Taylor & Francis
Taylor & Francis Group

Expert Review of Clinical Immunology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierm20

Clascoterone cream (1%) topical androgen receptor inhibitor for the treatment of acne in patients 12 years and older

Michael H. Gold

To cite this article: Michael H. Gold (2021): Clascoterone cream (1%) topical androgen receptor inhibitor for the treatment of acne in patients 12 years and older, Expert Review of Clinical Immunology, DOI: 10.1080/1744666X.2021.1894131

To link to this article: https://doi.org/10.1080/1744666X.2021.1894131

Accepted author version posted online: 22 Feb 2021.

Clascoterone Cream (1%) topical androgen receptor inhibitor for the treatment of acne in patients 12 years and older

For submission to:

Expert Review of Clinical Immunology
https://www.tandfonline.com/action/authorSubmission?show=instructions&journalCode=ierm20

Michael H. Gold, MD
Gold Skin Care Center
Nashville, TN

Address correspondences to:

Dr. Michael H. Gold
Gold Skin Care Center
2000 Richard Jones Road
Suite 220
Nashville, TN 37215 USA

Office: 615-383-2400
Fax: 615-385-0387

Conflict of Interest Disclosure: Dr. Gold is a consultant and performs clinical research for Cassiopea SpA.

Clascoterone cream (1%) topical androgen receptor inhibitor for the treatment of acne in patients 12 years and older

Michael H. Gold[1]*

[1] Gold Skin Care Center, Nashville, TN, USA.

***Corresponding author:**

Michael H. Gold, Gold Skin Care Center, 2000 Richard Jones Road, Suite 220, Nashville, TN 37215 USA

Office: 615-383-2400

Fax: 615-385-0387

Email: drgold@goldskincare.com

Abstract

Introduction: The efficacy of clascoterone cream was demonstrated in two phase three vehicle-controlled clinical trials that enrolled over 1,400 subjects. Its safety profile allowed it to be approved for treating patients as young as 12 years old. During clinical trials, the occurrence of local skin reactions (edema, erythema, pruritus, dryness) was similar to treatment with vehicle alone.

Areas covered: All publications describing the clinical development of clascoterone cream (cortexolone 17α-propionate) are reviewed and discussed in relation to with existing topical and systemic therapies for acne vulgaris.

Expert opinion: Clascoterone 1% cream is a novel first-in-class topical androgen receptor inhibitor for the treatment of acne vulgaris. Topical clascoterone 1% cream represents the first new type of therapy for acne treatment in almost 40 years and may become first-line therapy.

Keywords: Clascoterone, cortexolone 17α-propionate, acne vulgaris, clinical development

Article highlights:

- Acne vulgaris is a chronic inflammatory dermatosis of the face and torso and one of the most prevalent skin diseases, affecting nearly 10% of the global population.
- Androgens are hormones that regulate sebum production and play a key role in acne pathogenesis, contributing to symptom onset and persistence.
- Clascoterone (cortexolone 17α-propionate) is a novel topical androgen receptor inhibitor, recently approved for the treatment of acne vulgaris in patients 12 years of age or older.
- Subjects in two 12-week phase 3, double-blind, controlled studies achieved significant improvements in baseline noninflammatory and inflammatory lesion counts.
- The safety of topical clascoterone was demonstrated in a large 9-month extension study.
- The results of a comparative study showed topical clascoterone was clinically superior to topical tretinoin for treating mild-to-moderate acne vulgaris.

1.0 Introduction

Acne vulgaris is a chronic inflammatory dermatosis of the face and torso, characterized by open or closed comedones and inflammatory lesions including papules and pustules [1]. It is one of the most prevalent diseases, affecting nearly 10% of the global population [2]. Acne commonly causes scarring that can be very difficult to correct [3] and post-inflammatory dyschromia can occur in susceptible individuals [4]. The psychosocial effects of acne are also well-known [5,6] and are associated with depression, anxiety, loneliness and has a significant negative impact on interpersonal relationships and overall quality of life [7-9]. These detrimental effects are exacerbated by being negatively judged by the community at large [10]. Treatment is dependent on disease severity and may include topical prescription and over-the-counter products (benzoyl peroxide, antibiotics, retinoids), systemic antibiotics (doxycycline, tetracycline), hormonal therapies (oral contraceptives) and dietary changes (low-glycemic index), alone or in combination [1].

Acne has a complex etiology including overproduction and changes in the composition of sebum, altered keratinization of the pilosebaceous duct with sebaceous obstruction, over-colonization by *Cutibacterium acnes* and inflammation. Androgens are the most important hormones regulating sebum production and play a key role in acne pathogenesis, contributing to symptom onset and persistence [11]. The sebaceous glands are the main site of hormone biosynthesis [12]. During puberty, androgens stimulate sebum production and acne formation in young men and women. Sebum secretion is mediated by the potent androgens testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA) and androstenedione. Current anti-androgen drug therapies include off-label use of oral contraceptives, spironolactone, flutamide and finasteride [13]; however, their use can be associated with systemic adverse events [14,15].

Clascoterone (cortexolone 17α-propionate) is a novel topical androgen receptor inhibitor which has been developed and recently approved for the treatment of acne vulgaris in patients 12 years of age or older (Winlevi® [clascoterone] cream 1%, for topical use; Cassiopea SpA, Milan Italy) [16]. The safety and efficacy of clascoterone for the treatment of acne has been demonstrated in numerous preclinical and clinical trials described below.

2.0 Development program

2.1 Preclinical studies

In vitro studies have shown clascoterone binds to androgen receptors with high affinity ~~*in vitro*~~, inhibiting androgen receptor-regulated transcription, and antagonizing androgen-regulated lipid and inflammatory cytokine production in human primary sebocytes [17]. It was significantly better than spironolactone at inhibiting inflammatory cytokine synthesis [17]. Clascoterone inhibits androgen receptor transcription in cell culture with efficacy similar to finasteride, a 5α-reductase inhibitor [18], and is significantly more

potent at inhibiting IL-6 synthesis than the androgen receptor antagonist enzalutamide [18]. Importantly, clascoterone was significantly better than the direct androgen receptor antagonist enzalutamide at inhibiting IL-6 synthesis from DHT-stimulated primary cultures of human dermal papilla cells. As a topical antiandrogen, clascoterone is approximately four times more potent than progesterone, three times more potent than flutamide, twice as potent as finasteride and about as active as cyproterone acetate [19].

