Drugs
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ADISINSIGHT REPORT

Clascoterone: First Approval

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Abstract
Clascoterone (Winlevi®) is an androgen receptor inhibitor being developed as a topical cream and solution by Cassiopea (a spin-out company of Cosmo Pharmaceuticals) for the treatment of androgen-dependent skin disorders, including androgenetic alopecia and acne vulgaris. Although the exact mechanism of action of clascoterone for the topical treatment of acne vulgaris is unknown, the drug is believed to compete with the androgen dihydrotestosterone for binding to androgen receptors in the sebaceous gland and hair follicles to attenuate signalling necessary for acne pathogenesis. In August 2020, clascoterone cream 1% received its first approval in the USA for the topical treatment of acne vulgaris in patients 12 years of age or older. Clinical studies of a different formulation of clascoterone (a solution containing a higher concentration of the drug) for the treatment of androgenetic alopecia are underway in Germany and the USA. This article summarizes the milestones in the development of clascoterone leading to this first approval for the topical treatment of acne vulgaris.

Clascoterone (Winlevi®) cream 1%: Key points
An androgen receptor inhibitor being developed by Cassiopea for the treatment of androgen-dependent skin disorders
Received its first approval on 26 August 2020 in the USA
Approved for the topical treatment of acne vulgaris

1 Introduction

Advances in understanding of the pathogenesis of androgen-related diseases, such as of acne vulgaris and androgenetic alopecia (male pattern hair loss), has led to the development of therapies targeting the synthesis of androgens or their binding to androgen receptors [1, 2]. Clascoterone (Winlevi®) is an androgen receptor inhibitor being developed as a topical cream and solution by Cassiopea (a spin-out company of Cosmo Pharmaceuticals) for the treatment of androgen-dependent skin disorders, including androgenetic alopecia and acne vulgaris. Although the exact mechanism of action of clascoterone for the topical treatment of acne vulgaris is unknown [3], the drug is believed to compete with the androgen dihydrotestosterone (DHT) for binding to androgen receptors in the sebaceous gland and dermal papilla cells in hair follicles to attenuate signalling necessary for acne pathogenesis [4, 5]. On 26 August 2020 [6], clascoterone cream 1% received its first approval in the USA for the topical treatment of acne vulgaris in patients 12 years of age and older [3]. It is recommended that after cleaning the affected area gently, clascoterone be applied as a thin uniform layer (≈ 1 g) twice daily in the morning and evening. Clinical studies of a different formulation of clascoterone (a solution containing a higher concentration of the drug) for androgenic alopecia are underway in Germany and the USA; clascoterone cream 1% is not approved for use in androgenic alopecia.

1.1 Company Agreements

In March 2012, Cosmo Pharmaceuticals SpA announced that it had entered into an agreement with Intrepid Therapeutics to conduct phase 2 acne clinical trials in the US

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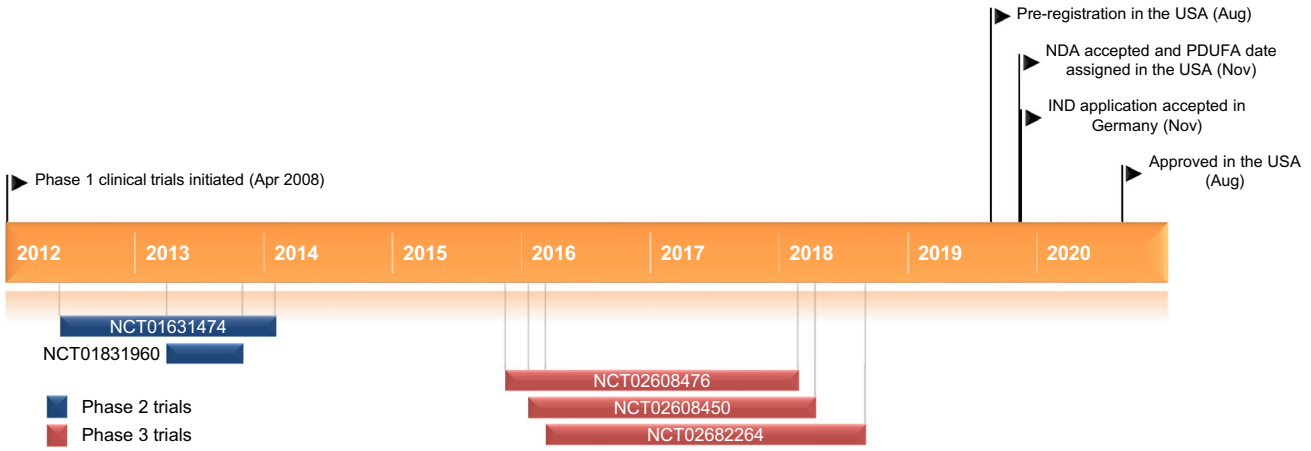


