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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

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ABSTRACT

Androgens play a key role in acne pathogenesis in both males and females. Clascoterone (CB-03-01, Cortexolone 17α propionate) cream is a topical anti-androgen under investigation for the treatment of acne. The results from a phase 2b dose escalating study are discussed.

Methods: Primary objective: to compare the safety and efficacy of topical creams containing clascoterone 0.1% (twice daily [BID]), 0.5% (BID), or 1% (daily [QD] or BID) versus vehicle (QD or BID) in male and female subjects ≥12 years with facial acne vulgaris. Efficacy was assessed by: Investigator's Global Assessment (IGA)–the overall severity of acne using a five-point scale (from 0=clear to 4=severe); inflammatory and non-inflammatory acne lesion counts (ALC); and subject satisfaction with treatment–subjects assessed overall treatment satisfaction using a 4-point scale. Safety assessments: local and systemic adverse events (AEs), physical examination/vital signs, laboratory tests, local skin reactions (LSRs), and electrocardiograms (ECGs). Treatment success required a score of "clear" or "almost clear" (IGA score of 0 or 1) and a two or more-grade improvement from baseline.

Results: 363 subjects (N=72, 0.1% BID; N=76, 0.5% BID; N=70, 1% QD; N=70, 1% BID; and N=75, vehicle QD or BID) enrolled. 304 subjects (83.7%) completed the study. Intention to Treat (ITT) population: 196/363 (54.0%) females; 167/363 46.0%) males; (257/363 (70.2%) were white; average age=19.7 years. Demographic and baseline characteristics were similar across all groups. Treatment success at week 12 were highest for the 1% BID (6/70, 8.6%) and 0.1% BID (6/72, 8.3%) groups versus vehicle (2/75, 2.7%). Absolute change in inflammatory (P=0.0431) and non-inflammatory (P=0.0303) lesions was statistically significant among the treatment groups. The median change from baseline at week 12 in inflammatory and non-inflammatory lesions was greatest in the 1% BID group -13.5 and -17.5, respectively. Similar results were observed for the secondary efficacy endpoints whereby the highest success rate and greatest reduction in lesion counts from baseline to week 12 occurred with 1% BID.
93/363 subjects (25.6%) reported ≥1 AEs; total number of AEs=123 with 2 probably/possibly related to treatment (N=1, 1% QD group). Subjects with ≥1AEs: 0.1% BID=25.0%, 0.5% BID=38.2%, 1% QD=22.9%, 1% BID=18.6%, and vehicle=22.7%. AEs were mostly mild in severity and similar across all groups. Most AEs (93/121 76.8%) resolved by the end of the study. Erythema was the most prevalent LSR; 36.8% had at least minimal erythema at some point during the study.

Conclusions: All clascoterone cream concentrations were well tolerated with no clinically relevant safety issues noted. Clascoterone 1% BID treatment had the most favorable results and was selected as the best candidate for further clinical study and development. Two Phase 3 investigations of clascoterone topical cream, 1% for the treatment of moderate-to-severe acne vulgaris in individuals ≥9 years recently concluded.

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INTRODUCTION

Acne vulgaris is a chronic inflammatory skin condition characterized by obstruction and inflammation of the pilosebaceous units within the skin. It is the most common skin disorder in the world affecting 85% of the population.[1] In the United States, approximately 50 million cases of acne occur annually.[2]

Endogenous androgens play a key role in acne pathogenesis in males and females.[3] Androgen-induced excess sebum production, inflammation, and hyperkeratinization clog hair follicles and produces a local environment that encourages *Cutibacterium acnes* (formerly *Propionibacterium acnes*) colonization and infection.[4] These acnegenic events contribute to the formation of acne comedones, pustules, papules, nodules, and/or cysts.

Clascoterone is a new entity whose chemical structure is

characterized by a fused 4-ring backbone identical to that of dihydrotestosterone (DHT).[5,6] Thus, it acts as an androgen receptor inhibitor, competing with DHT for binding to the androgen receptors in the skin and reducing DHT's proinflammatory and sebum inducing effects within the pilosebaceous unit.[6-9] Clascoterone is rapidly hydrolyzed by the skin and plasma esterases to cortexolone, an inactive metabolite found in all human cells and tissues.[5,10]

For this reason, unlike oral anti-androgens that are associated with numerous systemic side effects,[4] clascoterone acts at the site of application with minimal systemic exposure; no notable clinical systemic side effects,[6] such as prolonged hypothalamic-pituitary-adrenal axis activation or testosterone fluctuations, have been reported in clinical trials to date.[6-9]

