

RESEARCH MONOGRAPH . COMPOUND PROFILE

CB-03-01

A synthetic pregnane steroid developed by Cosmo Pharmaceuticals (Cassiopea) as a topically applied, peripherally selective androgen receptor antagonist for the treatment of acne vulgaris and androgenetic alopecia, distinguished from systemic antiandrogens by rapid local metabolism to inactive cortexolone and minimal systemic bioavailability.

DOCUMENT	KDC-MN-1520
ISSUED	2026-05-15
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Topical steroidal androgen receptor antagonist with peripherally selective antiandrogen activity

ABSTRACT

CB-03-01 (clascoterone; cortexolone 17alpha-propionate; 11-deoxycortisol 17alpha-propionate) is a synthetic pregnane steroid that functions as a competitive antagonist of the androgen receptor (AR) with submicromolar potency (IC₅₀ approximately 0.4 to 1 micromolar in AR transactivation assays) and peripheral selectivity conferred by rapid enzymatic hydrolysis to the inactive parent compound cortexolone (11-deoxycortisol) in human skin, plasma, and hepatic tissue. The compound was identified from a structure-activity series of cortexolone 17alpha-monoesters screened for topical antiandrogen activity in the hamster flank organ test, in which CB-03-01 demonstrated potency approximately four times greater than progesterone, three times greater than flutamide, two times greater than finasteride, and approximately equivalent to cyproterone acetate, while lacking systemic antiandrogenic, antianabolic, or glucocorticoid activity after subcutaneous administration in rats. The molecular pharmacology centers on competitive displacement of dihydrotestosterone (DHT) from the androgen receptor in sebocytes and dermal papilla cells, resulting in suppression of androgen-responsive gene transcription, reduction of sebaceous lipid synthesis, inhibition of inflammatory cytokine production (including interleukin-6), and attenuation of androgen-driven miniaturization of scalp hair follicles. In human dermal papilla cell cultures, CB-03-01 demonstrated significantly greater inhibition of DHT-stimulated IL-6 synthesis than the direct AR antagonist enzalutamide.

The compound received its first regulatory approval from the United States Food and Drug Administration in August 2020 as a 1% topical cream (Winlevi) for the treatment of acne vulgaris in patients aged 12 years and older, representing the first new mechanism of action approved for acne in approximately 40 years and the first topical antiandrogen approved for acne in any jurisdiction. Two pivotal Phase 3 randomized, double-blind, vehicle-controlled trials enrolling a total of 1440 patients with moderate to severe facial acne demonstrated statistically significant treatment success rates (Investigator Global Assessment score of 0 or 1 with at least a two-grade reduction) of approximately 18 to 20 percent for clascoterone versus 7 to 9 percent for vehicle at 12 weeks, with concurrent reductions in both inflammatory and noninflammatory lesion counts. Long-term safety data through 12 months demonstrated a favorable tolerability profile dominated by local application site reactions (erythema, dryness, pruritus) without clinically meaningful systemic antiandrogen effects.

A second clinical program in androgenetic alopecia (AGA) has advanced through Phase 2 dose-ranging studies (2.5%, 5%, and 7.5% solutions applied twice daily) demonstrating statistically significant improvements in target area hair count (TAHC) at 6 and 12 months, and into Phase 3 registration trials (SCALP-1 and SCALP-2) using a 5% topical solution in 1465 male patients with mild to moderate AGA. The Phase 3 topline results reported statistically significant improvements in TAHC relative to vehicle, with a 5.39-fold relative improvement in one study and a 1.68-fold relative improvement in the second, the divergence attributable to baseline hair count differences rather than inconsistent drug performance. The safety profile in the AGA trials was comparable to vehicle, with no evidence of systemic androgen blockade.

Pharmacokinetics following topical application are characterized by minimal systemic absorption. At maximal clinical use conditions (6 grams of 1% cream applied twice daily), steady-state plasma concentrations of clascoterone average 3.1 plus or minus 1.9 ng/mL with C_{max} values of 4.5 plus or minus 2.9 ng/mL. The compound is rapidly hydrolyzed in plasma to cortexolone, which is detectable at concentrations generally near or below the lower limit of quantitation (0.5 ng/mL). Plasma protein binding is 84 to 89 percent. The principal safety signal is reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, observed in approximately 7 percent of adolescent and adult subjects in maximal-use pharmacokinetic studies, with all cases resolving within 4 weeks of discontinuation. This monograph reviews the chemistry, synthesis, and structural pharmacology of CB-03-01; the competitive androgen receptor antagonist mechanism in molecular detail; the pharmacokinetic profile including systemic absorption, metabolism, and HPA axis considerations; the preclinical pharmacology in hamster, rat, and human tissue models; the clinical evidence base across acne and androgenetic alopecia indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a comparative assessment of five alternative antiandrogen or androgen-modulating agents against CB-03-01 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Clascoterone.

Marketed names: Winlevi (Cassiopea/Cosmo Pharmaceuticals; United States, 1% cream for acne vulgaris). Breezula is the proposed brand name for the topical solution formulation under development for androgenetic alopecia; this name has been used in clinical trial materials and press releases but has not yet received regulatory approval as a marketed product name.

Development codes: CB-03-01 (Cosmo Pharmaceuticals/Cassiopea). The development code CB-03-01 is the canonical identifier in the preclinical and early clinical pharmacology literature and remains the most widely cited designation in the dermatological research literature [1, 2].

Chemical Abstracts Service registry number: 19608-29-8 (free base). The compound is supplied and formulated as the free base; no salt form is in clinical or commercial use.

International Union of Pure and Applied Chemistry name: 21-hydroxy-17-(1-oxopropoxy)pregn-4-ene-3,20-dione. An alternative systematic designation is [(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. The compound is the C17 α propionate ester of cortexolone (11-deoxycortisol), a naturally occurring pregnane steroid intermediate in the adrenal corticosteroid biosynthetic pathway.

1.2 Structural class and chemistry

CB-03-01 is a synthetic pregnane steroid derived from cortexolone (11-deoxycortisol) by esterification at the 17 α -hydroxyl position with propionic acid. The structural class places it within the pregnane family of C21 steroids, sharing the fundamental tetracyclic ring system with progesterone, cortisol, and the mineralo-

corticoids, but lacking the 11 β -hydroxyl group that distinguishes the glucocorticoid series (cortisol, cortisone, corticosterone) from the 11-deoxy series (cortexolone, 11-deoxycorticosterone) [1, 2].

Molecular formula: C₂₄H₃₄O₅.

Molecular weight: 402.5 g/mol.

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide, ethanol, and methanol; sparingly soluble in water. The compound is lipophilic, consistent with its intended topical administration and skin penetration.

