that mediate sebum production and inflammation.[2-4] Antiandrogen medications for acne vulgaris include off-label use of spironolactone and combined oral contraceptives,[3,5] although these medications are not suitable for use in males.[3] Long-term spironolactone treatment is also associated with a potential risk of hyperkalemia, and laboratory monitoring is recommended, particularly for patients with impaired renal function or concomitant use of drugs that elevate potassium levels.[6]

Clascoterone cream 1%, a novel topical androgen receptor inhibitor,[7] was approved in the US in 2020 for the treatment of acne vulgaris in males and females ≥ 12 years of age.[8] Clascoterone has a steroidal structure similar to DHT and inhibits the binding of DHT to androgen receptors in vitro.[9,10] Clascoterone is rapidly hydrolyzed to cortexolone, a primary inactive metabolite, resulting in low quantifiable plasma levels of clascoterone after topical application, and therefore, low systemic exposure.[11,12] The efficacy and safety of clascoterone were assessed in 2 identical Phase 3 clinical trials and a long-term extension study in patients ≥ 9 years of age with moderate-to-severe acne vulgaris.[1,7] In the Phase 3 pivotal studies, treatment with clascoterone cream 1% resulted in significant clinical improvement compared with vehicle cream after 12 weeks of twice-daily application, with a favorable safety profile.[1] Clascoterone safety was well maintained for up to an additional 9 months of treatment in patients ≥ 9 years old with moderate-to-severe acne vulgaris.[7] Here, we present long-term

safety and efficacy data in the subgroup of clinical trial patients ≥ 12 years old who entered the long-term extension study.

MATERIALS AND METHODS

Study Design and Patients

The multicenter, open-label, long-term safety study of clascoterone cream 1% in patients with moderate-to-severe acne vulgaris ≥ 9 years of age (www.clinicaltrials.gov NCT 02682264) was previously described in detail.[7] The original study was conducted in accordance with principles of the Declaration of Helsinki, the current Good Clinical Practice guidelines, and all country-specific regulatory requirements. Institutional Review Board approval was obtained for the protocol and informed consent forms. Voluntary informed consent was given by every patient, and patients under the age of 18 years provided written informed consent and were accompanied by a parent or legal guardian; the parent or legal guardian also provided informed consent for the patient.

Patients completed one of the Phase 3 pivotal studies and enrolled within 3 days of the final pivotal study visit to be eligible for the extension study.[7] This analysis only included patients ≥ 12 years of age.

Treatments Administered

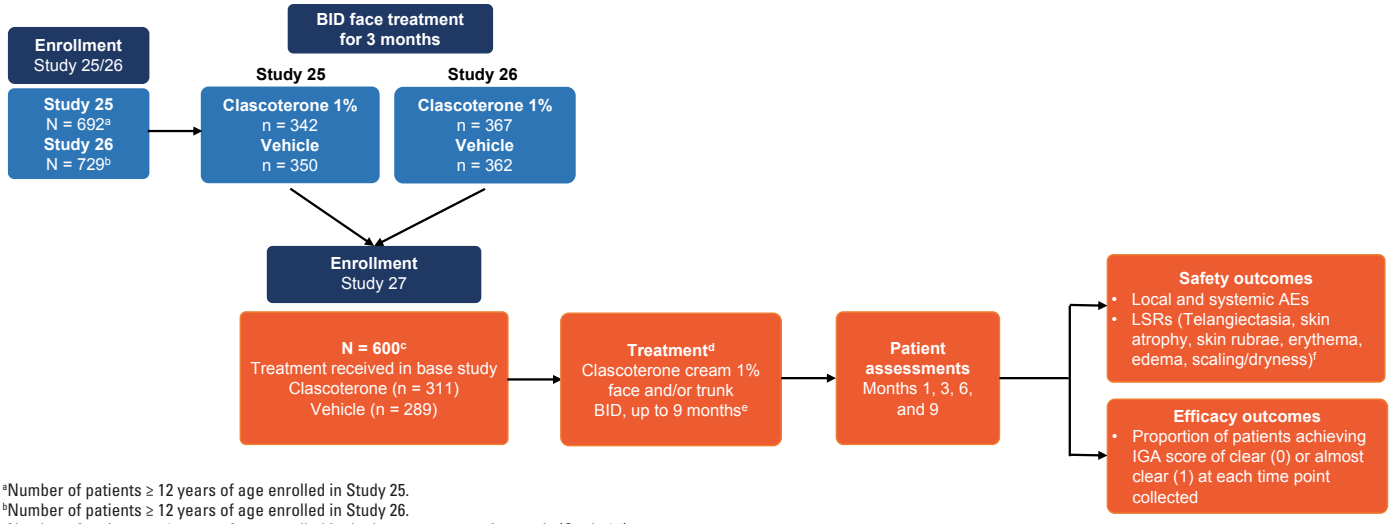
All patients applied clascoterone cream 1% twice daily to the entire face and, if desired by both patient and investigator, truncal acne for up to 9 additional months of treatment. Patients randomized to vehicle cream in the pivotal studies applied clascoterone cream in the long-term extension; patients originally randomized to clascoterone cream continued treatment. The maximum clascoterone treatment time in the pivotal and extension studies was 12 months for the face (3 months in the pivotal studies and 9 months in the extension study) and 9 months for the trunk. Patients who achieved Investigator's Global Assessment (IGA) score of 0 or 1 (IGA 0/1) could stop treatment and resume if/when acne worsened (Figure 1).