Topical application of clascoterone cream may reduce acne lesions at the site of application through multiple cellular and molecular mechanisms. For example, in cultured primary human seboctyes, clascoterone reduced sebum production and inflammatory cytokines.[7]

The purpose of this Phase 2b study was to evaluate the efficacy and safety of various concentrations of clascoterone cream. In this vehicle-controlled study, male and female patients ≥12 years with acne applied clascoterone cream or vehicle topically once or twice daily for 12 weeks. Treatment with clascoterone topical cream, 1% resulted in reductions in acne lesions and greater treatment success versus vehicle.

METHODS

This was a multicenter (N=13), randomized double-blind, vehicle controlled, consecutive groups dose escalation study. The study protocol, consent/assent form, participant recruitment materials/process, and other relevant documents were submitted to an institutional review board for review and approval prior to study initiation. The study was conducted in accordance with Title v21 of the U.S. Code of Federal Regulations, the International Conference on Harmonization guidelines, current Good Clinical Practice principles, the Declaration of Helsinki, and local regulatory requirements. All patients and their parents or guardians provided written informed consent before enrollment. Male and female subjects ≥12 years with moderate to severe facial acne vulgaris defined as an IGA of 2 (mild), 3 (moderate), or 4 (severe) and at least 20 (up to 75) inflammatory lesions (papules, pustules, and nodules/cysts) and 20 (up to 100) non-inflammatory lesions (open and closed) were eligible to enroll and assigned to a sequential treatment cohort, receiving either one of the clascoterone creams or vehicle cream to apply once or twice daily for 12 weeks.

Subjects in the first cohort (Cohort 1) were randomized (4:1) to twice daily treatments with clascoterone 0.1% cream vs vehicle cream. After all subjects in Cohort 1 completed at least four weeks of treatment, an interim safety review was completed by the medical monitor. Dose escalation occurred only after the medical monitor recommendation and sponsor approval to proceed to the next cohort.

Clinical efficacy evaluations included a) IGA describing the overall severity of acne using a five-point scale from 0=clear to 4=severe, and b) ALC — inflammatory lesions (papules, pustules and nodules/cysts) and non-inflammatory lesions (open and closed comedones), including those on the nose. All acne lesions on the nose were counted separately.

Treatment groups are defined as 1) 0.1% clascoterone cream (BID); 2) 0.5% clascoterone cream (BID); 3) 1% clascoterone cream (QD); 4) 1% clascoterone cream (BID); and 5) vehicle cream (QD or BID). The clascoterone and vehicle study creams were indistinguishable. At least eight hours was required between applications for BID dosing.

Efficacy

Primary endpoints were 1) the proportion of subjects achieving success in each treatment group at week 12/end of study (EOS) using the dichotomized IGA with success defined as a score of 0 (clear) or 1 (almost clear) and a two or more-grade improvement from baseline; and 2) change from baseline inflammatory and non-inflammatory ALC in each treatment group at week 12/EOS.

The investigator assessed efficacy as follows: 1) IGA (5-point scale) was used to calculate the overall severity of acne score of 0=clear to 4=severe–this is a static morphological scale that refers to a point in time and not a comparison to baseline — and a two or more grade improvement from baseline was assessed at each visit; 2) ALC — inflammatory lesions (papules, pustules and nodules/cysts) and non-inflammatory lesions (open and closed comedones) on the face were counted and recorded separately at each visit; and 3) overall study subject satisfaction with the treatment was evaluated during the week 12/EOS visit using the following scale: 1=excellent (very satisfied), 2=good (moderately satisfied), 3=fair (slightly satisfied), and 4=poor (not satisfied at all).

Safety

The investigator assessed safety by utilizing the following endpoints: 1) local and systemic AEs — every visit (baseline, weeks 2, 4, 8, and 12/EOS); 2) the absence or presence (and severity) of the following local skin reactions: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus at every visit; 3) physical examination/vital signs at baseline, weeks 4 and 12/EOS; 4) clinical laboratory testing (hematology, clinical chemistry, and urinalysis) at baseline, weeks 4, 8, and 12/EOS; 5) ECG at baseline, weeks 4 and

12/EOS; and 6) urine pregnancy testing in all women who were not postmenopausal or surgically sterile at baseline, weeks 4, 8, and 12/EOS.

