

RESEARCH MONOGRAPH . COMPOUND PROFILE

PP-405

A proprietary small-molecule mitochondrial pyruvate carrier inhibitor developed at UCLA and advanced by Pelage Pharmaceuticals as a topical therapy for androgenetic alopecia, distinguished from existing treatments by a first-in-class metabolic mechanism that reactivates quiescent hair follicle stem cells through lactate dehydrogenase upregulation.

DOCUMENT	KDC-MN-1521
ISSUED	2026-05-15
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	First-in-class dual mitochondrial pyruvate carrier (MPC1/MPC2) inhibitor for topical hair follicle stem cell activation

ABSTRACT

PP-405 is a first-in-class, topically administered small-molecule inhibitor of the mitochondrial pyruvate carrier (MPC), under clinical development by Pelage Pharmaceuticals for the treatment of androgenetic alopecia (AGA) in men and women. The compound acts as a dual inhibitor of MPC1 and MPC2, blocking pyruvate import into the mitochondrial matrix and thereby redirecting cellular metabolism toward glycolysis with concomitant elevation of intracellular lactate through stimulation of lactate dehydrogenase (LDH) activity. This metabolic shift activates quiescent hair follicle stem cells (HFSCs) residing in the bulge region of the hair follicle, driving telogen-to-anagen transition and the initiation of new hair growth cycles. The mechanistic rationale derives from the seminal Flores et al. (2017) demonstration in *Nature Cell Biology* that HFSCs utilize glycolytic metabolism, produce substantially more lactate than other epidermal cell populations, and that genetic deletion of lactate dehydrogenase A (*Ldha*) prevents HFSC activation, while genetic deletion of mitochondrial pyruvate carrier 1 (*Mpc1*) accelerates the hair cycle in murine models [1]. The medicinal chemistry program at UCLA, led by Michael Jung in collaboration with Heather Christofk and William Lowry, subsequently developed a series of novel MPC inhibitors based on the cyano-cinnamate pharmacophore, advancing from the prototype UK-5099 through iterative structure-activity relationship optimization to produce compounds with markedly enhanced potency and skin-penetration characteristics [2].

PP-405 is the proprietary clinical candidate selected from this program. Its chemical structure has not been publicly disclosed; Pelage Pharmaceuticals has confirmed that PP-405 is structurally distinct from JXL-069, the published 7-azaindole-bearing MPC inhibitor (CAS 2260696-63-5) described in the Jeong et al. (2021) Journal of Medicinal Chemistry report, though both compounds originate from the same UCLA medicinal chemistry effort [2, 3]. The compound has been engineered for preferential skin penetration over systemic absorption, with reported selectivity of approximately 1,000-fold for dermal over plasma distribution. In clinical pharmacokinetic assessments, no PP-405 was detected in circulating blood plasma following topical scalp application at the clinical dose of 0.05%, and the compound is reported to be unstable in blood, providing an intrinsic pharmacokinetic safety margin against systemic exposure [4, 5].

Clinical development has proceeded through a Phase 1 safety and pharmacokinetic study completed in January 2024 and a Phase 2a randomized, multicenter, double-blind, vehicle-controlled efficacy trial (NCT06393452) in 78 adults with androgenetic alopecia. The Phase 1 study demonstrated proof of mechanism through scalp biopsy analysis showing statistically significant upregulation of Ki67-positive proliferating cells in the hair follicle bulge region after seven days of 0.05% PP-405 topical application, with concurrent increases in LDH activity in hair follicle stem cells [4]. Ex vivo human scalp tissue experiments presented at the American Academy of Dermatology 2024 Annual Meeting confirmed that single topical applications of PP-405 at concentrations as low as 0.006% increased LDH activity in HFSCs within 24 hours [4]. The Phase 2a trial reported that 31% of PP-405-treated men with higher-grade hair loss demonstrated greater than 20% increases in hair density at eight weeks following

four weeks of daily treatment, compared with 0% in the vehicle-control group; additionally, PP-405 induced new hair growth in areas where no hair was previously present, suggesting regenerative capacity beyond the follicle-preserving activity of existing therapies [5, 6]. The compound was well tolerated with no treatment-related systemic adverse events and no detectable systemic absorption.