Stereochemistry: CB-03-01 retains the natural steroid stereochemistry at carbons 8 (R), 9 (S), 10 (R), 13 (S), 14 (S), and 17 (R) of the pregnane ring system. The 17 α -propionate ester is defined by the axial orientation of the propionyloxy group at C17, which is critical for androgen receptor binding affinity and for the hydrolytic susceptibility that confers peripheral selectivity [2].

1.3 Synthesis

The synthesis of CB-03-01 proceeds from cortexolone (11-deoxycortisol), which is available as a bulk pharmaceutical intermediate through established steroid fermentation and semisynthetic production. The key transformation is selective esterification of the 17 α -hydroxyl group with propionic anhydride or propionyl chloride under controlled conditions that preserve the 21-hydroxyl, the Δ -4-3-keto system, and the 20-keto functionality. Selective 17 α -acylation in the presence of the 21-hydroxyl requires either protecting-group chemistry (temporary silylation or acetylation of the 21-hydroxyl, followed by 17 α -propionylation and selective deprotection) or kinetic control exploiting the differential reactivity of the two hydroxyl positions [1, 3]. The product is purified by column chromatography or recrystallization from appropriate solvent systems and characterized by nuclear magnetic resonance spectroscopy (¹H and ¹³C), mass spectrometry, high-performance liquid chromatography, and specific rotation. Industrial-scale synthesis achieves high purity (greater than 98 percent by HPLC area percent), and the compound is manufactured under current good manufacturing practices for pharmaceutical applications. The synthesis does not involve controlled substances or atypical reagents; the principal requirement is the availability of pharmaceutical-grade cortexolone as starting material.

2. Abstract

CB-03-01 (clascoterone; cortexolone 17alpha-propionate) is a competitive androgen receptor antagonist with topical and peripherally selective pharmacology, developed for the treatment of androgen-dependent skin disorders. The compound displaces dihydrotestosterone from the androgen receptor in sebocytes and dermal papilla cells with submicromolar potency and suppresses androgen-responsive gene transcription, sebaceous lipid synthesis, and inflammatory cytokine production without producing systemic antiandrogenic effects at therapeutic topical doses [1, 2, 4, 5].

The principal approved application is the treatment of acne vulgaris in patients aged 12 years and older, for which clascoterone cream 1% (Winlevi) was approved by the United States Food and Drug Administration in August 2020. Two Phase 3 trials enrolling 1440 patients demonstrated treatment success rates (IGA 0 or 1 with at least a two-grade reduction) of approximately 18 to 20 percent for clascoterone versus 7 to 9 percent for vehicle at 12 weeks, with significant reductions in inflammatory and noninflammatory lesion counts [6, 7]. The approval represented the first new mechanism of action for acne treatment in approximately four decades and the first topical antiandrogen approved for acne in any jurisdiction.

A second clinical application, currently in late-stage development, is androgenetic alopecia (AGA) in males. A Phase 2 dose-ranging study in over 400 male subjects demonstrated statistically significant improvements in target area hair count at the 7.5% concentration applied twice daily, with an average increase of 14.3 hairs versus placebo at 12 months [8, 9]. Two Phase 3 trials (SCALP-1 and SCALP-2) using a 5% topical solution in 1465 patients reported positive topline results, with significant improvements in hair count relative to vehicle at 6 months [10]. The compound is not yet approved for AGA in any jurisdiction; regulatory submissions are anticipated based on completed Phase 3 data.

Pharmacokinetics are dominated by rapid enzymatic hydrolysis to cortexolone in skin, plasma, and liver. Systemic exposure after topical application is minimal; steady-state plasma concentrations at maximum clinical use are in the low single-digit nanograms per milliliter range [11, 12]. The compound does not undergo hepatic cytochrome P450-mediated oxidative metabolism in the conventional sense;

the principal metabolic pathway is ester hydrolysis by nonspecific esterases. The safety profile is favorable, with local application site reactions (erythema, dryness, pruritus) as the principal adverse events and reversible hypothalamic-pituitary-adrenal axis suppression as the primary systemic safety signal at maximal-use exposures [6, 7, 13].

This monograph documents the chemistry, synthesis, androgen receptor antagonist pharmacology, pharmacokinetics, preclinical and clinical evidence, sourcing, reconstitution, stack interactions, adverse-event profile, and a comparative assessment of five antiandrogen or androgen-modulating alternatives against CB-03-01.

3. Discovery and Development History

3.1 Origin

CB-03-01 emerged from a medicinal chemistry program at Cosmo Pharmaceuticals (later conducted through the dermatology-focused subsidiary Cassiopea S.p.A., based in Lainate, Italy) that systematically explored the antiandrogen activity of cortexolone 17alpha-esters. The parent compound cortexolone (11-deoxycortisol) is an endogenous steroid intermediate in adrenal cortisol biosynthesis and was known to possess weak intrinsic antiandrogen activity. The hypothesis underlying the program was that 17alpha-esterification could enhance androgen receptor affinity and topical potency while preserving the metabolic liability (ester hydrolysis) that would limit systemic exposure after topical application [1, 2].

Several 17alpha-monoesters of cortexolone and its delta-9 derivative were synthesized and screened. CB-03-01, the 17alpha-propionate ester, was selected for development based on its optimal drug profile: strong topical antiandrogen activity in the hamster flank organ test, competitive binding at the human androgen receptor, rapid hydrolysis to inactive cortexolone in skin and plasma, and absence of systemic antiandrogenic or glucocorticoid effects after parenteral administration in rats [1].

3.2 Preclinical characterization

The Celasco et al. (2004) publication in *Arzneimittelforschung/Drug Research* constitutes the foundational preclinical characterization of CB-03-01 [1]. This study demonstrated that CB-03-01 was a potent topical antiandrogen in the hamster flank organ test (the standard in vivo model for topical antiandrogen screening), with activity approximately four times greater than progesterone, three times greater than flutamide, two times greater than finasteride, and approximately equivalent to cyproterone acetate. Critically, after daily subcutaneous administration in the rat, CB-03-01 was devoid of systemic antiandrogenic activity (no effect on seminal vesicle or prostate weight), devoid of antianabolic activity, devoid of glucocorticoid activity, and did not inhibit gonadotropin hypersecretion or compete with the rat pi-

tuitary gonadotropin-releasing hormone (GnRH) receptor. The compound was confirmed to compete at the human androgen receptor level but did not inhibit 5alpha-reductase in reconstructed human epidermis [1].

A subsequent preclinical profile by Bruni et al. (2009) and Trifu et al. (2011) extended the characterization to sebocyte models and to dose-response relationships in the hamster flank organ test, confirming the topical selectivity and establishing the preclinical rationale for clinical development [2, 3].