Statistical Analysis

The SAS® 9.4 statistical software package and ClinPlus® Report v4 were used to provide all tables and data listings.

For continuous variables, descriptive statistics included the number of subjects with non-missing data (n), mean, median, standard deviation, minimum, and maximum. For categorical variables, the number and percentage of subjects within each category were presented. Subject data listings sorted by treatment group, study site, and subject number were provided for all data.

Summaries were provided for each treatment group. The vehicle group incorporated the data from vehicle-treated subjects in the four dose cohorts. The statistical analyses evaluated the five treatment groups without consideration of cohort.

Efficacy Analyses

The efficacy analyses were conducted on the ITT and Per Protocol populations with the ITT population considered the primary population for statistical analysis.

Treatment Success Based on IGA at Week 12

The treatment groups were compared with respect to the proportions of subjects with treatment success at week 12/EOS using Fisher's exact test. Treatment success was defined as a score of "clear" or "almost clear" (IGA score of 0 or 1) and a two or more-grade improvement from baseline.

Absolute Change in Inflammatory and Non-Inflammatory Lesion Counts at Week 12

The absolute change from baseline to week 12/EOS in total inflammatory and non-inflammatory lesion counts (including the lesions on the nose) was analyzed by rank analysis of covariance (ANCOVA). The model included terms for treatment and study site with the baseline total inflammatory and non-inflammatory lesion count serving as the covariate. Pairwise comparisons of the treatments were performed by rank ANCOVA.

Safety Analyses

All subjects in the study population were included in the summaries of safety data.

Dosing Compliance

Subjects were considered compliant with the dosing regimen if they applied at least 80% of the expected number of applications and were without significant protocol dosing deviations.

Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15. Verbatim terms were mapped into a MedDRA system organ class and preferred term.

Electrocardiogram

ECGs were evaluated by the San Diego Cardiac Center (San Diego, CA) for any clinically significant changes during the study period. Results and descriptive statistics were provided by treatment group at each visit. Changes in the overall interpretation (normal/borderline/abnormal) of the ECG from baseline to week 12/EOS were examined using shift tables.

Local Skin Reactions

The frequency distribution of the severity scores of LSRs were summarized by treatment group with frequency counts and percentages at baseline and all follow-up visits.

Vital Signs and Weight

Descriptive statistics were provided for the observed and change from baseline in vital signs and weight at weeks 4 and 12 by treatment group.

Safety Laboratory Tests

Change from baseline in the hematology, clinical chemistry, and urinalysis analytes were assessed at each follow-up visit using shift tables by analyte and by conventional reference range flags (low/normal/high).

Concomitant Medications and Concurrent Therapies/Procedures

Concomitant medications and concurrent therapies/procedures were provided in a subject listing and coded using the WHO drug dictionary (format C version March 2012).

Subject Satisfaction with Treatment

The frequency distributions of the subject satisfaction with treatment scores at week 12/EOS were provided by treatment group in the ITT population.

Determination of Sample Size

The sample size of 90 randomized subjects per cohort (72 on active treatment and 18 on vehicle) was selected empirically.

RESULTS

A total of 505 subjects were screened and 363 subjects enrolled in the ITT population (N=72, 0.1% BID; N=76, 0.5% BID; N=70, 1% QD; N=70, 1% BID; and N=75, vehicle (QD or BID).

Of the 363 enrolled subjects, 304 (83.7%) completed the study and 59 (16.3%) terminated early.

TABLE 1.

Demographics for the ITT Population	Clascoterone 0.1% BID (N = 72)	Clascoterone 0.5% BID (N = 76)	Clascoterone 1.0% QD (N = 70)	Clascoterone 1.0% BID (N = 70)	Vehicle QD or BID (N = 75)	All (N = 363)
Sex at Birth	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Female	36 (50.0%)	42 (55.3%)	38 (54.3%)	37 (52.9%)	43 (57.3%)	196 (54.0%)
Male	36 (50.0%)	34 (44.7%)	32 (45.7%)	33 (47.1%)	32 (42.7%)	167 (46.0%)
Ethnicity	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Hispanic or Latino	22 (30.6%)	20 (26.3%)	6 (8.6%)	15 (21.4%)	13 (17.3%)	76 (20.9%)
Non-Hispanic or Latino	50 (69.4%)	56 (73.7%)	64 (91.4%)	55 (78.6%)	62 (82.7%)	287 (79.1%)
Race	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
American Indian or Alaskan	0 (0.0%)	1 (1.3%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	3 (0.8%)
Asian	1 (1.3%)	3 (4.0%)	4 (5.7%)	4 (5.7%)	4 (5.3%)	16 (4.4%)
Black or African American	12 (16.7%)	14 (18.4%)	16 (22.9%)	20 (28.6%)	12 (16.0%)	74 (20.4%)
Native Hawaiian or Other	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	2 (0.6%)
Other	1 (1.3%)	2 (2.6%)	0 (0.0%)	2 (2.9%)	4 (5.3%)	9 (2.5%)
White	58 (80.6%)	54 (71.0%)	50 (71.4%)	42 (60.0%)	53 (70.7%)	257 (70.8%)
Age (years)						
N	72	76	70	70	75	363
Mean	19.8	20.4	18.3	21.0	19.2	19.7
Median	19.0	19.0	16.0	20.0	18.0	18.0
Standard Deviation	5.77	6.31	6.14	6.22	5.25	5.99
Minimum, Maximum	12.0, 43.0	12.0, 42.0	12.0, 35.0	12.0, 38.0	12.0, 35.0	12.0, 43.0