2.2 Phase 2 studies

The primary objectives of this phase 2a open-label study were to determine the pharmacokinetic (PK) properties and adrenal suppression potential of clascoterone 1% topical cream for treating subjects with acne vulgaris on the face, chest or back [20]. Subjects with moderate-to-severe acne (Grade 3-4) based on Investigator's Global Assessment (IGA) on the face, chest and/or back were enrolled. Subjects in Cohort 1 were >18 years old (mean age, 24.4 years) and included male (n=5) and female (n=15) subjects. Subjects in Cohort 2 were 12-18 years old (mean age, 15.6 years) and included male (n=10) and female (n=12) subjects. For ethical reasons, subjects in Cohort 2 were not treated until the safety results from Cohort 1 were established.

The primary safety endpoints included changes in hypothalamic-pituitary-adrenal (HPA) axis response with a Cosyntropin Stimulation Test [21] at screening on Day 1 and on Day 14. HPA axis suppression was defined as a post-stimulation serum cortisol level <18 µg/dL at Day 14. Blood samples were obtained 1, 2, 4, 6, 8, 10 and 12 hours after the initial application and after the final application to determine plasma clascoterone and cortexolone PK parameters including concentration-time profiles using a non-compartmental analysis. Secondary safety endpoints included clinical laboratory testing, local and systemic adverse events (AEs), physical examinations and vital signs, and electrocardiogram. The treated areas were examined on Days 4, 10 and 14.

Cohort 1 applied clascoterone 1% topical cream to acne-affected areas twice daily for 14 days. In this maximal use study, subjects applied 6 grams of 1% clascoterone cream to their entire face, shoulders, upper chest and upper back twice-daily (a total of 12 grams/day) except subjects <18 years with a body surface area <1.6 m^2 who applied 4 grams of test article twice daily for a total of 8 grams/day.

At that time, an abnormal HPA axis response was measured in three subjects (7%) with serum cortisol levels ranging from 14.9 to 17.7 µg/dL; however, all returned to normal 4 weeks later and none showed clinical evidence of adrenal suppression. Clascoterone plasma concentrations achieved PK steady state by Day 5 and clascoterone exposure was similar between both cohorts. At steady state, mean plasma clascoterone concentrations increased ~1.8- to 2.1-fold compared to the initial application in Cohorts 1 and 2, respectively, with plasma concentrations of 4.4 and 4.6 ng/mL. Plasma concentrations of cortexolone, a possible primary metabolite of clascoterone, were below the lower limit of quantitation in both cohorts. In addition to Cosyntropin Stimulation Test abnormalities, there was one report of folliculitis that was likely related to the cream. There were no discontinuations due to adverse events.

Subsequently, a 12-week phase 2b, randomized, double-blind vehicle-controlled study assessed the safety and efficacy of escalating concentrations of topical creams containing clascoterone 0.1%, 0.5% and 1% for treating subjects with facial acne vulgaris [22]. Enrolled subjects were male and female, ≥12 years old with mild-to-severe (Grade 2-4) facial acne based on IGA scores with 20 to 75 inflammatory lesions (papules, pustules, and nodules or cysts) and 20 to 100 non-inflammatory (open or closed) lesions. Subjects in Cohort 1 were randomized 4:1 to twice-daily clascoterone 0.1% or vehicle for 4 weeks. After 4 weeks of treatment, an interim safety review was performed, and treatment was escalated to the next dose escalation in the absence of concerning safety signals. Subsequent treatment groups were Cohort 2 (0.5% twice-daily), Cohort 3 (1% once-daily), Cohort 4 (1% twice-daily), and Cohort ~~Group~~ 5 (vehicle applied once- or twice-daily). An interval of at least 8 hours was required for twice-daily dosing. Efficacy assessments included 5-point IGA severity scores from 0 (clear) to 4 (severe), inflammatory and non-inflammatory acne lesion counts and subject satisfaction with treatment. Safety assessments included local and systemic AEs, physical examinations, vital signs, laboratory tests, local skin reactions and electrocardiograms. Predetermined study success required a score of Clear or Almost Clear (Grade 0 or 1) and a ≥2-grade improvement in baseline scores.

Enrolled subjects (*N*=363) were treated in Cohort 1 (n=72), Cohort 2 (n=76), Cohort 3 (n=70), Cohort 4 (n=70), and Cohort 5 (n=75) and 304 subjects (83.7%) completed the study. The Intent to Treat (ITT) population include female (n=196, 54.0%) and male (n=167, 46.0%) subjects with a mean age of 19.7 years (range, 12-43). Most subjects (n=257, 70.2%) were white. The demographic and baseline characteristics were similar across groups.

At Week 12, treatment success was reached in Cohort 1 (8.3%) and Cohort 4 (8.6%) versus vehicle (2.7%) (**Table 1**). Absolute change in inflammatory (p=0.0431) and non-inflammatory (p=0.0303) lesions was significant across treatment groups. Among subjects in Cohort 4, the median change from baseline inflammatory and non-inflammatory lesions was -13.5 and -17.5, respectively. Subjects in Cohorts 1 and 4 also had greatest response to secondary endpoints.

Overall, clascoterone cream concentrations were well-tolerated with no clinically relevant safety signals noted. Among 123 reported AEs by 93 subjects (25.6%), two were considered probably or possibly related to treatment in Cohort 3 (once daily 1% cream). Most AEs were mild in severity and similar across all groups and nearly all (76.8%) resolved by the end of the study. The most prevalent local skin reaction was erythema reported by 36.8% of subjects at some time during the study. There was one discontinuation due to a urinary tract infection which was unrelated to treatment.

