

Cassiopea S.p.A.

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# Cassiopea S.p.A.: Elevating the science of dermatology with new therapeutics

Millions of people affected by skin disorders with an emotional impact are eager for innovative therapies. Cassiopea is responding.

The Milan, Italy-based pharmaceutical company Cassiopea S.p.A. has created a new therapeutic topical drug class to treat acne. But that's just the beginning of its story. With its US subsidiary Cassiopea Inc., the company is dedicated to finding new treatments with novel mechanisms of action to treat major skin conditions that so often lead to low confidence, poor self-esteem, and emotional distress—and which have not seen new treatments for a long time.

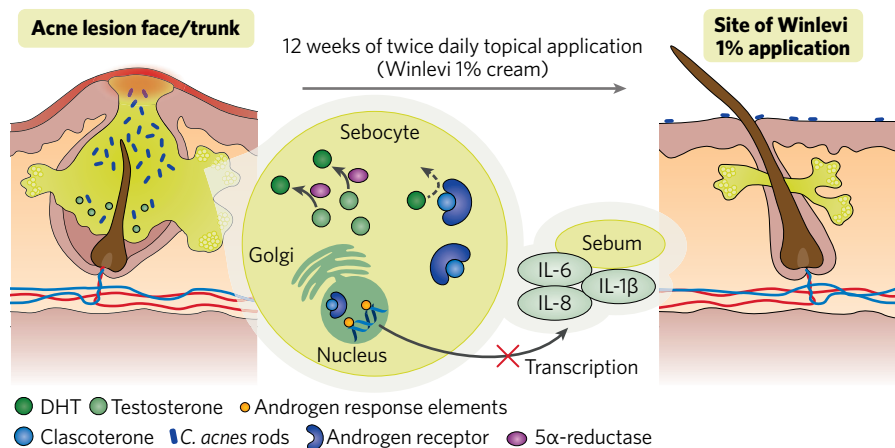
Cassiopea is focused on three therapeutic areas: acne, androgenetic alopecia (AGA) and genital warts. In August 2020, Cassiopea received US Food and Drug Administration (FDA) approval for its first-in-class acne topical treatment Winlevi (clascoterone) cream 1%, and it currently has three other products in clinical-stage development for which the company holds worldwide rights.

## Winlevi (clascoterone) cream 1%: a novel topical acne treatment

Acne is a chronic inflammatory skin disease affecting 50 million people in the USA each year. It is one of the most common skin conditions driving people to see a dermatologist, with more than 5 million patients actively seeking treatment—a market that is projected to grow by 6.5% by 2024. And yet, an acne topical treatment with a novel mechanism of action has not been approved by the FDA for nearly 40 years.

Acne is caused by four processes: 1. hyperkeratinization—the excess production of keratin protein coupled with decreased sloughing of dead skin leading to blocked pores; 2. excess sebum production—which further clogs the pore; 3. *Cutibacterium acnes* infection; and 4. local inflammation and reddening of the skin (Fig. 1).

Many current acne treatments target epithelial skin growth (retinoids) or *C. acnes* (antibiotics). Topical treatments targeting androgens that drive sebum production and inflammation have



**Fig. 1 | Acne and androgens.** Causes of acne (left panel). Hyperkeratinization and excess sebum (light green) clogs the pore, fostering infection with *Cutibacterium acnes* (dark blue rods) and causing inflammation (red skin). In acne, androgens including testosterone (light green circles) and 5α-dihydrotestosterone (DHT; dark green circles) bind to androgen receptors (ARs; blue crescents). The resulting androgen-AR complex then binds to genomic androgen response elements, initiating gene expression that leads to production of sebum and the pro-inflammatory cytokines IL-6, IL-8 and IL-1β. The mechanism of action of Winlevi is unknown. In vitro, clascoterone (light blue circles) competes with DHT for binding to ARs, inhibiting gene expression (middle panel) that reduces sebum production and inflammation (right panel). IL, interleukin.

been lacking. Cassiopea has filled that gap with a first-in-class acne treatment, Winlevi, a topical androgen receptor (AR) inhibitor. Although the exact mechanism of action is unknown, in vitro studies show Winlevi targets sebaceous activity and inflammation<sup>1,2</sup> (Fig. 1).

In pivotal phase 3 clinical trials in patients who applied Winlevi twice a day to the face for 12 weeks, significantly clearer skin was achieved, as indicated by Investigator's Global Assessment (IGA) scores and absolute reductions in non-inflammatory and inflammatory acne lesions<sup>3</sup>. An open-label safety study of 600 patients who participated in the pivotal trials revealed a favourable safety profile and demonstrated efficacy on truncal acne located on the chest, back and shoulders<sup>4</sup>. On the basis of these results, Winlevi received FDA approval in August 2020 as a first-in-class treatment for acne in patients ≥12 years old<sup>1</sup>. It is expected to be available to patients in the USA by early 2021.