TABLE 2.

Primary Efficacy Endpoint Results	Clascoterone 0.1% BID (N = 72) N (%)	Clascoterone 0.5% BID (N = 76) N (%)	Clascoterone 1.0% QD (N = 70) N (%)	Clascoterone 1.0% BID (N = 70) N (%)	Vehicle QD or BID (N = 75) N (%)
Primary Efficacy Endpoint #1					
IGA Treatment Failure at Week 12	66 (91.7%)	73 (96.1%)	68 (97.1%)	64 (91.4%)	73 (97.3%)
IGA Treatment Success at Week 12	6 (8.3%)	3 (3.9%)	2 (2.9%)	6 (8.6%)	2 (2.7%)
					P-value= 0.3065
Primary Efficacy Endpoint #2 Absolute Change, Inflammatory Lesions at Week 12 vs. Baseline					
Mean	-7.3	-5.6	-7.9	-11.1	-8.3
Median	-11.0	-7.5	-8.5	-13.5	-8.0
Standard Deviation	14.20	11.26	12.31	14.07	12.86
Range	-31 to +43	-23 to +32	-45 to +25	-39 to +38	-50 to +34
Absolute Change, Non-Inflammatory Lesions at Week 12 vs. Baseline					
Mean	-8.8	-6.3	-8.1	-15.8	-5.9
Median	-10.0	-10.0	-6.0	-17.5	-9.0
Standard Deviation	17.38	26.68	20.47	20.11	18.47
Range	-50 to +69	-56 to +171	-48 to +85	-63 to +34	-45 to +64

Subjects were included in the treatment group to which they were randomized. All subjects received the treatment to which they were randomized. The ITT population considered as the primary population for statistical analysis.

The Safety population included all subjects enrolled in the study who were randomized and applied a test article at least once (N=363). Subjects were included in the treatment group based on the treatment that they received.

Demographics

Demographics were generally comparable across all five treatment groups (Table 1).

At baseline, the majority of study subjects had moderate (Grade 3) acne (247/363, 68.0%) with the remainder of subjects evenly divided with mild (Grade 2; 60/363, 16.5%) or severe (Grade 4; 56/363, 15.4%) acne. The clascoterone 1% cream BID group had the most subjects with severe acne at baseline (20/70, 28.6%) and with mild acne (18/70, 25.7%), yet less than half of the subjects with moderate acne (32/70, 45.7%). Baseline acne severity by IGA was similar across all groups, with the exception of the clascoterone 1% BID group noted above.

Treatment Success

For the primary efficacy endpoints, treatment success parameters, previously defined at week 12/EOS, were highest for the clascoterone 1% cream BID (6/70, 8.6%) and clascoterone 0.1% BID (6/72, 8.3%) groups followed by clascoterone 0.5% BID (3/76, 3.9%), clascoterone 1% QD (2/70, 2.9%), and vehicle (2/75, 2.7%; Table 2). Although there was a higher proportion of treatment success in the clascoterone 1% BID group, there were no statistically significant differences among treatments with clascoterone cream at various concentrations with regard to IGA success at week 12/EOS.