Pelage Pharmaceuticals plans to initiate Phase 3 registration trials in 2026 to evaluate the safety and efficacy of PP-405 in both men and women with androgenetic alopecia. If successful, regulatory approval could be anticipated in the 2027 to 2029 timeframe. This monograph reviews the discovery and development history, the metabolic mechanism of action in molecular and cellular detail, the available pharmacokinetic and pharmacodynamic data, the preclinical and clinical evidence base, sourcing and handling considerations for the research-grade precursor compound JXL-069, stack-interaction considerations, adverse-event and safety data, and a comparative assessment of five alternative androgenetic alopecia therapies (minoxidil, finasteride, dutasteride, clascoterone, pyrilutamide) against PP-405 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proprietary name: PP-405 (also written PP405 or PP 405).

Developer: Pelage Pharmaceuticals, Inc. (Los Angeles, California, United States).

Development origin: University of California, Los Angeles (UCLA), Department of Chemistry and Biochemistry; Department of Molecular, Cell and Developmental Biology; and Department of Biological Chemistry, David Geffen School of Medicine.

Clinical trial registry identifier: NCT06393452 (ClinicalTrials.gov; Phase 2a, randomized, multicenter, double-blind, vehicle-controlled study in adults with androgenetic alopecia).

Chemical Abstracts Service registry number: Not publicly assigned. The chemical structure of PP-405 has not been disclosed. Pelage Pharmaceuticals has confirmed that PP-405 is not identical to JXL-069 (CAS 2260696-63-5) or to any other publicly disclosed MPC inhibitor from the UCLA program [3].

Related published compounds from the same medicinal chemistry program:

- JXL-069 (CAS 2260696-63-5): (E)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-cyanoacrylic acid. Molecular formula C₂₀H₁₁F₆N₃O₂. Molecular weight 439.31 g/mol. A potent MPC inhibitor (IC₅₀ approximately 40 to 43 nM) with a 7-azaindole heterocyclic core [2].
- UK-5099 (alpha-cyano-beta-(1-phenylindol-3-yl)acrylate): The prototype MPC inhibitor used in the foundational Flores et al. (2017) study to demonstrate topical acceleration of the murine hair cycle [1]. UK-5099 has lower potency and less favorable skin-penetration properties than the optimized JXL-series compounds.

1.2 Structural class and chemistry

PP-405 belongs to the class of cyano-cinnamate-derived mitochondrial pyruvate carrier inhibitors. Although the precise structure of PP-405 has not been publicly disclosed, the compound class is defined by the general pharmacophore of an al-

pha-cyano acrylic acid linked through the beta-carbon to an aromatic or heteroaromatic ring system bearing an N-alkyl substituent. The cyano-cinnamate moiety functions as a Michael acceptor and is the pharmacophoric element responsible for covalent or pseudo-covalent interaction with cysteine residues on the MPC1/MPC2 heterodimer [2, 7].

The medicinal chemistry optimization reported by Jeong et al. (2021) demonstrated that replacement of the indole core of UK-5099 with a 7-azaindole (pyrrolo[2,3-b]pyridine) heterocycle and substitution of the N1-alkyl group with a 3,5-bis(trifluoromethyl)benzyl moiety produced compounds with substantially enhanced MPC inhibitory potency and cellular lactate production activity compared to the prototype [2]. PP-405 is reported to have been further optimized beyond this published series for topical formulation properties, skin penetration, and metabolic instability in plasma (conferring the observed absence of systemic exposure) [3].

Physical properties (of the class): Compounds in this series are typically supplied as crystalline or amorphous solids. The cyano-acrylic acid functional group confers moderate aqueous solubility at physiological pH. The trifluoromethyl substituents (present in JXL-069 and related analogues) increase lipophilicity and skin penetration. Topical formulation of PP-405 is as a 0.05% gel for once-daily scalp application [4, 5].