Key milestones in the development of clascoterone in the treatment of acne vulgaris. *IND* investigational new drug, *NDA* new drug application, *PDUFA* Prescription Drug User Fee Act

for Cosmo's novel topical anti-androgen molecule [7]. In April 2012, Cosmo Pharmaceuticals signed a license agreement with a US public pharmaceutical company granting it exclusive world-wide rights for the development and commercialization of clascoterone for certain topical skin applications [8].

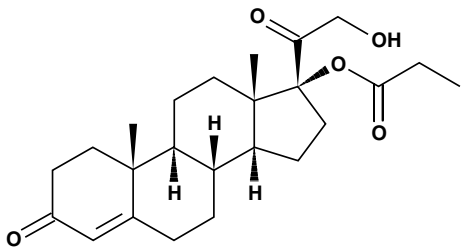
2 Scientific Summary

2.1 Pharmacodynamics

Clascoterone (cortexolone 17α-propionate), an ester derivative of cortexolone, is a potent antiandrogen with selective topical activity [9]. In vitro studies showed that clascoterone binds to androgen receptors with high affinity and inhibits DHT-stimulated signalling [4]. Clascoterone dose-dependently inhibited DHT-induced lipid synthesis and inflammatory cytokine production in human primary sebocytes [4]. In hair follicle dermal papilla cells, clascoterone selectively inhibited androgen receptor-regulated pathways that impede hair follicle growth, without affecting the production and secretion of pro-follicle growth factors [5].

In preclinical studies, clascoterone exhibited strong topical antiandrogenic activity, but was ineffective when administered subcutaneously [9]. The absence of systemic effects traditionally associated with oral antiandrogens/androgen receptor inhibitors (e.g. feminization of males, loss of libido), may be because of fast hydrolysis of clascoterone by the liver or other tissues, indicating that topical administration of the drug is unlikely to have systemic antiandrogenic effects. Subcutaneous clascoterone was not associated with anti-anabolic effects, suggesting that topical administration of the drug should not be associated with an increased risk of skin atrophy. When compared to other antiandrogens, topical clascoterone was four times more potent than progesterone, three times more potent than flutamide, approximately two times more effective than finasteride and approximately as active as cyproterone acetate [9].

As clascoterone is rapidly hydrolysed to cortexolone, its use may be associated with adrenal suppression [10]. In adults ($n = 20$) and adolescents ($n = 22$) with acne vulgaris administered clascoterone cream 1% twice daily (mean dose ≈ 6 g twice daily or ≈ 4 g twice daily in younger, smaller subjects) for 2 weeks in an open-label, multicentre phase 2a study evaluating the potential for hypothalamic–pituitary–adrenal (HPA) axis suppression (as well as pharmacokinetics) (NCT01831960), one adult and two adolescent patients had evidence of HPA axis suppression on day 14, as indicated by 30-min post-stimulation serum cortisol level of ≤ 18 μ/dL [3, 11]. All patients returned to normal HPA axis function at follow-up 4 weeks after the end of treatment [3, 11]. Elevated potassium levels have been observed in 5% of clascoterone-treated patients compared with 4% of vehicle-treated patients [3]. Clascoterone cream 1% at approximately two times the systemic exposure with the



Chemical structure of clascoterone

maximum dose did not prolong QT interval to a clinically significant extent [3].

2.2 Pharmacokinetics

Following topical application of clascoterone cream 1% (mean dose ≈ 6 g twice daily) for 2 weeks to 20 adults with moderate to severe acne vulgaris (NCT01831960), steady state systemic concentrations of clascoterone were reached by day 5 [3, 11]. Clascoterone systemic exposure in adolescents receiving clascoterone cream 1% (mean dose ≈ 6 g twice daily, or ≈ 4 g twice daily in younger, smaller subjects) for 2 weeks was similar to that in adults [3, 11]. In vitro plasma protein binding of clascoterone is 84–89% and independent of concentrations [3]. Incubation of clascoterone with human cryopreserved hepatocytes in vitro generated cortexolone as the possible primary metabolite and other unidentified metabolites, including conjugated metabolites. Following topical administration of clascoterone cream in patients aged ≥ 12 years with acne vulgaris, plasma concentrations of cortexolone (possible primary metabolite) were detectable and generally below or near the lower limit of quantitation (0.5 ng/mL). Excretion of clascoterone has not been fully characterized in humans [3].