Unlike oral medications that affect ARs, Winlevi can be used in both male and female patients, making it a truly innovative strategy and described as a potential game changer in acne therapy. "Winlevi's approval represents a major scientific achievement in the treatment of acne", said Martina Cartwright, Cassiopea's senior director of medical affairs.

"Our research underscores the role of androgens in common skin conditions, opening the door to therapeutic innovations."

Diana Harbort, CEO of Cassiopea, said: "This milestone approval marks the introduction of a new class of topical medication in dermatology. Dermatologists have said targeting androgen hormonal activity in the skin is 'the holy grail' of acne treatment for both males and females. We are proud to bring this new innovation to acne patients. This approval rewards many years of hard work and positions Cassiopea as a leader in dermatology. Now we look forward to expanding our franchise and advancing our next investigational drug candidate for AGA."

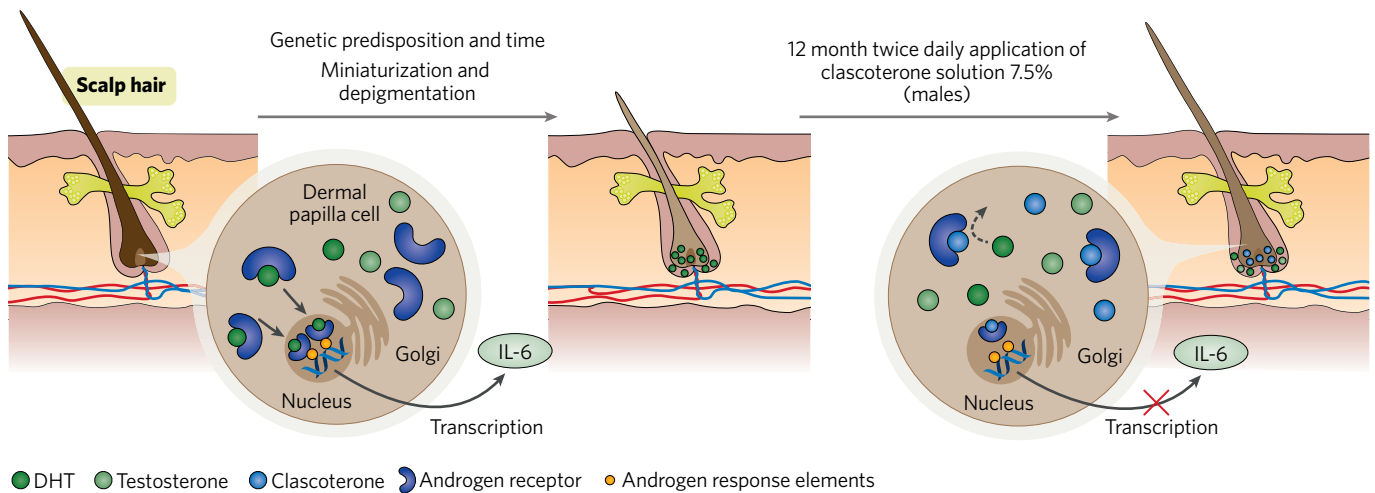
## Breezula (clascoterone) solution, 5.0–7.5%: a possible solution for AGA

Cassiopea is also developing a second clascoterone-based product in the form of a topical solution (5.0–7.5%), with the proposed brand name of Breezula, to target ARs in the scalp for the treatment of AGA in both male and female patients. AGA is the most common cause of hair loss, affecting up to 50% of men and women in their lifetime, and dramatically affecting people's confidence and self-esteem.

With just one prescription drug available for AGA

Our research underscores the role of androgens in common skin conditions, opening the door to therapeutic innovations

Martina Cartwright, Senior Director of Medical Affairs, Cassiopea



**Fig. 2 | Androgenetic alopecia.** In dermal papilla cells (DPCs) of genetically predisposed individuals, 5 $\alpha$ -dihydrotestosterone (DHT) binds to androgen receptors (ARs), creating a DHT-AR complex that binds to genomic androgen response elements (left-hand side), leading to gene expression that eventually results in hair miniaturization; thinner, shorter and less pigmented hairs; shortening of the hair growth cycle; and transcription of various proteins including pro-inflammatory cytokines such as IL-6 (middle). In vitro, clascoterone solution inhibits the synthesis of the inflammatory cytokine IL-6 from DHT-treated human follicular DPCs (right-hand side)<sup>6</sup>, which may account for changes from baseline hair counts observed after 12 months of bis in die (BID; twice per day) application<sup>5</sup>. However, the exact mechanism of action of clascoterone solution on hair growth is unknown. IL, interleukin.