Clascoterone 1% administered twice-daily had the most favorable results and was chosen as the best candidate for further clinical study and development.

2.3 Phase 3 studies

Two identical 12-week, randomized, double-blind, vehicle-controlled, parallel-group phase 3 studies assessed the efficacy and safety of topical clascoterone cream 1% for treating subjects with facial acne

vulgaris [23]. Male and female subjects ≥9 years older with IGA Scale scores of 3 (moderate) or 4 (severe) facial acne vulgaris were eligible for enrollment. Subjects had ≥30 to ≤75 inflammatory lesions and ≥30 to ≤100 noninflammatory lesions. Subjects had been on a consistent skin care program for at least 1 month prior to enrollment and agreed to continue this regimen for the entire study. Key exclusion criteria included >2 facial nodules and concurrent use of a topical or systemic acne therapy.

At Visit 1, subjects were randomized 1:1 to receive clascoterone cream 1% or vehicle cream and instructed to apply approximately 1g of cream to the entire face twice-daily for 12 weeks. Subjects were evaluated after 4, 8 and 12 weeks (Visits 2, 3 and 4). At each study visit, an IGA Scale score was obtained, noninflammatory and inflammatory lesions, and nodules were manually counted. Standardized color digital images of the face were obtained ~~face~~ looking straight ahead, up, down, left, and right. Local and systemic AEs including local skin reactions were also evaluated at each study visit. Investigators assessed local skin reactions using a 5-point scale: (0, none; 1, trace; 2, mild; 3, moderate; 4, severe). Subjects rated stinging, burning and pruritus severity on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Electrocardiograms obtained at Visits 1 and 4 were assessed by a cardiologist. Treatment noncompliance was evaluated and defined as <80%.

Three hierarchal coprimary efficacy end points were the proportion of subjects achieving treatment success at Week 12, absolute change in baseline noninflammatory lesion count (NILC), and inflammatory lesion count (ILC) at week 12. Treatment success was defined as a ≥2-point reduction in baseline IGA scores and a score of clear (0) or almost clear (1). Secondary efficacy end points were the percentage change in baseline total lesion count (TLC), NILC, ILC at Week 12, and absolute change in baseline TLC at Week 12. Safety end points included local and systemic AEs, local skin reactions, changes in ECGs at Week 12, and urine pregnancy test results.

In Study 1, 708 subjects were randomized to be treated with clascoterone cream 1%, (n=353) and vehicle cream (n=355). In Study 2, 732 subjects were randomized to be treated with clascoterone cream 1% (n=369), and vehicle cream (n=363). All enrolled subjects who received at ≥1 application of their assigned treatment and were included in the ITT and safety sets. Subject baseline demographic and clinical characteristics are presented in **Table 2** and were balanced between groups. Most subjects in both trials (>80%) were treatment-compliant.

The safety set included all subjects who received at ≥1 application of the test article, the intent-to-treat (ITT) population included all randomized subjects and the per-protocol (PP) population included subjects who completed the study. The results of both trials met the primary efficacy end points. At Week 12, significantly more clascoterone cream-treated subjects achieved treatment success in Study 1 (18.4% vs. 9.0%) and Study 2 (20.3% vs. 6.5%) (for each, $p<0.001$). The absolute changes from in baseline NILC at Week 12 were significantly greater following the use of clascoterone cream in Study 1 (-19.4 vs. -13.0) and Study 2 (-19.4 vs. -10.8) (for each, $p<0.001$) and also baseline ILC in Study 1 (-19.3 vs. -15.5) and Study 2 (-20.0 vs. -2.6) (for each, $p<0.001$). The TCA was also significantly greater among subjects treated with clascoterone cream in Study 1 (-39.1 vs. -28.8) and Study 2 (-40.0 vs. -23.6) (for each,

p<0.001). Secondary efficacy end points were also met, with significantly greater reductions in absolute change in baseline NILC, ILC and TLC at Week 12 (**Figure 3**).

Overall, clascoterone was well-tolerated and demonstrated a similar safety profile to that of vehicle (**Figure 4**). The most common treatment-emergent AEs in Study 1 and Study 2 were nasopharyngitis, headache, and oropharyngeal pain. AEs in Study 1 considered to be clascoterone cream-related (n=4) were mild application site pain, oropharyngeal pain, application site dryness, and application site hypersensitivity. AEs in Study 2 considered the be drug-related (n=9) were application site dryness, application site erythema, application site hypertrichosis, acne, dermatitis contact, hair color changes, eye irritation, peritonsillar abscess and headache. Most AEs in both studies were mild or moderate in severity. Two serious AEs of severe hematoma of the right thigh and severe pneumonia were unrelated to treatment. AEs leading to treatment discontinuation were mild application site hypersensitivity, oropharyngeal pain, sebaceous hyperplasia, facial acute contact dermatitis, and depigmented nose hair (for each, n=1).

2.4 Long-term study

The long-term safety of clascoterone 1% topical cream was assessed in a 9-month extension study [24] which enrolled subjects within 3 days of completing one of the two 12-week phase 3 studies [23]. Acne severity was assessed using the 5-point IGA scale from clear to severe. If the baseline IGA severity score was greater than mild, subjects continued treatment with clascoterone 1% cream applied twice-daily to the face and/or trunk (all subjects received facial treatment). If the IGA severity score was clear or almost clear, an off-treatment period was initiated. Subjects were evaluated at months 1, 3, 6, and 9. Disease severity, medications use, vital signs, and AEs were assessed. Urine pregnancy tests were administered to female subjects at baseline and 6 and 9 months. The primary study end point was the incidence of AEs and their relatedness to clascoterone cream.

The study screened and enrolled 609 subjects who had been previously treated with clascoterone cream (n=317) or vehicle ~~placebo~~ (n=292). Overall, most subjects were female (n=381, 62.6%) and white (n=541, 88.8%) with a mean (SD) age of 19.2 (6.3) years. Subject demographics were evenly distributed between groups. The safety population included 607 subjects and the study was completed by 347 subjects (57.2%) in the clascoterone cream (n=179, 56.5%) and vehicle ~~placebo~~ (n=168, 57.9%) 347 groups. The most common reasons for stopping the study were withdrawal of consent (n=101, 16.6%) and lost to follow-up (n=90, 14.8%). Only nine subjects (1.5%) withdrew due to an AE.