Assessments and Outcomes

Safety and efficacy were assessed at scheduled patient visits at months 1, 3, 6, and 9 (Figure 1).[7] As previously described,[7] primary safety endpoints included frequencies of local and systemic treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), and frequency and severity of local skin reactions (LSRs). The investigator evaluated the severity of telangiectasia, skin atrophy, striae rubrae, erythema, edema, and scaling/dryness using a 5-point scale from 0 (none) to 4 (severe); patients were asked to rate the severity of stinging/burning and pruritus using a 4-point scale from 0 (none) to 3 (severe).

Efficacy was determined based on measurement of the overall severity of acne using the 5-point IGA, ranging from 0 (clear) to 4 (severe), which was assessed separately for the face and trunk at each study visit. The efficacy endpoint was the number of patients with each IGA severity score for each treatment area, as applicable, at each time point collected (baseline and long-term follow-up at months 1, 3, 6, and 9); the proportion of patients achieving IGA 0/1 for each treatment area is reported. The facial IGA score at the end-of-study visit of the Phase 3 study and the truncal IGA score during the first extension study visit were used as baseline data.

FIGURE 1. Study design.



[a]Number of patients ≥ 12 years of age enrolled in Study 25.
[b]Number of patients ≥ 12 years of age enrolled in Study 26.
[c]Number of patients ≥ 12 years of age enrolled in the long-term extension study (Study 27).
[d]Patients who achieved IGA score of ≤ 1 could stop treatment and resume if/when acne worsened.
[e]Total clascoterone treatment duration was up to 12 months for patients treated with clascoterone for 3 months in the pivotal studies.
[f]The severity of LSRs was assessed using a five-point scale from 0 (none) to 4 (severe).
AE, adverse event; BID, twice daily; IGA, Investigator's Global Assessment; LSR, local skin reaction.

Statistical Analysis

All statistical analyses were performed using SAS® for Windows version 9.3. For demographic, efficacy, and safety data, continuous variables were described by descriptive statistics and categorical data by frequency counts and percentages of patients within each category. Sample size calculations were previously described.[7] No interim analyses were performed. Missing data were not imputed.

Patient demographics are reported for the intention-to-treat (ITT) population, which included all enrolled individuals. Safety was assessed in all enrolled patients who received at least 1 application of clascoterone during the extension study (safety population). Efficacy was assessed in the per-protocol (PP) population, which included all patients who completed the extension study without significant protocol deviations; criteria for PP exclusion included failure to satisfy inclusion/exclusion criteria, use of prohibited medications, noncompletion of study, lack of compliance, or failure to treat individual with clascoterone.