1.3 Synthesis

The synthesis of MPC inhibitors in the JXL series, as reported by Jeong et al. (2021), proceeds through a convergent route involving: (a) N-alkylation of the 7-azaindole (or indole) nitrogen with the appropriate benzyl halide; (b) Vilsmeier-Haack formylation at the 3-position of the heterocyclic ring to generate the aldehyde intermediate; and (c) Knoevenagel condensation of the aldehyde with cyanoacetic acid to install the (E)-2-cyanoacrylic acid pharmacophore [2]. The Knoevenagel condensation is typically conducted in the presence of ammonium acetate or piperidine as catalyst in acetic acid or ethanol solvent, yielding the thermodynamically favored (E)-isomer. Products are purified by recrystallization or column chromatography and characterized by nuclear magnetic resonance spectroscopy, high-resolution mass spectrometry, and high-performance liquid chromatography. The synthetic route for the clinical candidate PP-405 has not been publicly disclosed but is presumed to follow analogous chemistry given the shared pharmacophore class.

2. Abstract

PP-405 is a first-in-class mitochondrial pyruvate carrier (MPC) inhibitor under clinical development by Pelage Pharmaceuticals for the topical treatment of androgenetic alopecia. The compound targets MPC1 and MPC2, the two subunits of the heterodimeric inner mitochondrial membrane carrier responsible for importing pyruvate into the mitochondrial matrix for oxidative phosphorylation. By inhibiting MPC-mediated pyruvate transport, PP-405 redirects cellular metabolism in hair follicle stem cells (HFSCs) toward aerobic glycolysis, producing elevated intracellular lactate concentrations through stimulation of lactate dehydrogenase (LDH) activity. This metabolic shift activates quiescent HFSCs in the bulge niche of the hair follicle, driving transition from the resting telogen phase to the active anagen growth phase [1, 4].

The mechanistic rationale is grounded in the Flores et al. (2017) discovery that HFSCs are metabolically distinct from surrounding epidermal cells, relying on glycolytic metabolism and lactate production for activation [1]. Genetic ablation of *Mpc1* in murine HFSCs accelerated the hair cycle, while genetic deletion of *Ldha* prevented HFSC activation entirely. Topical application of the prototype MPC inhibitor UK-5099 to murine skin in telogen produced robust hair cycle acceleration within 6 to 9 days [1]. The UCLA medicinal chemistry program subsequently optimized the cyano-cinnamate scaffold for potency, selectivity, skin penetration, and plasma instability, producing the clinical candidate PP-405 [2, 3].

PP-405 is formulated as a 0.05% topical gel for once-daily scalp application. The compound demonstrates preferential dermal distribution with no detectable systemic plasma levels at the clinical dose, a pharmacokinetic profile engineered through deliberate optimization for skin penetration and plasma metabolic instability [4, 5]. This design eliminates the systemic adverse-event concerns that limit patient acceptance of oral finasteride (sexual dysfunction) and oral dutasteride (similar androgenic adverse events), positioning PP-405 as a topical-only therapy with a mechanistic approach entirely orthogonal to the androgen-pathway interventions that dominate the current treatment landscape.

Clinical development has produced two completed studies. The Phase 1 study (completed January 2024) demonstrated safety, tolerability, and proof of mechanism through scalp biopsy evidence of Ki67-positive HFSC proliferation after seven days of treatment [4]. The Phase 2a trial (NCT06393452) in 78 adults with androgenetic alopecia demonstrated that 31% of treated subjects with higher-grade hair loss achieved greater than 20% increases in hair density at eight weeks (versus 0% on vehicle control), with evidence of new hair growth in previously bare areas [5, 6]. Phase 3 registration trials are planned for 2026.

3. Discovery and Development History

3.1 Origin: metabolic control of hair follicle stem cell fate

The discovery of PP-405 traces to a fundamental investigation of stem cell metabolism at UCLA. In 2017, Aimee Flores, John Schell, Ajit Divakaruni, and colleagues in the laboratories of Heather Christofk (Department of Biological Chemistry) and William Lowry (Department of Molecular, Cell and Developmental Biology) published a landmark study in *Nature Cell Biology* demonstrating that lactate dehydrogenase activity is a metabolic driver of hair follicle stem cell activation [1]. The key findings were: (a) HFSCs in the bulge niche utilize glycolytic metabolism and produce substantially more lactate than neighboring epidermal cell populations; (b) conditional genetic deletion of *Ldha* in HFSCs prevented their activation and blocked hair cycle progression; (c) conditional genetic deletion of *Mpc1* in HFSCs, which forces pyruvate into the cytoplasmic LDH pathway rather than into mitochondrial oxidative phosphorylation, accelerated HFSC activation and the hair cycle; and (d) topical application of the known MPC inhibitor UK-5099 to murine dorsal skin during telogen accelerated hair cycle entry within 6 to 9 days [1].