In the safety group, the total mean drug exposure was 415.6 g (range, 8.0-2,368.40 g) with a mean daily dose of 2.28 g/day (range, 0.22-12.95 g/day). In this group, 110 subjects (18.1%) reported 191 treatment-emergent AEs and were similar in the clascoterone cream (n=58, 18.3%) and vehicle ~~placebo~~ (n=52, 17.9%) groups. AE severity was mild (n=51, 8.4%), moderate (n=71, 64.5%) and severe (n=10, 1.2%). The severe events were eosinophilic gastroenteritis, nephrolithiasis, pancreatitis, sciatica, pruritus, dizziness, suicide attempt, coronary artery dissection, toothache, and fatigue. Six subjects reported seven

serious AEs of moderate depression, severe eosinophilic gastroenteritis, severe dizziness, severe suicide attempt, moderate medical abortion induced, severe coronary artery dissection, and severe fatigue; however, none were treatment-related.

Nine subjects experienced AEs that led to discontinuation including 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. Clascoterone cream-related AEs (n=19) were mild sunburn, moderate application site swelling, moderate application site pruritus, moderate application site erythema, mild or moderate application site dryness, mild or moderate application site acne, mild or moderate application site pain, mild dysgeusia, moderate acne (for each, n=2), moderate cystic acne, moderate acne conglobata, mild contact dermatitis, severe pruritus, and moderate hair color changes. There were no systemic events or any differences between genders.

2.5 Comparative study

The objective of this randomized, double-blind, vehicle-controlled comparative trial was to assess the efficacy and tolerability of clascoterone 1% topical cream compared to a clascoterone vehicle control and topical tretinoin 0.05% cream for treating mild-to-moderate acne vulgaris [25]. Healthy white male subjects (*N*=77) between 18 and 45 years old with mild-to-moderate facial acne vulgaris (IGA score of 2 or 3) were enrolled. Subjects had total lesion counts (TLC) including noninflammatory (comedones) and inflammatory (papules, pustules and nodules) lesions between 20 and 100 and inflammatory lesion counts (ILC) between 10 and 50 at enrollment. Subjects with facial lesions other than acne vulgaris, had used systemic acne medications during the previous month or topical acne medications during the last 2 weeks or had a hypersensitivity to the trial medications were excluded.

Subjects were randomized to receive treatment with clascoterone 1% topical cream (n=30), vehicle control (n=15) or tretinoin 0.05% cream (n=32). Subjects applied their assigned treatment to the affected areas of the face once daily at bedtime for 8 weeks. Subjects agreed not to use any other acne medication during the study or start any new medication without consulting the investigator.

Subjects were evaluated at the Screening Visit and at Weeks 2 (Visit 1), 4 (Visit 2), 6 (Visit 3) and 8 (Visit 4). Assessments included TLC and ILC performed on the right and left sides of the face including the chin, forehead, left and right cheeks [26]. The acne severity index (ASI) was assessed for each type of using the following correction factors: comedones x 0.5, papules x 1, pustules x 2, and nodules x 3 [27]. The total severity scores were obtained by multiplying the number of each type of lesion with its correction factor and adding them together. The IGA assessment was made on an ordinal scale with five severity grades from 0 (clear skin without inflammatory or noninflammatory lesions) to 4 (many noninflammatory and inflammatory lesions, but no more than a few nodular lesions) [28]. The IGA success outcome was defined as grade ≤1 with a grade 0 or 1 for subjects with baseline scores of 3 and 0 for subjects with baseline scores of 2.

Safety assessment included local tolerability with an irritancy score (IS) based on redness, peeling, dryness, swelling, itching and burning severity scored from 0 to 3 at Weeks 2, 4, 6 and 8. Other safety measures included standard hematology, clinical laboratory, urinalysis,
physical examination and vital signs performed at Screening and Week 8. AEs were monitored during the study and for 2 weeks after treatment discontinuation.

Ten subjects did not complete the study due to withdrawn consent (n=4) and noncompliance (n=6). Seventy-two subjects included in the ITT and safety population comprised subjects treated with clascoterone 1% (n=28), vehicle control (n=14) and tretinoin (n=30). Subject groups were well-balanced with respect to demographic characteristics, assessment parameter severity and proportion of subjects with IGA grades 2 and 3.

Beginning at Week 2, the mean reduction of TLC was greatest in the clascoterone 1.0% group, poorest in the vehicle control group and intermediate reduction in the tretinoin 0.05% group. The mean (SD) percent improvement at Week 8 was 65.7 (31.4) in the clascoterone 1% group, 52.51 (25.7) in the tretinoin 0.5% group, and 37.0 (33.3) in the control group. Clascoterone was significantly more active than vehicle ~~placebo~~ at Week 2 (17.9%, *p*=0.0447), Week 4 (19.9%, *p*=0.0254), Week 6 (22.4%, *p*=0.0124) and Week 8 (28.3%, *p*=0.0017). Clascoterone had numerically superior TLC compared to tretinoin but did not achieve statistical significance. There were no significant differences between tretinoin a vehicle control groups. The time to achieve 50% occurred improvement was reached in 43.5 days for clascoterone 1%, 57.0 days for tretinoin 0.05% and 58.0 days for vehicle control (*p*=0.0199).