As previously described,[7] all TEAEs were coded using the Medical Dictionary for Regulatory Activities version 18.1 and were listed by preferred term and system organ class.

RESULTS

Patients and Demographics

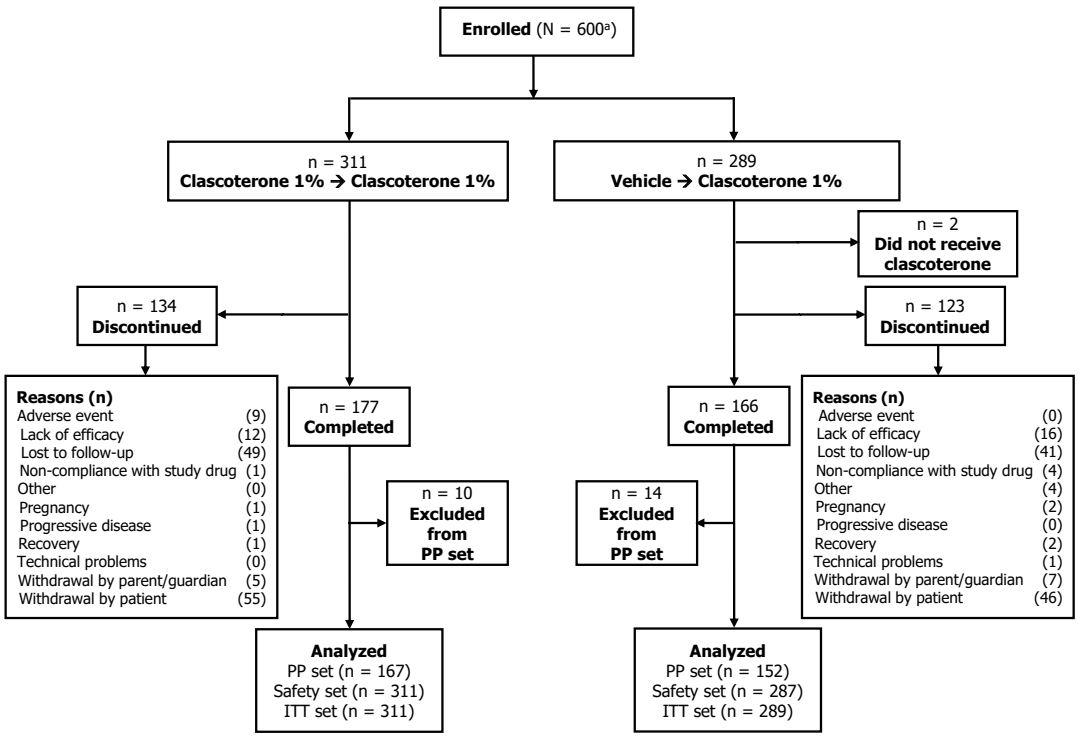
Of 609 patients who entered the extension study,[7] 600 were ≥ 12 years of age; of these, 311 were originally randomized to treatment with clascoterone and 289 to vehicle in the pivotal studies (Figure 2). The mean ± standard deviation age was 19.3 ± 6.2 in the ITT population (n = 600) and 19.8 ± 6.6 in the PP population (n = 319). The majority of patients were female (ITT, 62.2%; PP, 60.8%), and the population was predominantly White (Table 1). The safety population included 598 patients treated with clascoterone.

Patient disposition is shown in Figure 2. A total of 134 and 123 patients originally treated with clascoterone and vehicle, respectively, discontinued the study, most frequently because of patient withdrawal (55 [17.7%] and 46 [15.9%]) and loss to follow-up (49 [15.8%] and 41 [14.2%]). Overall, 245 patients in the safety population (126 originally randomized to clascoterone and 119 to vehicle) and 124 patients in the PP population (67 originally randomized to clascoterone and 57 to vehicle) treated truncal acne.