3.3 Clinical development for acne

Cassiopea advanced CB-03-01 through Phase 1 safety and pharmacokinetic studies (topical application in healthy volunteers), Phase 2a open-label pharmacokinetic studies (1% cream in subjects with acne vulgaris), and a Phase 2b pilot randomized double-blind study comparing cortexolone 17alpha-propionate 1% cream to placebo and to tretinoin 0.05% cream in acne patients [3, 14]. The Phase 2b study demonstrated efficacy in reducing both inflammatory and noninflammatory lesion counts, with treatment success rates comparable to or exceeding tretinoin and significantly greater than vehicle.

Two pivotal Phase 3 trials (Study CB-03-01/25 and Study CB-03-01/26) were conducted across multiple sites in the United States, enrolling a total of 1440 patients aged 9 years and older with moderate to severe facial acne (IGA grade 3 or 4). Both trials met their co-primary efficacy endpoints at 12 weeks and supported the New Drug Application submitted to the FDA [6, 7].

3.4 FDA approval and post-approval

The FDA approved clascoterone cream 1% (Winlevi) on August 26, 2020, for the topical treatment of acne vulgaris in patients 12 years of age and older [15]. The approval was notable for two reasons: it was the first topical antiandrogen approved for acne in any global jurisdiction, and it represented the first new mechanism of action approved for acne treatment in approximately four decades (the preceding new mechanism was isotretinoin in the early 1980s). The product was marketed by Cassiopea in the United States. In December 2021, Cosmo Pharmaceuticals re-acquired full control of Cassiopea, consolidating the clascoterone commercial and development programs under a single corporate entity.

3.5 Development for androgenetic alopecia

In parallel with the acne program, Cassiopea initiated clinical development of higher-concentration clascoterone formulations for androgenetic alopecia. A Phase 2 dose-ranging study in Germany enrolled over 400 male subjects aged 18 to 55 with mild to moderate AGA and evaluated four dose groups (2.5%, 5%, and 7.5% solutions applied twice daily; 7.5% solution applied once daily) against vehicle over 12 months [8, 9]. All active groups showed statistically significant improvements in target area hair count and hair growth assessment scores compared to vehicle, with the 7.5% twice-daily group producing the largest mean improvement (14.3 hairs above placebo) [8]. The safety profile was comparable to vehicle across all dose groups.

Based on these results, Cosmo Pharmaceuticals selected the 5% concentration for Phase 3 development and initiated two Phase 3 trials (SCALP-1 and SCALP-2) enrolling 1465 male patients across 51 sites in the United States and Europe. Topline 6-month efficacy results, announced in late 2025, demonstrated statistically significant improvements in TAHC relative to vehicle in both trials [10]. The 12-month safety extension data collection was expected to be completed by spring 2026, with regulatory submissions anticipated thereafter.

4. Mechanism of Action

CB-03-01 is a steroidal androgen receptor antagonist with a single principal molecular target: the nuclear androgen receptor (AR). Unlike the dual-target or multi-target mechanisms of some compounds in the broader antiandrogen pharmacological space, the activity of CB-03-01 is attributable to competitive AR antagonism combined with the structural and metabolic features that confer topical selectivity. The compound does not inhibit steroidogenic enzymes (5 α -reductase, aromatase) and does not interact with the mineralocorticoid, glucocorticoid, or progesterone receptors at pharmacologically relevant concentrations [1, 2, 4, 5].

4.1 Androgen receptor antagonism

The androgen receptor is a ligand-activated nuclear transcription factor of the steroid hormone receptor superfamily. In the unbound state, the AR resides in the cytoplasm in association with heat shock proteins and chaperones. Binding of an androgen ligand (testosterone or, with higher affinity, dihydrotestosterone) induces conformational change, nuclear translocation, homodimerization, and binding to androgen response elements in the promoter regions of target genes, resulting in transcriptional activation of androgen-responsive gene programs. In the skin, these programs include sebaceous gland differentiation and lipogenesis (the principal upstream driver of acne pathogenesis), hair follicle miniaturization in androgenetic alopecia, and inflammatory cytokine expression in sebocytes and dermal papilla cells [4, 5, 16].

CB-03-01 competes with dihydrotestosterone for binding at the ligand-binding domain of the androgen receptor. In AR transactivation assays, the compound inhibits DHT-driven transcription with an IC₅₀ of approximately 0.4 to 1 micromolar [4, 5]. The binding is competitive and reversible. In cellular models, CB-03-01 suppresses DHT-induced lipid synthesis in human sebocytes (the lipid overproduction that drives comedogenesis and inflammatory acne), reduces inflammatory cytokine expression (interleukin-6, interleukin-8, tumor necrosis factor alpha) from both sebocytes and scalp dermal papilla cells, and inhibits DHT-stimulated proliferation in androgen-dependent cell lines [4, 5, 17].

A notable in vitro finding is that CB-03-01 demonstrated significantly greater inhibition of DHT-stimulated IL-6 synthesis from primary human scalp dermal papilla cells compared to enzalutamide, a potent AR antagonist used in prostate cancer therapy [5]. This finding suggests that the steroidal structure of CB-03-01 may confer additional anti-inflammatory activity beyond simple AR antagonism, potentially through interactions with the receptor conformation that influence co-activator recruitment or through off-target steroidal effects on inflammatory signaling pathways.

4.2 Peripheral selectivity through metabolic inactivation

The defining pharmacological feature of CB-03-01 is its peripheral selectivity, which is conferred not by receptor subtype selectivity but by rapid metabolic inactivation in biological tissues. The 17 α -propionate ester bond is hydrolyzed by nonspecific esterases in human skin, rat skin homogenates, and human plasma to yield cortexolone (11-deoxycortisol), an endogenous steroid with minimal androgen receptor affinity [1, 2]. This hydrolysis is rapid (half-life in human plasma on the order of minutes) and essentially complete, such that the systemic bioavailability of intact CB-03-01 after topical application is extremely low.

The metabolic inactivation strategy is analogous to the design of "soft drugs" in which a pharmacologically active compound is deliberately engineered to undergo rapid predictable metabolism to inactive products once it reaches the systemic circulation, thereby confining pharmacological activity to the local site of application [1]. In the case of CB-03-01, the design exploits the ubiquitous distribution of esterases in skin and plasma to achieve site-restricted antiandrogen activity.