These findings established the mitochondrial pyruvate carrier as a druggable target for hair growth modulation and provided the conceptual foundation for a small-molecule therapeutic program.

3.2 Medicinal chemistry optimization

The translation from the prototype UK-5099 to a clinical candidate required substantial medicinal chemistry optimization. Michael Jung (Department of Chemistry and Biochemistry, UCLA) led the structure-activity relationship program in collaboration with Christofk and Lowry. The results were published by Jeong et al. in the *Journal of Medicinal Chemistry* in 2021 [2].

The optimization explored four structural positions: the N1-alkyl substituent on the heterocyclic nitrogen; substituents on the indole or azaindole core ring; variation of the aromatic and heteroaromatic core structure itself (indole, 4-azaindole, 6-azaindole, 7-azaindole); and modifications to the Michael acceptor pharmacophore. Key findings included the discovery that 3,5-bis(trifluoromethyl)benzyl substitu-

tion at N1 produced markedly enhanced cellular lactate production activity compared to the UK-5099 parent, and that the 7-azaindole heterocyclic core (pyrrolo[2,3-b]pyridine) conferred superior MPC inhibition among the azaindole positional isomers [2]. The optimized compound JXL-069 demonstrated MPC inhibitory potency with an IC₅₀ of approximately 40 to 43 nanomolar, representing a substantial improvement over UK-5099, and showed robust topical hair cycle acceleration in murine models [2].

3.3 Founding of Pelage Pharmaceuticals

Pelage Pharmaceuticals was founded in 2018 as a UCLA spinout by Lowry, Christofk, and Jung to advance the clinical development of MPC inhibitor therapeutics for hair loss [8]. The company licensed the underlying technology from UCLA and undertook further proprietary optimization to produce the clinical candidate PP-405, which is structurally distinct from JXL-069 and from other published compounds in the series [3]. The proprietary optimization focused on topical formulation, skin-penetration enhancement, and engineering of plasma metabolic instability to ensure dermal-restricted pharmacology.

3.4 Clinical development timeline

Pelage initiated the first-in-human Phase 1 clinical study of PP-405 in 2023 in Orange County, California. The Phase 1 trial evaluated safety, tolerability, and pharmacokinetics of 0.05% PP-405 topical gel in adults with androgenetic alopecia, with scalp biopsy endpoints to assess proof of mechanism. The study was completed in January 2024 [4].

Late-breaking data from the Phase 1 study and from ex vivo human scalp tissue experiments were presented at the American Academy of Dermatology (AAD) 2024 Annual Meeting in San Diego in March 2024 [4]. The presentation reported that PP-405 activated human hair follicle stem cells both ex vivo and in vivo, establishing proof of mechanism in human tissue for the first time.

The Phase 2a randomized, multicenter, double-blind, vehicle-controlled trial (NCT06393452) was initiated in mid-2024, enrolling 78 adults (men and women) with androgenetic alopecia. Results were announced in June 2025, reporting positive primary safety and secondary pharmacokinetic and efficacy endpoints [5, 6]. Phase 3 registration trials are planned for initiation in 2026.

4. Mechanism of Action

PP-405 acts through inhibition of the mitochondrial pyruvate carrier, a mechanism that is entirely distinct from the androgen-pathway modulation (finasteride, dutasteride, clascoterone, pyrilutamide) and the vasodilatory/potassium channel-opening mechanism (minoxidil) employed by existing androgenetic alopecia therapies. The pharmacology is described at three levels: the molecular target, the cellular metabolic consequences, and the downstream stem cell biology.

4.1 Mitochondrial pyruvate carrier: molecular target

The mitochondrial pyruvate carrier is a heterodimeric complex of MPC1 and MPC2, located in the inner mitochondrial membrane. It is the obligate transporter for pyruvate entry into the mitochondrial matrix, where pyruvate undergoes oxidative decarboxylation by the pyruvate dehydrogenase complex and enters the tricarboxylic acid (TCA) cycle. Both MPC1 and MPC2 are required for functional carrier activity; loss of either subunit abolishes mitochondrial pyruvate import [7, 9].