Treatment Exposure

During the extension study period, 184/598 (30.8%) patients in

FIGURE 2. Patient disposition.



[a]Number of patients ≥ 12 years of age enrolled in the long-term extension study.
Patients are summarized according to the original treatment they received in the Phase 3 pivotal studies. All patients in the long-term extension study applied clascoterone cream 1%.
ITT, intention-to-treat; PP, per-protocol.

TABLE 1.

Patient Demographics						
Characteristic	Clascoterone		Vehicle		Overall	
	ITT n = 311	PP n = 167	ITT n = 289	PP n = 152	ITT N = 600	PP N = 319
Sex						
Male	118 (37.9)	70 (41.9)	109 (37.7)	55 (36.2)	227 (37.8)	125 (39.2)
Female	193 (62.1)	97 (58.1)	180 (62.3)	97 (63.8)	373 (62.2)	194 (60.8)
Race						
Caucasian	279 (89.7)	157 (94.0)	257 (88.9)	134 (88.2)	536 (89.3)	291 (91.2)
Asian	5 (1.6)	2 (1.2)	8 (2.8)	5 (3.3)	13 (2.2)	7 (2.2)
Black or African American	16 (5.1)	5 (3.0)	16 (5.5)	9 (5.9)	32 (5.3)	14 (4.4)
Other	11 (3.5)	3 (1.8)	8 (2.8)	4 (2.6)	19 (3.2)	7 (2.2)
Ethnicity						
Hispanic or Latino	26 (8.4)	9 (5.4)	15 (5.2)	7 (4.6)	41 (6.8)	16 (5.0)
Not Hispanic or Latino	285 (91.6)	158 (94.6)	274 (94.8)	145 (95.4)	559 (93.2)	303 (95.0)
Age, years						
Mean	19.3	19.7	19.3	19.9	19.3	19.8
Median	17.0	18.0	17.0	18.0	17.0	18.0
Standard deviation	5.77	6.13	6.68	7.04	6.22	6.57
Range	12–50	12–50	12–50	12–50	12–50	12–50

Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Data shown as n (%) unless otherwise specified.
ITT, intention-to-treat; PP, per-protocol.

the safety population were treated with clascoterone for facial acne for up to 3 months, 85/598 (14.2%) for 3 to 6 months, 176/598 (29.4%) for 6 to 9 months, and 153/598 (25.6%) for ≥ 9 months. Among patients treated with clascoterone for truncal acne, 70/245 (28.6%) were treated for up to 3 months, 31/245 (12.7%) for 3 to 6 months, 74/245 (30.2%) for 6 to 9 months, and 70/245 (28.6%) for ≥ 9 months. The amount of cream applied daily and total duration of exposure to clascoterone in the extension study were similar among patients previously treated with clascoterone vs vehicle in the pivotal studies. Patients originally randomized to clascoterone in the pivotal studies had 3 months of treatment with clascoterone for facial acne prior to entering the extension study.

Safety

Overall, 108/598 (18.1%) patients in the safety population experienced a total of 187 TEAEs, with similar frequency between patients previously treated with clascoterone (56/311 [18.0%]) vs vehicle (52/287 [18.1%]; Table 2). The majority of reported TEAEs were mild or moderate in severity, and most were not considered related to clascoterone treatment. A total of 6/598 (1.0%) patients reported SAEs, none of which was considered related to clascoterone treatment, and 9/598 (1.5%) patients had TEAEs leading to study discontinuation. The most frequent TEAEs by percentage of patients affected included nasopharyngitis (17 [2.8%]), upper respiratory tract infection (11 [1.8%]), sinusitis (5 [0.8%]), viral respiratory tract infection (5 [0.8%]), and application site acne (4 [0.7%]) among all patients; TEAE frequencies were similar among patients originally randomized to clascoterone compared with vehicle in the pivotal Phase 3 studies (Table 3). No deaths were reported during the study.