Clinical studies evaluating the drug interaction potential of clascoterone cream have not been conducted. Clascoterone cream did not affect the pharmacokinetics of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4 to a clinically meaningful extent [3].

2.3 Therapeutic Trials

2.3.1 Acne Vulgaris

Clascoterone cream 1% applied topically twice daily was more effective in achieving treatment success and reducing acne lesions in patients with facial acne vulgaris than topically applied vehicle cream in two identically-designed, 12-week, randomized, double-blind, multicentre phase 3 trials (NCT02608450 and NCT02608476) [12]. Eligible patients were aged ≥ 9 years with moderate to severe facial acne vulgaris [grade 3 or 4 on the Investigator's Global Assessment (IGA) scale], 30–75 inflammatory lesions and 30–100 noninflammatory lesions. Patients ($n = 1440$) were randomized (1:1) to treatment with clascoterone cream 1% (≈ 1 g) or vehicle cream applied to the entire face twice daily for 12 weeks in the two trials [trial 1 (NCT02608450) $n = 353$ and 355, respective groups; trial 2 (NCT02608476) $n = 369$ and 363]. At week 12, significantly more patients receiving clascoterone than vehicle achieved treatment success (coprimary endpoint) in both trials (18.4% vs 9.0% in trial 1; 20.3% vs 6.5% in trial 2; both $p < 0.001$), where treatment success was defined as ≥ 2-point reduction in IGA compared to baseline and an IGA score of 0 (clear) or 1 (almost clear). Likewise, at week 12, clascoterone was associated with significantly greater reductions in noninflammatory lesions (mean absolute change from baseline − 19.4 vs − 13.0 in trial 1 and − 19.4 vs − 10.8 in trial 2; both $p < 0.001$) and inflammatory lesions

Features and properties of clascoterone

Alternative names	Breezula; CB-03-01; cortexolone 17alpha-propionate; Winlevi®
Class	Antiacnes; esters; pregnenediones; propionates; skin disorder therapies; small molecules
Mechanism of Action	AR antagonist competing with DHT for binding to ARs to attenuate signalling necessary for acne pathogenesis
Route of Administration	Topical
Pharmacodynamics	Selective topical antiandrogenic activity
	Dose-dependently inhibited DHT-induced lipid synthesis and inflammatory cytokine production in human primary sebocytes
	Selectively inhibited AR-regulated pathways in hair follicle dermal papilla cells that impede hair follicle growth, without affecting the production and secretion of pro-follicle growth factors
Pharmacokinetics	Steady state reached by day 5; plasma protein binding 84–89%
Adverse events	
Most frequent TEAEs	Nasopharyngitis, headache, oropharyngeal pain, vomiting
New or worsening LSRs	Erythema/redness, scaling/dryness, pruritus
Systemic	Hypothalamic–pituitary–adrenal suppression, elevated serum potassium
ATC codes	
WHO ATC code	D10A (anti-acne preparations for topical use); D11A (other dermatological preparations)
EphMRA ATC code	D10A (topical anti-acne preparations); D11A (other dermatological preparations)
Chemical Name	[(8R,9S,10R,13S,14S,17R)-17-(2-hydroxyacetyl)-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-17-yl] propanoate

AR androgen receptor, *DHT* dihydrotestosterone, *LSRs* local skin reactions, *TEAEs* treatment-emergent adverse events

(mean absolute change from baseline − 19.3 vs − 15.5 in trial 1 and − 20.0 vs − 12.6 in trial 2; both $p \leq 0.003$) (coprimary endpoints). The three coprimary endpoints were assessed hierarchically in the order discussed [12]. Similar outcomes were evident in the subgroup of patients (n = 1421) enrolled in these trials who were aged 12 years and older (trial 1 n = 342 and 350, respectively, in the clascoterone cream 1% and vehicle groups; trial 2 n = 367 and 362). At week 12, a higher proportion of patients receiving clascoterone than vehicle in both trials achieved treatment success (18.8% vs 8.7% in trial 1; 20.9% vs 6.6% in trial 2) and greater reductions in noninflammatory lesions (mean absolute change from baseline − 20.4 vs − 13.0 in trial 1 and − 19.5 vs − 10.8 in trial 2) and inflammatory lesions (mean absolute change from baseline − 19.3 vs − 15.4 in trial 1 and − 20.1 vs − 12.6 in trial 2) [3].