The greatest median change from baseline at week 12/EOS in inflammatory and non-inflammatory lesions was detected in subjects treated with clascoterone cream 1% BID (-13.5 and -17.5, respectively). Regarding inflammatory lesions change at week 12/EOS from baseline, the clascoterone 1% BID group had significantly greater decrease (P<0.05) than the clascoterone 0.5% BID, clascoterone 1% QD, and vehicle groups. With respect to non-inflammatory lesions, the clascoterone 1% BID group had significantly greater decrease (P<0.05) than the clascoterone 0.5% BID, clascoterone 1% QD, and vehicle groups at week 12/EOS from baseline.

Subject Satisfaction with Treatment

Subject satisfaction at week 12/EOS was similar across all five treatment groups. The highest satisfaction score (ie, excellent and good) was reported by subjects treated with clascoterone cream 1% BID (72.6%), followed by clascoterone 0.1% BID (68.3%), clascoterone 1% QD (66.7%), vehicle (64.2%), and clascoterone 0.5% BID (61.4%).

Safety

Of the 123 total AEs, only two (burning at application site) occurred in the same subject, were mild in severity and were deemed possibly related to clascoterone 1% cream QD,. AEs, related and unrelated to test article application, by treatment group are shown in Table 3.

With the exception of three AEs that were severe (miscarriage, right ankle fracture, right arm fracture), all other AEs were mild (88/121, 72.7%) or moderate (30/121, 24.8%). Only one AE (urinary tract infection; deemed unrelated to test article) led to the subject's discontinuation from the study. The majority of AEs (93/121; 76.9%) were resolved without sequelae at the conclusion of the study. Of the remaining AEs, 9 were in the process of resolving, 4 were not resolved, 3 were resolved with sequelae, and 12 had no known outcome at the conclusion of the study.

Local Skin Reactions

The results of this study demonstrated that application of clascoterone cream once or twice daily at a variety of concentrations (0.1%, 0.5%, and 1%) was well-tolerated upon application. The incidence of all LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus) was similar across treatment groups and minimal throughout the study. The majority of subjects (>98%) across all five treatment groups had an absence of telangiec-

TABLE 3.

Adverse Events Observed in Treatment Groups						
	Clascoterone 0.1% BID (N = 72) N (%)	Clascoterone 0.5% BID (N = 76) N (%)	Clascoterone 1.0% QD (N = 70) N (%)	Clascoterone 1.0% BID (N = 70) N (%)	Vehicle QD or BID (N = 75) N (%)	All (N = 363) N (%)
Number of Events†	19 (15.4%)	43 (35.0%)	23 (18.7%)	19 (15.4%)	19 (15.4%)	123 (100.0%)
Number of Subjects‡	18 (25.0%)	29 (38.2%)	16 (22.9%)	13 (18.6%)	17 (22.7%)	93 (25.6%)

†Percentages are based on the total number of events
‡Each subject counted once. Percentages are based on the number of subjects in the treatment group.

tasia. Three subjects had severe skin atrophy at baseline that persisted throughout the study; no new cases of atrophy were observed. Most subjects did not have skin atrophy (>84%), striae rubrae (>92%), edema (>95%), stinging/burning (>93%) or scaling/dryness (>84%) during any assessment. Most cases of scaling/dryness were mild and only a few cases of moderate scaling/dryness (maximum number in any group throughout the study was N=1). More than >63% did not experience erythema. Pruritus was absent in >82% of subjects during the study, yet a few mild and moderate cases occurred at baseline pre-application. During the follow-up visits (maximum number in any group throughout the study was N=2), most LSRs were mild in severity and no new cases occurred. Erythema was the most frequently observed LSR.

Safety Laboratory Tests

No notable laboratory tests' trends were noted in any of the treatment groups, similarly laboratory changes from baseline during the study period were generally unremarkable from baseline to week 12/EOS.

DISCUSSION

Clascoterone cream represents the first potential topical androgen receptor inhibitor for the treatment of acne vulgaris. This study provides preliminary evidence of the efficacy and safety of clascoterone topical cream, 1% in persons with facial acne and the foundation for determining the concentration of clascoterone cream for advancement to Phase 3.

Two pivotal Phase 3 trials were initiated to assess the efficacy and safety of clascoterone topical cream, 1% compared with vehicle in >1400 subjects, ≥9 years of age, with moderate to severe acne (NCT 02608476) and recently concluded with final results forthcoming. An open label extension study is underway (NCT: 02682264).

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DISCLOSURE

This study was sponsored and funded by Cassiopea SpA, Milan, Italy. Drs. Mazzetti and Moro are employees of Cassiopea SpA; Dr. Gerloni is a consultant to Cassiopea SpA and Dr. Cartwright is an employee of Cassiopea Inc.

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