Beginning at Week 2, the mean reduction of ILC was greater in the clascoterone 1% group than in the vehicle ~~placebo~~ and tretinoin groups. The mean (SD) percent improvement at Week 8 was 67.3% (32.0) for the clascoterone 1% group, 50.7% (34.5) for the tretinoin group and 38.9% (33.2) in the control group. Clascoterone 1% was significantly more effective than vehicle ~~placebo~~ at Week 4 (22.7%, *p*=0.0424), Week 6 (22.2%, *p*=0.0472) and Week 8 (27.9%, *p*=0.0134). Clascoterone 1% was superior to tretinoin at each observation time which was significant at Week 6 (19.2%, *p*=0.0374). There were no significant differences between tretinoin and vehicle control groups. The time to achieve 50% improvement was reached in a median of 36.5 days for clascoterone 1%, 44.0 days for tretinoin and 58.0 days for the vehicle control group (*p*=0.0490).

Similar to the other efficacy measures, the mean ASI improvement was greater among subjects in the clascoterone 1% group compared to control-treated subjects beginning at Week 2 while the tretinoin group demonstrated intermediate efficacy. The mean (SD) percent improvement at Week 8 was 68.4% (30.8) for the clascoterone 1% group, 53.1% (33.5) in the tretinoin group and 39.5% (31.6) in the control group. Clascoterone 1% was consistently superior to control treatment reaching significance at Week 2 (22.2%, *p*=0.0113), Week 6 (22.3%, *p*=0.0385) and Week 8 (23.4%, *p*=0.0090). Clascoterone 1% was clinically but not statistically superior to tretinoin at each time point. There were no significant differences between tretinoin a vehicle control groups. The time to achieve 50% improvement was reached in a

median of 42.5 days for clascoterone 1%, 44.0 days for tretinoin and 57.0 days for the control group (p=0.0438)

The IGA success outcome was numerically greater for subjects treated with clascoterone 1% (22%) compared with tretinoin (12%) and control groups (7%); however, it did not achieve statistical significance. The proportion of subjects reaching IGA grade 0 to 1 was higher in the clascoterone 1% group (41%) than in the tretinoin (27%) and control (14%) groups (**Table 5**).

Clascoterone 1% demonstrated good local tolerability while the tretinoin and control groups showed worsening irritancy scores during the first 2 weeks; however, they returned to near normal value (≤1) by Week 8. An exploratory analysis revealed a significant difference between the clascoterone 1% and control groups at Week 2 (p=0.0412). There were no clinically important changes in hematology, clinical laboratory, urinalysis, vital signs or other safety assessment in any group. Eight subjects (11%) reported 14 AEs in the clascoterone 1% group (n=3), tretinoin group (n=6) and control group (n=5). The most frequently reported events were mild or moderate laryngitis, herpes simplex, pruritus and acne worsening. None lead to withdrawal from the study.

3.0 Conclusion

Clascoterone 1% cream is a novel first-in-class topical androgen receptor inhibitor for the treatment of acne vulgaris and represents the first new mechanism of action for acne treatment in almost 40 years and is an excellent antiandrogen therapy for topical use.

4.0 Expert opinion

As acne vulgaris has a complex etiology [29], a wide range of therapies have been developed to treat it [30]. The choice of therapy may be based on patient age, gender, anatomic site, ethnicity and severity [31,32]. All therapies are effective for some patients but not all therapies work for all patients. First-line treatment for mild or moderate acne vulgaris includes topical benzoyl peroxide or a topical retinoid, or a combination of topical medications consisting of benzoyl peroxide and erythromycin or clindamycin, a retinoid or both. Due to the possibility of development of *Cutibacterium acnes* resistance, topical antibiotics must not be used as monotherapy [1]. Oral therapies for acne include antibiotics, retinoids, antiandrogens and combined oral contraceptives, all of which may have distinct drawbacks for some patients [33]. Severe acne may require a combination of oral and topical products [1].

Oral antibiotics are the most common systemic agent prescribed for the treatment of acne. Their use may be associated with a variety of adverse outcomes including bacterial resistance and disruption of the microbiome [33,34]. Doxycycline and minocycline are most commonly used. Oral erythromycin and azithromycin should be used only in patients for whom tetracyclines are contraindicated. The tetracycline class may cause photosensitivity reactions [35]. Oral retinoids are contraindicated in female patient of childbearing potential at risk of becoming pregnant due to an extremely high risk of severe birth defects [36] and topical retinoids should be used with caution if at all [37].

As hormones and especially androgens are involved in the pathogenesis of acne, the use of androgen antagonists for treating acne is a logical option. Currently available agents include combined oral contraceptives, spironolactone, flutamide, cyproterone acetate and finasteride [13]; however, each has disadvantages. Finasteride is a 5α-reductase inhibitor indicated for the treatment of androgenetic alopecia in men [38]. Its use is contraindicated in women who are or may potentially become pregnant due to the risk of birth defects. Flutamide and cyproterone acetate are antiandrogens indicated for the treatment of prostate cancer [39,40] but are used off-label for treating acne [1]. Due to the risk of hepatotoxicity [41,42], they should not be used unless the clinical benefit outweighs the potential risk. Cyproterone acetate is not commercially available in the United States.

Spironolactone is a synthetic 17-lactone steroid that has antagonistic effects at androgen and progesterone receptors. It is indicated for the treatment of hypertension [43] but is used off-label use for treating acne. Spironolactone can be of benefit in some female patients but randomized, controlled trials are lacking [44]. The use of spironolactone is generally avoided in men due to possible feminization effects such as gynecomastia [43,45].

Clascoterone 1% cream is a novel first-in-class topical androgen receptor inhibitor for the treatment of acne vulgaris and represents the first new type of acne treatment in almost 40 years. It blocks circulating and locally produced testosterone and dihydrotestosterone at the androgen receptors found in the sebaceous glands, sebocytes and dermal papilla cells [18] and effective in both male and female patients. It also inhibits the synthesis of inflammatory cytokines in sebocytes [17]. Its efficacy is similar to 5α-reductase inhibitor finasteride in vitro [18].