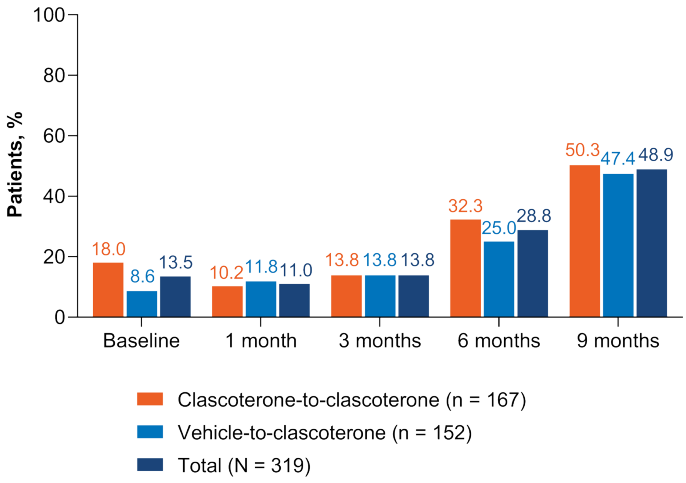
The frequency of LSRs was low throughout the study in patients previously treated with either clascoterone or vehicle. The most common new or worsening LSRs in patients previously treated with clascoterone/vehicle were scaling/dryness (face, 10.0%/7.3%; trunk, 3.5%/4.5%) and erythema (face, 8.0%/7.7%; trunk, 6.1%/7.3%; Table 4).

Efficacy

The percentage of PP patients who achieved facial IGA 0/1 (clear or almost clear) increased over time from 43/319 (13.5%) at baseline to 156/319 (48.9%) at the end of the study (9 months of treatment), with improvement observed at most visits (Figure 3). The percentage of patients with facial IGA 0/1 was higher at baseline in patients previously treated with clascoterone (30/167 [18.0%]) vs vehicle (13/152 [8.6%]) and increased over time in both cohorts to 84/167 (50.3%) and 72/152 (47.4%), respectively, at the end of the study.

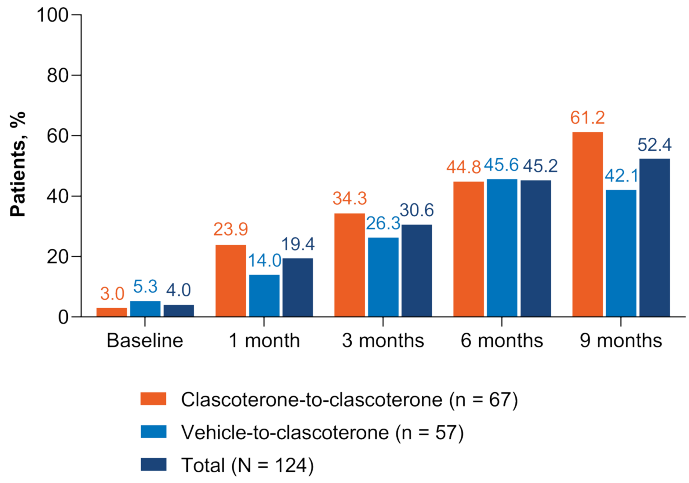
For truncal acne, the percentage of PP patients with truncal IGA 0/1 at baseline was low overall (5/124 [4.0%]) and increased to 65/124 [52.4%]) at the end of the study, with improvement

FIGURE 3. Percentage of patients ≥ 12 years of age with facial IGA 0/1 by visit.



Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Per-protocol population. Data shown as % unless otherwise specified.
All patients in the per-protocol population were assessed at all visits.
IGA 0/1, Investigator's Global Assessment score of 0 or 1.

FIGURE 4. Percentage of patients ≥ 12 years of age with truncal IGA 0/1 by visit.



Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Per-protocol population. Data shown as % unless otherwise specified.
All patients in the per-protocol population were assessed at all visits.
IGA 0/1, Investigator's Global Assessment score of 0 or 1.

TABLE 2.