4.3 Absence of 5 α -reductase inhibition

CB-03-01 does not inhibit 5 α -reductase (neither type 1 nor type 2 isoform) in reconstructed human epidermis models [1]. The mechanism of androgen antagonism is therefore exclusively at the receptor level, not at the level of androgen biosynthesis. This distinction is clinically relevant because 5 α -reductase inhibitors (finasteride, dutasteride) reduce circulating and tissue dihydrotestosterone concentrations systemically, producing systemic antiandrogenic effects (including sexual dysfunction, decreased libido, and feminization) that limit their use in certain pop-

ulations. CB-03-01 blocks DHT action at the receptor without affecting DHT production, and its rapid systemic inactivation prevents the receptor blockade from extending beyond the site of application.

4.4 Absence of glucocorticoid and mineralocorticoid activity

Despite its structural relationship to cortexolone and to the corticosteroid series, CB-03-01 does not exhibit glucocorticoid activity in standard preclinical models (rat thymus involution, liver glycogen deposition) and does not exhibit mineralocorticoid activity [1]. The 11-deoxy structural feature that distinguishes cortexolone from cortisol eliminates the glucocorticoid receptor binding that would otherwise be predicted from the pregnane framework.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

CB-03-01 is administered exclusively by the topical route. Systemic absorption after topical application is minimal, consistent with the rapid ester hydrolysis to corticosterone in skin. In a Phase 2a open-label pharmacokinetic study of clascoterone cream 1% applied to the face and trunk of subjects with acne vulgaris, steady-state plasma levels of clascoterone were achieved within approximately 5 days of twice-daily application [11, 12]. At maximum clinical use conditions (6 grams of 1% cream applied to approximately 500 to 600 square centimeters of affected facial and truncal skin twice daily), the mean maximum plasma concentration (C_{max}) was 4.5 plus or minus 2.9 ng/mL, the mean area under the curve over the dosing interval (AUC_{tau}) was 37.1 plus or minus 22.3 hour-ng/mL, and the mean average steady-state concentration was 3.1 plus or minus 1.9 ng/mL [11].

For the higher-concentration solution formulations used in androgenetic alopecia (5% and 7.5%), systemic exposure data from the Phase 2 and Phase 3 programs have not demonstrated clinically meaningful systemic absorption, though detailed pharmacokinetic results from the Phase 3 SCALP trials have not yet been published in peer-reviewed form.

5.2 Distribution

Plasma protein binding of clascoterone is 84 to 89 percent, independent of concentration over the range studied [12]. The volume of distribution has not been formally characterized in humans because the compound is not administered systemically; the low systemic concentrations achieved after topical application limit the interpretability of conventional distribution parameters.

5.3 Metabolism

The principal metabolic pathway is ester hydrolysis of the 17 α -propionate group by nonspecific plasma and tissue esterases, yielding cortexolone (11-deoxycortisol) and propionic acid [1, 2, 12]. Cortexolone is an endogenous steroid that enters the normal adrenal steroid metabolic pool and is cleared through established corticosteroid metabolic pathways. Following topical treatment with clascoterone cream 1%, plasma concentrations of cortexolone were detectable but generally at or below the lower limit of quantitation (0.5 ng/mL) [12].

The compound does not undergo significant cytochrome P450-mediated oxidative metabolism. In vitro studies in human liver microsomes and hepatocytes identified cortexolone as the primary metabolite, with no significant CYP-mediated oxidative products detected at clinically relevant concentrations [12]. This metabolic profile minimizes the potential for drug-drug interactions through CYP inhibition or induction.

5.4 Elimination

Formal renal and fecal excretion studies have not been conducted in humans because the compound is not systemically administered. The metabolite cortexolone is eliminated through established adrenal steroid metabolic and excretion pathways, predominantly renal excretion of conjugated metabolites.

5.5 Routes of administration

The compound is formulated exclusively for topical application. Two formulations are in clinical use or development:

Cream, 1%: Approved formulation for acne vulgaris (Winlevi). Applied as a thin, uniform layer to affected areas of the face twice daily. Each gram of cream contains 10 mg of clascoterone.

Solution, 5%: Investigational formulation for androgenetic alopecia (Breezula). Applied to affected scalp areas twice daily. Previously, a 7.5% solution was evaluated in Phase 2, but the 5% concentration was selected for Phase 3 development.

Oral, intravenous, intramuscular, and subcutaneous routes are not applicable. The compound is designed for and limited to topical use; systemic administration would result in rapid hydrolysis and loss of activity.

5.6 Special populations

Pediatric populations aged 9 to less than 12 years were included in the Phase 3 acne studies. HPA axis suppression was observed at a higher rate in this age group (approximately 7 to 10 percent) compared to adults (approximately 5 percent), reflecting the greater ratio of body surface area to body mass and the resultant higher relative systemic exposure [13]. The product is approved for patients aged 12 years and older; use in patients younger than 12 years is not recommended. Geriatric pharmacokinetics have not been formally studied; the target populations for both approved and investigational indications are predominantly adolescent and adult. No dose adjustment for hepatic or renal impairment is recommended given the minimal systemic exposure [12].

6. Preclinical Pharmacology

6.1 Hamster flank organ model

The hamster flank organ is a standard *in vivo* model for the evaluation of topical antiandrogen activity. The flank organs are paired sebaceous structures that respond to androgen stimulation with increases in size, pigmentation, and sebum production. In the Celasco et al. (2004) study, topical application of CB-03-01 produced dose-dependent inhibition of testosterone-stimulated flank organ growth [1]. The topical antiandrogen potency of CB-03-01 was approximately four times greater than progesterone, approximately three times greater than flutamide, approximately two times greater than finasteride, and approximately equivalent to cyproterone acetate. These potency rankings established CB-03-01 as among the most potent topical antiandrogens characterized in this model.

6.2 Systemic antiandrogen evaluation in the rat

After daily subcutaneous injection in the castrated rat supplemented with exogenous testosterone, CB-03-01 did not reduce seminal vesicle weight, prostate weight, or other androgen-dependent organ weights [1]. This finding confirmed the absence of systemic antiandrogen activity and established that the topical potency was not attributable to systemic absorption. The compound also did not affect body weight gain (absence of antianabolic activity), did not produce thymus involution or liver glycogen deposition (absence of glucocorticoid activity), and did not inhibit gonadotropin hypersecretion in parabiotic rats (absence of central antagonistic activity) [1].

6.3 *In vitro* androgen receptor studies

In AR transactivation reporter assays using human AR-expressing cell lines, CB-03-01 competitively inhibited DHT-driven luciferase expression with an IC₅₀ of approximately 0.4 to 1 micromolar [4, 5]. The compound did not activate the androgen receptor (absence of agonist activity) and demonstrated no significant cross-reactivity with the glucocorticoid receptor, mineralocorticoid receptor, or progesterone receptor at concentrations up to 10 micromolar.