Topical clascoterone provides the therapeutic benefit of systemic antiandrogen agents without the undesirable adverse events. The efficacy of clascoterone cream was demonstrated in two phase three vehicle-controlled clinical trials that enrolled over 1,400 subjects and its safety profile in a 9-month extension study allowed it to be approved for treating patients as young as 12 years old. During clinical trials, it provided benefit to subjects with severe acne. The occurrence of local skin reactions (edema, erythema, pruritus, dryness, was similar to treatment with vehicle alone. Hypothalamic-pituitary-adrenal (HPA) axis suppression was observed during one clinical trial in subjects receiving the highest dose [20] and may be associated with use over large surface areas, prolonged use, and the use of occlusive dressings [16]. There was no evidence of clinical HPA suppression, and all subjects returned to normal HPA axis function after stopping treatment. In time, clascoterone cream may become first-line therapy for treating acne vulgaris.

Funding

This manuscript was supported by Cassiopea Inc.

Declaration of interest

Dr. Gold is a consultant and performs clinical research for Cassiopea SpA. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

One peer reviewer is an employee of Cassiopea Inc. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

Acknowledgement

The author acknowledges the editorial assistance of Dr. Carl S. Hornfeldt, Apothekon, Inc., during the preparation of this manuscript with funding provided by Cassiopea, Inc.

Company review

Cassiopea provided a scientific accuracy review at the request of the journal editor.

References

1. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945-73.
2. Tan JK, Bhate K. A global perspective on the epidemiology of acne. Br J Dermatol. 2015;172 3-12.
3. Fife D. Practical evaluation and management of atrophic acne scars: tips for the general dermatologist. J Clin Aesthet Dermatol. 2011;4:50-7.
4. Goh CL, Abad-Casintahan F, Chow SK, et al. Evaluating acne-related post-inflammatory hyperpigmentation is a challenge even amongst experts. J Dermatol. 2014;41:1106-8.
5. Stamu-O'Brien C, Jafferany M, Carniciu S, et al. Psychodermatology of acne: psychological aspects and effects of acne vulgaris. J Cosmet Dermatol. 2020;10:1111.
6. Sood S, Jafferany M, Sushruth V. Depression, psychiatric comorbidities and psychosocial implications associated with acne vulgaris. J Cosmet Dermatol. 2020 Oct 2; Epub ahead of print.
7. Layton AM, Thiboutot D, Tan J. Reviewing the global burden of acne: how could we improve care to reduce the burden? . Br J Dermatol. 2020;10:1111.
8. Öztekin C, Öztekin A. The association of depression, loneliness and internet addiction levels in patients with acne vulgaris. Biopsychosoc Med. 2020;14:17.
9. Haroon MZ, Alam A, Ullah I, et al. Quality of life and depression among young patients suffering from acne. J Ayub Med Coll Abbottabad. 2019;31:436-440.
10. Loh KC, Chan LC, Phang LF. Perceptions and psychosocial judgement of patients with acne vulgaris. Med J Malaysia. 2020;75:18-23.
11. Chen W, Thiboutot D, Zouboulis CC. Cutaneous androgen metabolism: basic research and clinical perspectives. J Invest Dermatol. 2002;119:992-1007.
12. Ju Q, Tao T, Hu T, et al. Sex hormones and acne. Clin Dermatol. 2017;35:130-137.
13. Hassoun LA, Chahal DS, Sivamani RK, et al. The use of hormonal agents in the treatment of acne. Semin Cutan Med Surg. 2016;35:68-73.
14. Elsaie ML. Hormonal treatment of acne vulgaris: an update. Clin Cosmet Investig Dermatol. 2016;9:241-8.
15. Chen C, Puy LA, Simard J, et al. Local and systemic reduction by topical finasteride or flutamide of hamster flank organ size and enzyme activity. J Invest Dermatol. 1995;105:678-82.
16. Winlevi® (clascoterone) cream for topical use. [Prescribing Information, 2020]. Cassiopea, Inc., San Diego, CA.
17. Rosette C, Agan FJ, Mazzetti A, et al. Cortexolone 17α-propionate (clascoterone) is a novel androgen receptor antagonist that inhibits production of lipids and inflammatory cytokines from sebocytes in vitro. J Drugs Dermatol. 2019;18:412-418.
18. Rosette C, Rosette N, Mazzetti A, et al. Cortexolone 17α-propionate (clascoterone) is an androgen receptor antagonist in dermal papilla cells in vitro. J Drugs Dermatol. 2019:18:197-201.

19. Celasco G, Moro L, Bozzella R, et al. Biological profile of cortexolone 17alpha-propionate (CB-03-01), a new topical and peripherally selective androgen antagonist. Arzneimittelforschung. 2004;54:881-6.
20. Mazzetti A, Moro L, Gerloni M, et al. Pharmacokinetic profile, safety, and tolerability of clascoterone (cortexolone 17-alpha propionate, CB-03-01) topical cream, 1% in subjects with acne vulgaris: an open-label phase 2a study. J Drugs Dermatol. 2019;18:563.
21. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med. 2003;139:194-204.
22. Mazzetti A, Moro L, Gerloni M, et al. A phase 2b, randomized, double-blind vehicle controlled, dose escalation study evaluating clascoterone 0.1%, 0.5%, and 1% topical cream in subjects with facial acne. J Drugs Dermatol. 2019;18:570.
23. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. JAMA Dermatol. 2020;156:621-630.
24. Eichenfield L, Hebert A, Gold LS, et al. Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris. J Am Acad Dermatol. 2020;83:477-485.
25. Trifu V, Tiplica GS, Naumescu E, et al. Cortexolone 17α-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study vs. placebo and tretinoin 0·05% cream. Br J Dermatol. 2011;165:177-183.
26. Burke BM, Cunliffe WJ. The assessment of acne vulgaris--the Leeds technique. Br J Dermatol. 1984;111:83-92.
27. Mokhtari F, Shajari A, Iraji F, et al. The effectiveness of adapalene 0.1% with intense pulsed light versus benzoyl peroxide 5% with intense pulsed light in the treatment of acne vulgaris: a comparative study. J Res Med Sci. 2019;24:101.
28. Food and Drug Administration. Guidance for industry acne vulgaris: developing drugs for treatment. Available: www.fda.gov/downloads/Drugs/Guidances/UCM071292.pdf. Accessed: November 27, 2020.
29. Cong TX, Hao D, Wen X, et al. From pathogenesis of acne vulgaris to anti-acne agents. Arch Dermatol Res. 2019;311:337-349.
30. Cooper AJ, Harris VR. Modern management of acne. . Med J Aust. 2017;206:41-45.
31. Callender VD. Acne in ethnic skin: special considerations for therapy. Dermatol Ther. 2004;17:184-95.
32. American Family Physician. Acne Vulgaris: Treatment Guidelines from the AAD. J Am Acad Dermatol. 2016;74:945-973.