Summary of TEAEs in Patients ≥ 12 Years of Age

Category	Clascoterone n = 311	Vehicle n = 287	Overall N = 598
Subjects with any TEAE	56 (18.0)	52 (18.1)	108 (18.1)
Mild	35 (11.3)	36 (12.5)	71 (11.9)
Moderate	27 (8.7)	23 (8.0)	50 (8.4)
Severe	4 (1.3)	3 (1.0)	7 (1.2)
Any test article–related TEAE	11 (3.5)	2 (0.7)	13 (2.2)
Any TEAE leading to discontinuation	9 (2.9)	0	9 (1.5)
Any serious TEAE	3 (1.0)	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
Number of TEAEs, N	102	85	187
Related to test article	16	2	18
Not related to test article	86	83	169
Mild	55	53	108
Moderate	40	29	69
Severe	7	3	10

Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Safety population. Data shown as n (%) unless otherwise specified.
TEAE, treatment-emergent adverse event.

TABLE 3.

Most Frequent TEAEs in Patients ≥ 12 Years of Age

Most Frequent TEAEs	Clascoterone n = 311		Vehicle n = 287		Overall N = 598	
	Events, n	Patients	Events, n	Patients	Events, n	Patients
Application site acne	4	4 (1.3)	0	0	4	4 (0.7)
Nasopharyngitis	7	6 (1.9)	14	11 (3.8)	21	17 (2.8)
Respiratory tract infection viral	1	1 (0.3)	4	4 (1.4)	5	5 (0.8)
Sinusitis	3	3 (1.0)	2	2 (0.7)	5	5 (0.8)
Upper respiratory tract infection	9	8 (2.6)	3	3 (1.0)	12	11 (1.8)

Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Safety population. Data shown as n (%) unless otherwise specified.
TEAE, treatment-emergent adverse event.

TABLE 4.

New or Worsening LSRs on the Face and Trunk in Patients ≥ 12 Years of Age

Symptom	Clascoterone n = 311		Vehicle n = 287	
	Face	Trunk	Face	Trunk
Edema	5 (1.6)	1 (0.3)	5 (1.7)	5 (1.7)
Erythema	25 (8.0)	19 (6.1)	22 (7.7)	21 (7.3)
Pruritus	13 (4.2)	5 (1.6)	16 (5.6)	4 (1.4)
Scaling/Dryness	31 (10.0)	11 (3.5)	21 (7.3)	13 (4.5)
Skin atrophy	3 (1.0)	1 (0.3)	4 (1.4)	4 (1.4)
Stinging/Burning	11 (3.5)	1 (0.3)	8 (2.8)	2 (0.7)
Striae rubrae	1 (0.3)	2 (0.6)	2 (0.7)	1 (0.3)
Telangiectasia	3 (1.0)	1 (0.3)	4 (1.4)	1 (0.3)

Patients are summarized according to the original treatment they received in the Phase 3 pivotal studies.
Safety population. Data shown as n (%) unless otherwise specified.
LSR, local skin reaction.

observed at each visit (Figure 4). The percentage of patients with truncal IGA 0/1 generally increased over time regardless of prior exposure to facial clascoterone treatment, although the greatest percentage was observed at the end of the study in patients originally randomized to clascoterone (41/67 [61.2%]).

Among the original study population of patients ≥ 9 years of age, the proportion of PP patients with clear or almost clear skin on the face and trunk at the end of the study was comparable to that observed in the subgroup of patients ≥ 12 years old (facial IGA 0/1, 156/324 [48.1%]; truncal IGA 0/1, 66/126 [52.3%] for patients ≥ 9 years old).

DISCUSSION

This 9-month extension study confirmed the favorable safety profile of clascoterone cream 1% in the long-term treatment of patients ≥ 12 years of age with moderate-to-severe facial and/or truncal acne vulgaris. The frequencies of TEAEs and LSRs were low throughout the study; most reported TEAEs were mild in severity, and there was no accumulation of AEs observed over time. The proportions of patients with facial and truncal IGA 0/1 increased over time and were highest at the end of the study, indicating that clascoterone efficacy continued to increase with long-term treatment. These results suggest that clascoterone may be a suitable option for long-term topical treatment of both facial and truncal acne vulgaris in patients ≥ 12 years of age.