Earlier, a 12-week, randomized, double-blind, multicentre, phase 2b dose-escalation study (NCT01631474) in 363 patients (aged ≥ 12 years) with facial acne vulgaris (IGA 2–4 with 20–75 inflammatory and 20–100 non-inflammatory lesions) had shown that the highest efficacy was achieved with clascoterone cream 1% administered twice daily [13]. At week 12, although there were no significant between-group differences, the highest treatment success (coprimary endpoint) was achieved with clascoterone 1% twice daily (8.6%) and clascoterone 0.1% twice daily (8.3%), followed by clascoterone 0.5% twice daily (3.9%), clascoterone 1% once daily (2.9%) and vehicle once or twice daily (2.7%). Clascoterone 1% was also associated with the greatest reduction from baseline in inflammatory (− 13.5) and non-inflammatory (− 17.5) lesions (coprimary endpoints), with the treatment groups differing significantly in terms of the absolute change from baseline in both lesion types ($p = 0.0431$ and $p = 0.0303$). Based on these results, clascoterone 1% twice daily dosage was selected for further assessment in the phase 3 trials [13].

A pilot, 8-week randomized, double-blind phase 2 study (EudraCT no. 2008-004335-37) had previously demonstrated the potential efficacy of clascoterone cream 1% ($n = 30$ patients) versus that of topical tretinoin 0.05% cream ($n = 32$) and placebo ($n = 15$) in 77 men with facial acne (IGA 2–3) [14]. At week 8, clascoterone cream 1% was significantly more effective than placebo in reducing total lesion count (28.3% improvement; $p = 0.0017$), inflammatory lesion count (27.9% improvement; $p = 0.0134$) and acne severity (23.4% improvement in acne severity index; $p = 0.009$). Clascoterone 1% cream was clinically, but not statistically significantly, more effective than tretinoin 0.05% cream in reducing total lesion count (mean improvement 65.7% vs 52.5%), inflammatory lesion count (67.3% vs 50.7%) and acne severity (68.4% vs 53.1%) [14].

2.3.2 Androgenetic Alopecia

Clascoterone solution was effective in treating androgenetic alopecia in a phase 2, randomized, double-blind, dose-ranging clinical trial (EudraCT2016-003733-23) in male subjects (aged 18–55 years) with mild to moderate disease in the temple and vertex region [15]. Preliminary results from the study were announced by Cassiopea. Patients (per-protocol population $n = 344$) applied clascoterone solution (2.5% or 5.0% twice daily, or 7.5% once or twice daily) or vehicle to the balding areas of the scalp twice daily for 12 months. At 12 months, significantly greater improvements in target area headcount (TAHC) were observed with all clascoterone dosages relative to vehicle, with the greatest improvement seen with clascoterone 7.5% twice daily (mean changes from vehicle: 10.2, 13.8, 12.7 and 14.3 with clascoterone 2.5% twice daily, 5.0% twice daily, 7.5% once daily and 7.5% twice daily, respectively; all $p < 0.01$). In addition, significantly more patients in all clascoterone groups saw an increase in hair growth relative to vehicle, as assessed by the hair growth assessment (HGA) questionnaire [favourable HGA (+ 1, + 2, + 3): 60.8%, 60.0%, 56.1%, 61.8% and 50.0% of patients in clascoterone 2.5% twice daily, 5% twice daily, 7.5% once daily, 7.5% twice daily and vehicle groups] [15].

Key clinical trials of clascoterone

Drug(s)	Indication	Phase	Status	Location(s)	Sponsor	Identifier
Clascoterone cream 1%, vehicle cream	Acne vulgaris	III	Completed	USA, Georgia, Ukraine	Cassiopea SpA	NCT02608450; CB-03–01/25
Clascoterone cream 1%, vehicle cream	Acne vulgaris	III	Completed	Multinational	Cassiopea SpA	NCT02608476; CB-03–01/26
Clascoterone cream 1%	Acne vulgaris	III	Completed	Multinational	Cassiopea SpA	NCT02682264; CB-03–01/27
Clascoterone cream, vehicle cream	Acne vulgaris	IIb	Completed	USA	Cassiopea SpA	NCT01631474; 171–7151-201
Clascoterone cream 1%	Acne vulgaris	IIa	Completed	USA	Intrepid Therapeutics	NCT01831960; 171–7151-202
Clascoterone solution 5%, 7.5%, minoxidil solution 2%, vehicle	Androgenetic alopecia	II	Recruiting	Germany	Cassiopea SpA	EudraCT2019-000950–78; CB03-01-35