33. Barbieri JS, Spaccarelli N, Margolis DJ, et al. Approaches to limit systemic antibiotic use in acne: Systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments. J Am Acad Dermatol. 2019.;80:538-549.
34. Aslan Kayiran M, Karadag AS, Al-Khuzaei S, et al. Antibiotic resistance in acne: mechanisms, complications and management. Am J Clin Dermatol. 2020;21:813-819.
35. Sloan B, Scheinfeld N. The use and safety of doxycycline hyclate and other second-generation tetracyclines. Expert Opin Drug Saf. 2008;7:571-7.
36. Absorica® (isotretinoin) capsules for oral use [Prescribing Information 2019]. Sun Pharmaceutical Industries, Inc., Cranbury, NJ.
37. Han G, Wu JJ, Del Rosso JQ. Use of topical tazarotene for the treatment of acne vulgaris in pregnancy: a literature review. J Clin Aesthet Dermatol. 2020;13:E59-65.
38. Propecia® (finasteride) tablets for oral use [Prescribing Information 2012]. Merck & Co., Inc., Whitehouse Station, NJ.
39. Goldspiel BR, Kohler DR. Flutamide: an antiandrogen for advanced prostate cancer. DICP. 1990;24:616-23.
40. Goldenberg SL, Bruchovsky N. Use of cyproterone acetate in prostate cancer. Urol Clin North Am. 1991;18:111-22.
41. Wysowski DK, Freiman JP, Tourtelot JB, et al. Fatal and nonfatal hepatotoxicity associated with flutamide. Ann Intern Med. 1993;118:860-4.
42. Savidou I, Deutsch M, Soultati AS, et al. Hepatotoxicity induced by cyproterone acetate: a report of three cases. World J Gastroenterol. 2006;12:7551-5.
43. Aldactone® (spironolactone) tablets for oral use {Prescribing Information 2020]. Pfizer, Inc., New York, NY.
44. Trivedi MK, Shinkai K, Murase JE. A Review of hormone-based therapies to treat adult acne vulgaris in women. Int J Womens Dermatol. 2017;3:44-52.
45. Mosenkis A, Townsend RR. Gynecomastia and antihypertensive therapy. J Clin Hypertens (Greenwich). 2004;6:469-70.

Tables

Table 1. Primary Efficacy Endpoints, Phase 2b Study

	Cohort 1 (n=72)	**Cohort 2** (n=76)	**Cohort 3** (n=70)	**Cohort 4** (n=70)	**Cohort 5** (n=75)
Treatment Outcomes, n (%)					
Failure	66 (91.7)	72 (96.1)	68 (97.1)	64 (91.4)	72 (97.3)
Success	6 (8.3)	3 (3.9)	2 (2.9)	6 (8.6)	2 (2.7)
Change in Inflammatory Lesions					
Mean (SD)	-7.3 (14.2)	-5.6 (11.3)	-7.9 (12.3)	-11.1 (14.1)	-8.3 (12.9)
Median (min, max)	-11.0 (-31,43	-7.5 (-23, 32)	-8.5 (-45, 25)	-13.5 (-39, 38)	-8.0 (-50, 34)
Change in Non-Inflammatory Lesions					
Mean (SD)	-8.8 (17.4)	-6.3 (26.7)	-8.1 (20.5)	-15.8 (20.1)	-5.9 (18.5)
Median (min, max)	-10.0 (-50, 69)	-10.0 (-56, 171)	-6.0 (-48, 85)	-17.5 (-63, 34)	-9.0 (-45, 64)

Cohort 1, twice-daily clascoterone 0.1% or vehicle; Cohort 2, 0.5% twice-daily; Cohort 3, 1% once-daily; Cohort 4, 1% twice-daily; Group 5, vehicle once- or twice-daily. Reused with permission from [22].

Table 2. Baseline Demographic and Clinical Characteristics of Subjects in Phase 3 Studies

	Study 1		Study 2	
Characteristic, n (%)	Clascoterone (n=353)	Vehicle (n=355)	Clascoterone (n=369)	Vehicle (n=363)
Gender				
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)
Median Age, years (min, max)	18.0 (10, 58)	18.0 (9, 50)	18.0 (10, 50)	18.0 (11, 42)
Race				
White	298 (84.4)	297 (83.7)	357 (96.7)	348 (95.9)
Black/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)
Other	15 (4.2)	10 (2.8)	5 (1.4)	5 (1.4)
Fitzpatrick Skin Type				
I	7 (2.0)	7 (0.2)	7 (1.9)	12 (3.3)
II	111 (31.4)	111 (31.3)	122 (33.1)	107 (29.5)
III	122 (34.6)	121 (34.1)	170 (46.1)	166 (45.7)
IV	63 (17.8)	64 (18.0)	57 (15.4)	54 (14.9)
V	27 (7.6)	23 (6.5)	7 (1.9)	21 (5.8)
VI	23 (6.5)	29 (8.2)	6 (1.6)	3 (0.8)
Baseline IGA Scores				
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)
Mean TLC (SD)	101.5 (25.1)	103.6 (26.1)	105.7 (25.8)	104.6 (24.2)
Mean NILC (SD)	59.1 (22.2)	60.7 (22.1)	62.8 (21.4)	63.3 (20.5)
Mean ILC (SD)	42.4 (11.8)	42.9 (12.3)	42.9 (12.2)	41.3 (11.0)

IGA, Investigator Assessment; NILC, noninflammatory lesion count; ILC, inflammatory lesion count, TLC, total lesion count. From [23].