The findings from this and previous studies support clascoterone as an option for long-term treatment of acne vulgaris. Systemic exposure is low following topical clascoterone treatment[12]; and systemic antiandrogen effects associated with oral androgen receptor blockers and other hormonal treatments[3] were not observed in patients treated with clascoterone cream 1% in this long-term study or previous studies.[1,12,13] Laboratory abnormalities were not evaluated in this study or the Phase 3 pivotal studies; shifts from normal to elevated potassium levels were observed in some patients treated with clascoterone in the Phase 1 and Phase 2 studies, although none were reported as AEs. Hypothalamic-pituitary-adrenal (HPA) axis suppression was observed in 3/42 (7%) patients treated with clascoterone in a Phase 2 safety study in patients ≥ 12 years of age with moderate-to-severe acne vulgaris; HPA axis function returned to normal in all patients at follow-up 4 weeks after stopping treatment.[12] During 9 additional months of clascoterone treatment, the most common new or worsening LSRs on both the face and trunk in

patients ≥ 12 years of age were erythema and scaling/dryness, consistent with previously published long-term findings in patients ≥ 9 years of age[7] and short-term studies.[1,13]

These findings expand upon results from the Phase 3 pivotal studies, in which clascoterone cream 1% was significantly more efficacious vs vehicle cream after 12 weeks of treatment.[1,14] In this long-term extension study, approximately half of PP patients ≥ 12 years of age achieved IGA 0/1 for both the face and trunk. The proportion of patients who were clear or almost clear increased at each visit and was highest at the end of the study, indicating that clascoterone efficacy improved over time for up to 12 months in patients with moderate-to-severe acne vulgaris.

The study was designed primarily to evaluate long-term safety, and therefore, there was no ongoing comparator planned for efficacy evaluation. Additionally, concomitant acne medications were not evaluated in this study; therefore, the safety and efficacy of combined treatment with clascoterone and other topical medications should be evaluated in future clinical studies.

CONCLUSION

Clascoterone cream 1% exhibited favorable long-term safety and efficacy during treatment up to 12 months in patients ≥ 12 years of age with moderate-to-severe acne vulgaris and may be a safe and effective alternative to traditional acne medications for long-term treatment.

DISCLOSURES

LFE, AAH, and LSG were study investigators. LFE, AAH, and LSG were also compensated advisors to Cassiopea. AAH is an employee of the McGovern Medical School of The University of Texas Health Science Center in Houston, which received compensation from Cassiopea S.p.A., for study participation; she also received an honorarium for serving on the Cassiopea advisory board; all research grant funds were paid to her institution. She has also received personal fees for advisory, speaking, consulting, and/or other services with Almirall, Incyte, Pfizer, Aslan, Galderma Laboratories, Novartis, and Sun Pharma. LFE is an employee of the University of California San Diego, which received compensation from Cassiopea S.p.A., for study participation; he has also served as an investigator, advisor, or consultant for Almirall, Dermata, Galderma Laboratories, and Ortho Dermatologics. LSG is an employee of the Henry Ford Health System in Detroit, Michigan, which received compensation from Cassiopea S.p.A., for study participation; she has also received personal fees for advisory, speaking, consulting, research, and/or other services with Almirall, Foamix, Galderma Laboratories, Novartis, Sol-Gel, and Sun Pharma. MC is employed as the Vice President of Medical Affairs at Novan Inc.; was employed as the senior director of medical affairs at Cassiopea, Inc. at the time of the study; received personal fees as a consultant from Cassiopea S.p.A.; and receives personal fees as an adjunct faculty member from the University of Arizona. LM is an employee of Cassiopea S.p.A., and holds stock options in the company. JH is an employee of Pharmapace Inc. NS is an employee of Sun Pharmaceutical Industries, Inc. AM is employed as the chief medical officer for Cassiopea S.p.A., and holds stock options in the company; and has served as the chief medical officer of Cosmo Pharmaceuticals.

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