6.4 Sebocyte studies

In primary human sebocyte cultures, CB-03-01 suppressed DHT-stimulated lipid synthesis in a concentration-dependent manner and reduced the expression of inflammatory cytokines including interleukin-6, interleukin-8, and tumor necrosis factor alpha [4, 17]. The anti-inflammatory activity is potentially relevant to the clinical efficacy in acne, as the inflammatory component of acne pathogenesis is driven in part by androgen-stimulated cytokine release from sebocytes and perilesional inflammatory cells.

6.5 Dermal papilla cell studies

Cortexolone 17alpha-propionate was characterized as an androgen receptor antagonist in human scalp dermal papilla cells by Rossi et al. (2019) [5]. The compound inhibited DHT-driven AR-regulated transcription and significantly reduced DHT-stimulated IL-6 production. Notably, clascoterone was significantly more effective than enzalutamide at inhibiting IL-6 synthesis in these cells, suggesting potential advantages in the anti-inflammatory component of the androgenetic alopecia mechanism [5]. The compound also reduced DHT-stimulated expression of dickkopf-1 (DKK-1), a Wnt signaling inhibitor implicated in hair follicle miniaturization.

6.6 5alpha-reductase studies

In reconstructed human epidermis models, CB-03-01 did not inhibit the conversion of testosterone to dihydrotestosterone, confirming the absence of 5alpha-reductase inhibitory activity [1]. The antiandrogen mechanism is therefore exclusively receptor-mediated.

7. Clinical Evidence Base

7.1 Acne vulgaris: Phase 2

A pilot randomized, double-blind, vehicle-controlled Phase 2b study compared cortexolone 17alpha-propionate 1% cream applied twice daily to vehicle and to tretinoin 0.05% cream in patients with moderate facial acne [3, 14]. CB-03-01 produced significant reductions in inflammatory and noninflammatory lesion counts compared to vehicle. In a direct comparison with tretinoin, clascoterone was more efficacious in decreasing inflammatory lesion counts (67.3 percent versus 50.7 percent reduction) and demonstrated a higher incidence of IGA treatment success (22.0 percent versus 12.0 percent), though the IGA difference did not reach statistical significance in this pilot-sized study [14].

7.2 Acne vulgaris: Phase 3

Two pivotal Phase 3 randomized, double-blind, vehicle-controlled trials (Study CB-03-01/25 and Study CB-03-01/26) evaluated clascoterone cream 1% applied twice daily for 12 weeks in patients aged 9 years and older with moderate to severe facial acne (IGA grade 3 or 4) [6, 7]. The trials enrolled a total of 1440 patients (approximately 720 per trial) randomized in a 1:1 ratio to clascoterone or vehicle.

The co-primary efficacy endpoints were the proportion of patients achieving IGA treatment success (IGA score of 0 or 1 with at least a two-grade reduction from baseline) and the absolute change from baseline in inflammatory and noninflammatory lesion counts at week 12.

Results across the pooled per-protocol population demonstrated:

IGA treatment success rates of 17.3 percent versus 3.8 percent (clascoterone versus vehicle) in patients aged 12 to 17 years (P less than 0.0001); 25.3 percent versus 8.6 percent in patients aged 18 years and older (P less than 0.0001); and 32.6 percent versus 10.1 percent in females aged 25 years and older (P equals 0.0009) [6, 7].

Significant reductions in both inflammatory and noninflammatory lesion counts were observed across age and sex subgroups. Treatment effect was evident as early as week 2 and continued to increase through week 8, with sustained effect to week

12. The onset of action was comparable to or faster than that observed with standard topical acne therapies.

Long-term safety and efficacy data through 12 months from open-label extension studies demonstrated sustained efficacy and a stable adverse-event profile without evidence of tachyphylaxis or cumulative toxicity [18].

7.3 Androgenetic alopecia: Phase 2

A Phase 2 dose-ranging study enrolled over 400 male subjects aged 18 to 55 with mild to moderate androgenetic alopecia (Hamilton-Norwood classification II to V) across multiple sites in Germany [8, 9]. Subjects were randomized to one of five arms: clascoterone solution at 2.5%, 5%, or 7.5% applied twice daily; clascoterone solution at 7.5% applied once daily; or vehicle applied twice daily. Treatment duration was 12 months with efficacy assessments at 6 and 12 months.

At 12 months, statistically significant improvements in target area hair count were observed in all active groups compared to vehicle. The mean improvement above placebo was 10.2 hairs for 2.5% twice daily, 13.8 hairs for 5% twice daily, 14.3 hairs for 7.5% twice daily, and 12.7 hairs for 7.5% once daily [8]. Hair width and hair growth assessment scores also showed statistically significant improvements. The safety profile was comparable to vehicle across all dose groups with no systemic antiandrogenic effects observed [8, 9].

7.4 Androgenetic alopecia: Phase 3

Two Phase 3 registration trials (SCALP-1 and SCALP-2) enrolled 1465 male patients with mild to moderate AGA across 51 sites in the United States and Europe [10]. The trials evaluated clascoterone topical solution 5% applied twice daily versus vehicle, with SCALP-1 assessing efficacy and safety over 6 months and SCALP-2 designed as a safety extension for an additional 6 months.

Topline 6-month results demonstrated statistically significant improvements in target area hair count in both trials. The relative improvement over vehicle was 5.39-fold (539 percent) in one trial and 1.68-fold (168 percent) in the second. The divergence in relative magnitudes was attributable to differences in baseline TAHC between the trial populations rather than inconsistent drug performance [10]. Treatment-emergent adverse events were similar between active treatment and ve-

hicle groups, and there was no evidence of clinically meaningful systemic androgen blockade, including absence of sexual dysfunction, gynecomastia, or feminization in male participants.

7.5 Sebum reduction

A 12-week interim analysis of facial sebum production in patients with acne vulgaris treated with clascoterone cream 1% demonstrated significant reductions in sebum excretion rates compared to vehicle [19]. The sebum reduction provides a measurable pharmacodynamic biomarker linking the androgen receptor antagonist mechanism to the clinical anti-acne effect and supports the mechanistic model of CB-03-01 as acting upstream of comedogenesis and inflammation by suppressing androgen-driven sebaceous lipogenesis.

8. Sourcing and Quality Verification

Pharmaceutical-grade clascoterone in the approved 1% cream formulation (Winlevi) is available by prescription in the United States for the acne indication. This is the highest quality and most rigorously characterized source, manufactured under current good manufacturing practices with lot-to-lot analytical certification.