in the US market, there is a large need for new treatments. Cassiopea has formulated clascoterone as a 7.5% solution that is applied to the scalp to interfere with DHT's effect on scalp hair loss. Research shows a potential AGA treatment effect with  $\geq 5\%$  clascoterone solutions, likely because of the unique characteristics of scalp skin. Lower strengths did not show potential in AGA studies<sup>5</sup>.

In vitro, clascoterone inhibits the synthesis of inflammatory mediators involved with hair loss, such as interleukin-6 (IL-6), from DHT-treated human follicular dermal papilla cells (DPC), without affecting synthesis of basic fibroblast growth factor (bFGF)<sup>6</sup> (Fig. 2). IL-6 inhibits elongation of hair follicle shafts, while bFGF promotes DPC proliferation and increases follicle size. These data suggest that clascoterone inhibits the AR-regulated pathways that reduce hair follicle size without altering pro-growth pathways. In addition, this study demonstrated that clascoterone inhibits IL-6 synthesis significantly more than the anti-androgen enzalutamide, and inhibits AR-regulated transcription with similar efficacy to the 5 $\alpha$ -reductase inhibitor finasteride, which is used to promote hair growth.

## Research shows a potential AGA treatment effect with $\geq 5\%$ clascoterone solutions

A 12-month phase 2 dose-ranging study of clascoterone solution in males with AGA, completed in 2019, found that twice daily application of a 7.5% clascoterone solution to balding scalp was the dosing regimen with the greatest impact on hair growth, based on change from baseline in non-velvus target area hair count at 6 months and 12 months<sup>7</sup>. A phase 3 adult male AGA study is set to begin shortly. A phase 2 study involving female AGA subjects completed enrolment in September 2020, with results expected in Q2 2021.

## Cassiopea's pipeline of other clinical development candidates

Cassiopea's pipeline is completed by two further drugs in development. CB-06-02, also known as AS-101, is a topical treatment for genital warts caused by the human papillomavirus (HPV). Up to 80% of sexually active people will contract HPV in their lives, with 360,000 people in the USA developing genital warts every year.

Although topical genital wart treatments are available, they typically require multiple applications and are often ineffective, resulting in recurrence. CB-06-02 has completed a phase 2 proof-of-concept (POC) clinical trial and demonstrated statistically significant successful clearance rates of external genital warts in the per protocol patient group (n=56). This study, conducted in Israel, showed a 15% concentration of CB-06-02, a tellurium-based gel, applied once a day for up to 14 weeks resulted in 75% of the CB-06-02 group achieving complete clearance of external genital warts, while 40.6% of vehicle subjects achieved complete clearance.

Cassiopea's final drug candidate is CB-06-01, a novel topical antibiotic currently under development for acne. CB-06-01 has successfully completed a POC study and is now in formulation optimization. The POC trial met its pre-defined primary end point, reducing the median inflammatory lesion count; and secondary end points, the reduction of total lesion count and a two-point reduction in the IGA score. In this study, no serious adverse events were reported and there were no increased local skin reactions compared with vehicle.

For the near future, Cassiopea's focus is on US commercialization of Winlevi for a March 2021 launch and advancing its rich pipeline. Cosmo Pharmaceuticals, Cassiopea's major shareholder, will provide support in these efforts. Cassiopea is also keen to explore new partnerships to enable the company to further develop its pipeline in alopecia, acne and genital warts, and bring truly innovative treatments in dermatology to the patients who need them.

**We are proud to bring this new innovation to acne patients and look forward to expanding our franchise and advancing our next investigational drug**

Diana Harbort, CEO, Cassiopea

1. WINLEVI. [Package insert]. Milan, Italy, Cassiopea S.p.A. 2020. [www.winlevi.com](http://www.winlevi.com) for full prescribing information and important safety information.
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4. Eichenfield, L. et al. *J. Am. Acad. Dermatol.* **83**, 447-485 (2020).
5. Blume-Peytavi, U. et al. S11223—Clascoterone Topical Solution, An Investigational, Selective Androgen Receptor Antagonist: Results from a Pivotal Phase II Dose Ranging Study in Men with Androgenetic Alopecia (AGA). Presented at the 2019 AAD Annual Conference (2019).
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