2.4 Adverse Events

Clascoterone was generally well tolerated in patients with facial acne vulgaris, with a tolerability profile generally similar to that of vehicle, according to results from the two identically designed phase 3 studies (NCT02608450 and NCT02608476) [12]. Treatment-emergent adverse events (AEs) were reported in 11.3% of patients receiving clascoterone (vs 11.5% of patients receiving vehicle) in trial 1 and 11.4% (vs 13.8%) of patients in trial 2, with the majority of AEs being mild or moderate in severity. The most common treatment-emergent AEs with clascoterone were nasopharyngitis (1.7% vs 3.7% with vehicle in trial 1; 1.1% vs 1.9% in trial 2), headache (0.6% vs 0.3%; 1.1% vs 0.8%), oropharyngeal pain (0.6% vs 0.3%; 1.1% vs 1.1%) and vomiting (0.6% vs 0.6%; 0.5% vs 0.3%). No patient receiving clascoterone had a severe treatment-emergent AE; in patients receiving vehicle, there were two severe AEs in trial 1 (pneumonia and application-site acne) and one severe AE in trial 2 (contusion) [12].

Across the two studies, the most frequent (incidence > 5%) new or worsening local skin reactions with clascoterone were erythema/redness (12.2% vs 15.4% with vehicle), scaling/dryness (10.5% vs 10.4%) and pruritus (7.7% vs 8.2%) [3]. There were 4 treatment-related AEs in patients receiving clascoterone (vs 9 events in patients receiving vehicle) in trial 1 and 9 treatment-related AEs in clascoterone recipients (vs 13) in trial 2 [12]. No treatment-related serious AE or death was reported in any treatment group in either study. Treatment-emergent AEs resulted in discontinuation of therapy in three clascoterone recipients (vs four vehicle recipients) in trial 1 and two clascoterone recipients (vs eight vehicle recipients) in trial 2 [12].

Clascoterone cream 1% was also generally well tolerated during long-term therapy (≤ 9 months) in an open-label, multicentre extension study (NCT02682264) involving patients who initially had participated in the 12-week phase 3 pivotal studies [16]. All patients (safety population $n = 607$) received clascoterone twice daily applied to the face or trunk, or both. During 9 months' therapy, 18.1% (110/609) of patients experienced 191 treatment-emergent AEs, with 106 AEs reported in 18.3% (58/317) of patients who had originally received clascoterone and 85 AEs in 17.9% (52/290) of patients who had received vehicle. The majority (181 AEs) of treatment-emergent AEs were mild or moderate in severity, with the most common (incidence > 1%) being nasopharyngitis (2.6% of patients) and upper respiratory tract infection (1.3%). Seven patients (1.2%) experienced 10 severe treatment-emergent AEs; six patients had seven serious treatment-emergent AEs, none of which were treatment related. Treatment-related AEs (19 events) occurred in 14 patients (2.3%), with moderate application-site erythema and moderate acne occurring most commonly (2 events each). Nine patients discontinued therapy because of nine treatment-emergent AEs; there were no deaths in the study. Treatment-emergent local skin reactions occurred in 18.1% (110/607) patients, with the most common AEs on the face and trunk being erythema, scaling/dryness and pruritus (largely of minimal or mild severity) [16].

2.5 Ongoing Clinical Trials

Recruitment is underway in Germany for a phase 2, randomized, double-blind, multicentre, dose-ranging study (EudraCT2019-000950-78; CB03-01-35) to evaluate the efficacy and safety of clascoterone solution (5% and 7.5% twice daily) versus minoxidil solution (2% twice daily) and vehicle for the treatment of androgenetic alopecia in females [17]. The 6-month study plans to enrol ≈ 280 female subjects aged 18–55 years with mild to moderate androgenetic alopecia; the coprimary endpoints are change from baseline to month 6 in non-vellus TAHC, and HGA score at month 6 [17]. In July 2020, Cassiopea reported submission of a special protocol assessment to the US FDA for a prospective phase 3 trial of clascoterone solution 7.5% for the treatment of androgenetic alopecia in males [18].

3 Current Status

On 26 Aug 2020 [6], clascoterone cream 1% received its first approval in the USA for the topical treatment of acne vulgaris in patients 12 years of age and older [3].

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Declarations

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Ethics approval, Consent to participate and consent for publication, Availability of data and material, Code availability Not applicable.

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