Research-grade cortexolone 17alpha-propionate (CB-03-01) is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, catalog number 28392; MedChemExpress; Sigma-Aldrich; BOC Sciences; ChemScene; AbMole BioScience; others) at greater than 98 percent purity by HPLC [20]. Supply is typically in milligram to gram quantities as the free base. Pricing is moderate, in the range of \$100 to \$500 per gram of research-grade material depending on quantity and supplier.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 403.2)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structural identity, particularly the 17alpha-propionate ester signals
- Specific rotation measurement to confirm stereochemical integrity
- Thin-layer chromatography or HPLC comparison to an authenticated reference standard
- Residual solvent analysis by gas chromatography

Third-party analytical verification is recommended for research applications where dose-response precision is critical, as the ester bond is susceptible to hydrolysis during storage and handling, and partial degradation to cortexolone would reduce the effective antiandrogen potency of the preparation.

9. Reconstitution and Handling

CB-03-01 is a lipophilic compound with limited aqueous solubility. For research applications, the compound is typically supplied as a white to off-white crystalline powder and is reconstituted in organic solvents.

Stock solution preparation: Dimethyl sulfoxide (DMSO) is the standard solvent for concentrated stock solutions, with solubility exceeding 50 mg/mL. Stock solutions at 10 to 100 mM in DMSO are standard for in vitro work. Ethanol and methanol are suitable alternative solvents at lower concentrations. Aqueous solutions require the addition of a co-solvent (DMSO, ethanol, or polyethylene glycol) to achieve concentrations above approximately 0.1 mg/mL.

Storage: The solid compound should be stored at minus 20 degrees Celsius, protected from moisture and light. DMSO stock solutions should be stored at minus 20 degrees Celsius in tightly sealed vials; the compound is stable under these conditions for at least 12 months. Repeated freeze-thaw cycles should be minimized; aliquoting of stock solutions for single-use is recommended.

Handling precautions: The 17alpha-propionate ester bond is susceptible to hydrolysis under acidic or basic conditions and in the presence of esterases. Stock solutions should be prepared in anhydrous solvents, and aqueous working solutions should be prepared fresh and used promptly. Buffer pH should be maintained at neutral (pH 7.0 to 7.4) to minimize hydrolysis. Biological matrices (plasma, tissue homogenates) will rapidly hydrolyze the compound; if measurement of intact CB-03-01 in biological samples is required, immediate acidification or esterase inhibitor addition at the time of sample collection is necessary.

Topical formulation: For research applications requiring topical administration in animal models, the compound can be formulated in ethanol-propylene glycol vehicles, in hydroxypropyl cellulose gels, or in other standard dermatological vehicles. The commercial Winlevi formulation uses a cream base; the investigational AGA formulation uses an alcoholic solution base.

10. Stack Interaction Considerations

CB-03-01 has a favorable drug interaction profile attributable to its minimal systemic exposure and the absence of cytochrome P450-mediated metabolism. Investigators conducting research with clascoterone in combination with other compounds should consider the following:

CYP enzyme interactions: CB-03-01 does not undergo significant CYP-mediated metabolism and is not a meaningful inhibitor or inducer of CYP isoforms at clinically achieved systemic concentrations [12]. Drug-drug interactions through CYP pathways are not expected to be clinically significant.

Other topical antiandrogens: Concurrent topical application of CB-03-01 with other androgen receptor antagonists (topical spironolactone preparations, topical finasteride) would produce additive or synergistic AR antagonism at the local level but has not been studied in controlled clinical trials. The combination is pharmacologically plausible but uncharacterized.

Systemic antiandrogens: Concurrent use with systemic antiandrogens (oral spironolactone, oral cyproterone acetate, oral finasteride, oral dutasteride, enzalutamide, apalutamide) would produce additive antiandrogen activity. Although the systemic exposure to CB-03-01 is minimal, the theoretical additive effect should be considered, particularly in populations using oral antiandrogen therapy for polycystic ovary syndrome, acne, or androgenetic alopecia.

Topical corticosteroids: Concurrent use with topical corticosteroids may increase the risk of HPA axis suppression through additive hypothalamic-pituitary-adrenal axis effects. The cortexolone metabolite has weak intrinsic cortisol-like activity, and concurrent potent topical corticosteroid use may lower the threshold for clinically significant HPA axis suppression.

Topical retinoids: Concurrent use with topical retinoids (tretinoin, adapalene, tazarotene) is common in acne treatment and has been studied in the Phase 2 pilot trial, in which clascoterone was directly compared with tretinoin 0.05% cream [14]. No pharmacokinetic interaction was observed. The combination may produce additive efficacy through complementary mechanisms (antiandrogen plus retinoid) and additive local irritation.

Oral contraceptives and hormonal therapies: The minimal systemic exposure to clascoterone is not expected to interfere with the efficacy of hormonal contraceptives or other hormonal therapies. No interaction studies with oral contraceptives have been conducted, but the pharmacokinetic profile does not predict a clinically meaningful interaction.

Cosyntropin stimulation test: Investigators using clascoterone in research protocols should be aware that the compound may produce mild HPA axis suppression detectable on cosyntropin stimulation testing, potentially confounding endocrine research protocols that use this assay as an endpoint [13].

11. Adverse Events and Safety

11.1 Common adverse events (acne indication)

The principal adverse events observed in the Phase 3 acne trials were local application site reactions [6, 7, 18]:

- Erythema at the application site (approximately 12 percent)
- Skin dryness or scaling (approximately 10 percent)
- Pruritus at the application site (approximately 8 percent)
- Skin atrophy (rare, less than 1 percent, typically minimal and reversible)
- Contact dermatitis (rare)

These local reactions were mostly minimal to mild in severity and did not require discontinuation in the majority of cases. The incidence was modestly higher than vehicle but substantially lower than that observed with some standard topical acne therapies (tretinoin, benzoyl peroxide).

Systemic adverse events reported at low frequency included headache (approximately 2 percent), nasopharyngitis (approximately 2 percent), and oropharyngeal pain (approximately 1 percent), with incidences similar to vehicle [6, 7].

11.2 HPA axis suppression

The principal systemic safety signal is hypothalamic-pituitary-adrenal axis suppression, assessed by cosyntropin stimulation testing in dedicated pharmacokinetic studies [13]. In maximal-use pharmacokinetic studies:

- Overall, 5 of 69 clascoterone-treated patients had an abnormal cosyntropin stimulation test result at day 14
- Among adults, 1 of 20 (5 percent) showed HPA axis suppression
- Among patients aged 12 to less than 18 years, 2 of 22 (approximately 9 percent) showed suppression
- Among patients aged 9 to less than 12 years, 2 of 27 (approximately 7 percent) showed suppression

All cases of HPA axis suppression resolved within approximately 4 weeks of discontinuation, indicating reversibility [13]. The mechanism is presumably related to the cortexolone metabolite exerting weak cortisol-like activity at the adrenal axis, producing negative feedback on ACTH secretion. The clinical significance of this mild, reversible suppression in the general acne-treatment population is considered minimal, but the prescribing label includes a warning regarding HPA axis suppression, particularly in pediatric patients, patients applying to large body surface areas, and patients using occlusive dressings.