Table 3. Efficacy Results from Phase 3 Trials

	Study 1		**Study 2**	
	Clascoterone (n=353)	Vehicle (n=355)	Clascoterone (n=369)	Vehicle (n=363)
Week 12 Treatment Success	57 (16.1)	25 (7.0)	69 (18.7)	17 (4.7)
Adjusted Proportions, Treatment Success (%)	18.4	9.0	20.3	6.5
Point Estimate (95% CI)	2.3 (1.4, 3.8)	NA	3.7 (2.2, 6.3)	NA
2-Sided P-value for Treatment Effect	<0.001	NA	<0.001	NA
Week 12 Change in Baseline NILC	-19.4	-13.0	-19.4	-10.8
Point Estimate, Difference (95%CI)	-6.4 (-10.3, -2.6)	NA	-8.6 (-12.3, -4.9)	NA
2-Sided P-value for Treatment Effect	<0.001	NA	<0.001	NA
Week 12 Change in Baseline ILC	-19.3	-15.5	-20.0	-12.6
Point Estimate, Difference (95%CI)	-3.8 (-6.4, -1.3)	NA	-7.4 (-9.8, -5.1)	NA
2-Sided P-value for Treatment Effect	0.003	NA	<0.001	NA
Week 12 Change in Baseline TLC	-39.1	-28.8	-40.0	-23.6
Point Estimate, Difference (95%CI)	-10.3 (-15.7, -4.9)	NA	-26.4 (21.8, -11.0)	NA
2-Sided P-value for Treatment Effect	<0.001	NA	<0.002	NA
Week 12 Change in Baseline TLC (%)	-37.0	-28.4	-37.3	-22.1
Point Estimate, Difference (95%CI)	-8.6 (-13.9, -3.3)	NA	-15.2 (-20.5, -9.9)	NA
2-Sided P-value for Treatment Effect	0.001	NA	<0.001	NA
Week 12 Change in Baseline NILC (%)	-30.6	-21.6	-29.3	-15.6
Point Estimate, Difference (95%CI)	-9.0 (-15.8, -2.3)	NA	-13.7 (-19.9, -7.6)	NA
2-Sided P-value for Treatment Effect	0.009	NA	<0.001	NA
Week 12 Change in Baseline ILC (%)	-44.8	-36.5	-46.9	-29.6
Point Estimate, Difference (95%CI)	-8.3 (-14.2, -2.4)	NA	-17.2 (-22.9, -11.6)	NA
2-Sided P-value for Treatment Effect	0.005	NA	<0.001	NA

ILC, inflammatory lesion count; NA, not applicable; NILC, noninflammatory lesion count; AE, adverse event; TLC, total lesion count [23].

Table 4. Safety Results from Phase 3 Trials

	Study 1		**Study 2**	
	Clascoterone (n=353)	Vehicle (n=355)	Clascoterone (n=369)	Vehicle (n=363)
Subjects with ≥1 AE, n (%)	40 (11.30	41 (11.5)	42 (11.4)	50 (13.8)
AEs by Severity, n (%)				
Mild	31 (8.8)	24 (6.8)	32 (8.7)	33 (9.1)
Moderate	9 (2.5)	15 (4.2)	10 (2.7)	16 (4.4)
Severe	0	2 (0.6)	0	1 (0.3)
Serious	0	1 (0.3)	0	1 (0.3)
Treatment-Related	4 (1.1)	9 (2.5)	8 (2.2)	13 (3.6)
Leading to Discontinuation	3 (0.8)	4 (1.1)	2 (0.5)	8 (2.2)
Most Frequently Reported AEs, n (%)				
Nasopharyngitis	6 (1.7)	13 (3.7)	4 (1.1)	7 (1.9)
Headache	2 (0.6)	1 (0.3)	4 (1.1)	3 (0.8)
Oropharyngeal Pain	2 (0.6)	1 (0.3)	4 (1.1)	4 (1.1)
Vomiting	2 (0.6)	2 (0.6)	2 (0.5)	1 (0.3)

AE, adverse event [23].

Table 4. Safety Results, Long-term Extension Study

Variable, n (%)	Clascoterone (n=317)	Vehicle (n=290)
Subjects with Any AE	58 (18.3)	52 (17.9)
Mild AEs	36 (11.4)	36 (12.4)
Moderate AEs	28 (8.8)	23 (7.9)
Severe AEs	4 (1.3)	3 (1.0)
Treatment-related AEs	12 (3.8)	2 (0.7)
Related AEs Leading to Discontinuation	9 (2.8)	0
Serious AEs	3 (0.9)	3 (1.0)
Treatment-related Serious AEs	0	0
Serious AEs Leading to Discontinuation	1 (0.3)	0
AEs Leading to Death	0	0
Total AEs	106	85
Treatment-related AEs	17	2
Treatment-unrelated AEs	89	83
Mild	57	53
Moderate	42	29
Severe	7	3
Serious AEs	4	3
Treatment-related	0	0
Serious AEs Leading to Discontinuation	1	0
Death	0	0
Most Common AEs	58 (18.3)	52 (17.9)
Nasopharyngitis	6 (1.9)	10 (3.4)
Upper Respiratory Tract Infection	7 (2.2)	1 (0.3)
Sinusitis	3 (0.9)	2 (0.7)
Application Site Acne	4 (1.3)	0

AE, adverse event [24].

Table 5. Efficacy Outcomes from the Comparative Study

	Subjects Achieving IGA Treatment Success, n (%)[a]	Subject Improvement in IGA Scores from 2 or 3 to 0 or 1, n (%)
Vehicle, n=14	1 (7)	2 (14)
Tretinoin 0.5%, n=26	3 (12)	7 (27)
Clascoterone 1%, n=27	6 (22)	11 (41)

IGA, Investigator Global Assessment.

[a]IGA success outcome was defined as grade ≤1 with a grade 0 or 1 for subjects with baseline scores of 3 and 0 for subjects with baseline scores of 2. Reused with permission from [24].