11.3 Hyperkalemia

Hyperkalemia was observed in approximately 5 percent of clascoterone-treated subjects and approximately 4 percent of vehicle-treated subjects in Phase 2 studies [12]. Causality was not established, as the incidence was similar between groups. The finding is noteworthy because systemic antiandrogens with mineralocorticoid receptor activity (spironolactone) produce clinically significant hyperkalemia; however, CB-03-01 lacks mineralocorticoid receptor activity and the hyperkalemia observed may represent baseline laboratory variation rather than a drug effect.

11.4 Absence of systemic antiandrogen effects

Across all clinical studies, including long-term (12-month) safety data, there were no reports of systemic antiandrogen effects such as decreased libido, erectile dysfunction, gynecomastia, feminization, or menstrual irregularity attributable to clascoterone [6, 7, 10, 18]. This absence is consistent with the minimal systemic exposure and rapid metabolic inactivation that define the peripheral selectivity of the compound.

11.5 Post-marketing experience

Post-marketing surveillance data accumulated since the August 2020 approval have been consistent with the clinical trial safety profile, with local skin reactions as the most frequently reported events and no unexpected systemic adverse effects identified [18]. The absence of post-marketing systemic safety signals provides additional reassurance regarding the peripheral selectivity mechanism.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five antiandrogen or androgen-modulating agents against CB-03-01, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal pharmacological approaches to androgen-dependent skin disorders, with priority given to compounds with substantive clinical evidence in acne or androgenetic alopecia.

12.1 Finasteride (oral, 1 mg for AGA; 5 mg for benign prostatic hyperplasia)

Mechanism: Selective inhibitor of 5alpha-reductase type 2 (and, at higher doses, type 1), blocking the conversion of testosterone to dihydrotestosterone. Systemically administered; reduces circulating and tissue DHT concentrations by approximately 70 percent at the 1 mg dose [21].

Novelty: Low. Finasteride has been available since 1992 for benign prostatic hyperplasia and since 1997 for androgenetic alopecia. The mechanism is well established and has been the subject of extensive clinical and mechanistic research over three decades.

Effect size: Moderate. In the pivotal AGA trials, finasteride 1 mg daily produced a mean increase in hair count of approximately 12 to 15 percent over baseline at 12 months [21]. Long-term studies (5 years) demonstrated maintenance of hair count in approximately 90 percent of treated subjects. The effect in acne has not been a registered indication, though systemic DHT reduction produces sebum suppression.

Promising potential: Stable. Finasteride is a mature, generically available compound with well-characterized efficacy and safety. It is not in active clinical development for new indications in dermatology. It remains the standard of care for male androgenetic alopecia.

Side-effect profile: The principal concern is sexual adverse events (decreased libido, erectile dysfunction, ejaculatory dysfunction) reported in approximately 1 to 5 percent of treated men in registration trials, with persistent post-finasteride syndrome reported in a subset of patients following discontinuation [21, 22]. Depression and suicidal ideation have been reported in post-marketing surveillance. These systemic effects are the primary limitation of finasteride and the principal driver of interest in topical alternatives such as CB-03-01.

Overall validation: High. Extensive clinical evidence across multiple large trials and decades of clinical use. The efficacy is well established; the safety profile is well characterized but includes systemic antiandrogen effects that are absent with CB-03-01.

Comparison to CB-03-01: Finasteride acts upstream of the androgen receptor (reducing DHT production) while CB-03-01 acts at the receptor (blocking DHT binding). Finasteride requires systemic administration and produces systemic DHT reduction with associated sexual side effects; CB-03-01 is topical with minimal systemic exposure and no reported sexual side effects. The effect sizes in AGA appear broadly comparable (finasteride approximately 12 to 15 hairs, CB-03-01 approximately 10 to 14 hairs above placebo at 12 months), though direct head-to-head comparison data are not available.

12.2 Spironolactone (oral, 25 to 200 mg for acne and AGA in females)

Mechanism: Non-selective mineralocorticoid receptor antagonist with antiandrogen activity through direct AR antagonism and inhibition of androgen biosynthesis. Used off-label in dermatology for female acne and female pattern hair loss [23].

Novelty: Low. Spironolactone has been used off-label for antiandrogen dermatological applications for over four decades. The mechanism is well established.

Effect size: Moderate to high. A systematic review and network meta-analysis found that spironolactone 200 mg was the most effective treatment for total acne lesion count reduction, ranking higher than clascoterone 1% twice daily [24]. However, the comparison is confounded by the systemic nature of spironolactone's activity. In female AGA, spironolactone produces modest improvements in hair density at doses of 100 to 200 mg daily.

Promising potential: Stable. Spironolactone is a generically available, inexpensive compound that is not in active development for new dermatological indications. Its use is limited to females due to feminizing effects in males.

Side-effect profile: Significant. Systemic antiandrogen effects include menstrual irregularity, breast tenderness, and feminization. Hyperkalemia is the principal medical safety concern, particularly in patients with renal impairment or concurrent potassium-sparing diuretic use. Teratogenicity (feminization of male fetuses) contraindicates use in pregnancy. These systemic effects are absent with topical CB-03-01 [23, 24].

Overall validation: Moderate. Extensive off-label clinical experience over decades, but limited randomized controlled trial data compared to CB-03-01. The OPAL trial (the first large randomized trial of spironolactone for acne) provided recent high-quality evidence supporting efficacy, but spironolactone has never received regulatory approval for any dermatological indication.

Comparison to CB-03-01: Spironolactone may produce greater overall antiandrogen effect through systemic activity but at the cost of significant systemic side effects. CB-03-01 offers a fundamentally different risk-benefit profile: topical application with minimal systemic exposure, applicable to both male and female patients, with no hyperkalemia risk, no feminizing effects, and no teratogenicity concern. The two agents are complementary rather than directly competitive.

12.3 Dutasteride (oral, 0.5 mg for benign prostatic hyperplasia; off-label for AGA)

Mechanism: Dual inhibitor of 5alpha-reductase types 1 and 2, producing approximately 90 percent reduction in circulating DHT [25]. More potent than finasteride in DHT suppression due to dual-isoform inhibition.

Novelty: Low. Approved since 2001 for benign prostatic hyperplasia. Used off-label for AGA.

Effect size: Moderate to high. Head-to-head studies suggest that dutasteride 0.5 mg produces modestly greater hair count increases than finasteride 1 mg in male AGA, consistent with the greater DHT suppression [25]. Effect sizes of approximately 15 to 20 hairs above placebo at 24 weeks have been reported.

Promising potential: Moderate. The compound is approved in Japan and South Korea for AGA; it is not approved for this indication in the United States or European Union but is widely used off-label. Active clinical development for AGA is limited.

Side-effect profile: Similar to finasteride but potentially more pronounced due to greater DHT suppression. Sexual adverse events, depression, and post-discontinuation syndrome have been reported [25]. The long half-life (approximately 5 weeks) prolongs the duration of adverse effects after discontinuation.

Overall validation: Moderate to high. Substantial clinical evidence for AGA, though less extensive than finasteride. The efficacy advantage over finasteride is modest and may not be clinically meaningful in all patients.

Comparison to CB-03-01: Dutasteride represents the maximally potent systemic DHT suppression approach, while CB-03-01 represents the topical, receptor-level antagonism approach. The systemic side effects and long half-life of dutasteride contrast sharply with the minimal systemic exposure and rapid local metabolism of CB-03-01. For patients who cannot tolerate or prefer to avoid systemic antiandrogen therapy, CB-03-01 offers a mechanistically distinct and safer alternative.

12.4 Enzalutamide (oral, 160 mg for prostate cancer)

Mechanism: Potent, non-steroidal androgen receptor antagonist that binds the AR ligand-binding domain, prevents nuclear translocation, and inhibits AR binding to DNA. Developed and approved for metastatic castration-resistant prostate cancer [26].

Novelty: Moderate in the prostate cancer context (approved 2012); high in the dermatological context. Enzalutamide has not been developed or studied for dermatological indications, but it serves as a mechanistic comparator to CB-03-01 as a direct AR antagonist.

Effect size: Not applicable to dermatological endpoints. In prostate cancer, enzalutamide produces substantial clinical benefit. In the in vitro dermal papilla cell study by Rossi et al. (2019), enzalutamide was significantly less effective than CB-03-01 at inhibiting DHT-stimulated IL-6 production [5], suggesting that systemic AR antagonist potency does not predict topical dermatological efficacy.

Promising potential: Not applicable for dermatological use. The compound is an oncology therapy with profound systemic antiandrogen effects that preclude dermatological application.

Side-effect profile: Severe systemic antiandrogen effects appropriate to the oncology context: fatigue, hot flashes, hypertension, seizure risk, and comprehensive androgen deprivation syndrome [26]. These effects are unacceptable for dermatological use and highlight the advantage of CB-03-01's peripheral selectivity.

Overall validation: High in oncology; absent in dermatology. Serves as a mechanistic reference compound demonstrating that potent systemic AR antagonism is not equivalent to topically selective AR antagonism.

Comparison to CB-03-01: Enzalutamide and CB-03-01 share the fundamental mechanism of competitive AR antagonism but differ fundamentally in design philosophy. CB-03-01 was designed for topical selectivity through metabolic inactivation; enzalutamide was designed for maximal systemic activity and metabolic stability. The Rossi et al. (2019) finding that CB-03-01 outperforms enzalutamide in dermal papilla IL-6 inhibition suggests that the steroidal structure of CB-03-01 confers additional activity beyond simple AR antagonism in skin target cells [5].

12.5 Topical minoxidil (2% or 5% solution/foam for AGA)

Mechanism: Potassium channel opener and vasodilator with direct stimulatory effects on hair follicle keratinocytes. The mechanism of hair growth promotion is not fully elucidated but is believed to involve increased follicular blood flow, stimulation of prostaglandin synthesis, and direct effects on the hair cycle (prolongation of anagen phase) [27]. Minoxidil is not an antiandrogen and does not interact with the androgen receptor.

Novelty: Low. Minoxidil has been available for AGA treatment since 1988. It is the oldest approved topical treatment for hair loss.

Effect size: Moderate. In registration trials, minoxidil 5% solution produced mean hair count increases of approximately 12 to 18 hairs above baseline at 48 weeks [27]. The effect is dependent on continued use; hair loss resumes upon discontinuation.

Promising potential: Stable. Minoxidil is a generically available, over-the-counter treatment that remains a first-line therapy for AGA. No novel development is anticipated.

Side-effect profile: Local irritation and hypertrichosis (unwanted facial hair growth, particularly in females) are the principal adverse effects. Systemic absorption can produce cardiovascular effects (hypotension, tachycardia) in sensitive individuals. The safety profile is generally favorable for a topical treatment [27].

Overall validation: High. Decades of clinical use and extensive evidence base. The compound is the standard topical comparator for any new AGA treatment.

Comparison to CB-03-01: Minoxidil and CB-03-01 operate through entirely different mechanisms: minoxidil is a vasodilator/growth stimulator, while CB-03-01 is an antiandrogen. The two agents are mechanistically complementary and could theoretically be used in combination for additive or synergistic benefit in AGA, though this combination has not been studied in controlled trials. CB-03-01 addresses the underlying androgenic driver of follicular miniaturization, while minoxidil promotes hair growth through androgen-independent pathways.

12.6 Comparator summary

The five comparators represent distinct pharmacological approaches to androgen-dependent skin disorders. **Finasteride** and **dutasteride** are systemic 5 α -reductase inhibitors that reduce DHT production; they are effective but carry the burden of systemic antiandrogen side effects including sexual dysfunction. **Spirolactone** is a systemic AR antagonist and mineralocorticoid receptor antagonist with substantial off-label dermatological use, limited to females due to feminizing effects. **Enzalutamide** is a potent systemic AR antagonist developed for oncology, serving as a mechanistic reference that demonstrates the infeasibility of systemic AR antagonism for dermatological applications. **Minoxidil** is a mechanistically distinct topical treatment for AGA that promotes hair growth through androgen-independent pathways.

CB-03-01 occupies a unique position in this landscape as the only topical androgen receptor antagonist with regulatory approval for a dermatological indication, the only antiandrogen with demonstrated peripheral selectivity through designed metabolic inactivation, and the only compound in this panel that can be used in both male and female patients without systemic antiandrogen effects. Its principal

limitation relative to the systemic agents is the inherent constraint of topical delivery (efficacy limited to the treated surface area) and the absence of long-term efficacy data exceeding 12 months in AGA. The compound's positioning as a topical, peripherally selective antiandrogen distinguishes it from all current alternatives and supports its continued clinical and research development as a complementary or alternative approach to androgen-dependent skin disorders.

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