PP-405 is reported to be a dual inhibitor of MPC1 and MPC2, blocking pyruvate transport across the inner mitochondrial membrane [3, 5]. The cyano-cinnamate pharmacophore characteristic of this compound class interacts with conserved cysteine residues on the MPC complex, producing sustained inhibition of pyruvate import. In vitro studies with the related compound JXL-069 demonstrated nanomolar MPC inhibitory potency (IC₅₀ approximately 40 to 43 nM) and dose-dependent increases in cellular lactate production in treated cell systems [2].

4.2 Cellular metabolic consequences

Inhibition of MPC-mediated pyruvate import into mitochondria produces a metabolic shift in treated cells. Pyruvate, unable to enter the mitochondrial matrix, accumulates in the cytoplasm. Cytoplasmic pyruvate is the substrate for lactate dehydrogenase (LDH), which reduces pyruvate to lactate with concomitant oxidation of NADH to NAD⁺. The net metabolic consequence is: (a) increased cytoplasmic lactate concentration; (b) increased LDH enzymatic activity; (c) regeneration of cyto-

plasmic NAD⁺, which sustains glycolytic flux; (d) decreased mitochondrial oxidative phosphorylation; and (e) a global shift toward aerobic glycolysis (the Warburg-like metabolic phenotype) [1, 2].

Metabolomic analysis of murine HFSCs treated with UK-5099 confirmed increased total cellular lactate levels in sorted stem cell populations [1]. The LDH activity increase was confirmed in human tissue by the ex vivo scalp experiments presented at AAD 2024, in which single topical applications of PP-405 at concentrations as low as 0.006% increased LDH activity in hair follicle stem cells within 24 hours [4].

4.3 Hair follicle stem cell activation

The hair follicle cycles between three principal phases: anagen (active growth, lasting 2 to 6 years on the human scalp), catagen (regression, approximately 2 weeks), and telogen (resting, 2 to 4 months). In androgenetic alopecia, the anagen phase progressively shortens and the telogen phase lengthens, producing progressive miniaturization of terminal hairs to vellus hairs and eventual follicular quiescence [10].

Hair follicle stem cells reside in the bulge region of the outer root sheath. These cells are activated at the telogen-to-anagen transition to generate the transit-amplifying matrix cells that drive new hair shaft production. The Flores et al. (2017) study established that HFSCs are metabolically poised for glycolysis relative to other epidermal cell types, and that lactate availability functions as a metabolic gate controlling their activation state [1].

The mechanistic chain from PP-405 application to hair growth is therefore: topical PP-405 penetrates the epidermis and reaches the hair follicle bulge; MPC inhibition in bulge HFSCs blocks mitochondrial pyruvate uptake; cytoplasmic pyruvate accumulates and is converted to lactate by LDH; elevated intracellular lactate concentration crosses the activation threshold for HFSCs; activated HFSCs initiate the proliferative program and generate transit-amplifying cells; the follicle transitions from telogen to anagen and produces a new hair shaft [1, 4].

The Flores et al. study further demonstrated that this mechanism involves downstream signaling through Myc, a transcription factor that promotes glycolytic gene expression and is itself elevated in HFSCs upon lactate-driven activation [1]. Small

molecules that increase Myc activity or inhibit MPC function both produced hair cycle acceleration in murine models, establishing convergent pathway validation.

4.4 Differentiation from existing mechanisms

The MPC-inhibition mechanism is orthogonal to the two established mechanistic approaches in androgenetic alopecia therapy. Finasteride and dutasteride inhibit type II and types I/II 5-alpha reductase, respectively, reducing conversion of testosterone to dihydrotestosterone (DHT), the primary androgen driving follicular miniaturization. Minoxidil acts through potassium channel opening and vasodilation to improve follicular blood supply and through poorly characterized direct effects on follicular keratinocytes. Neither mechanism addresses the metabolic quiescence of HFSCs directly. PP-405, by targeting the metabolic machinery of the stem cells themselves, offers a complementary and potentially additive approach that may be combined with androgen-pathway or vasodilatory therapies without mechanistic redundancy.

5. Pharmacokinetics and Routes of Administration

5.1 Route of administration

PP-405 is administered exclusively by the topical route as a 0.05% gel applied once daily to the affected areas of the scalp. No oral, parenteral, or other routes of administration have been studied or proposed for clinical use [4, 5].

5.2 Dermal absorption and distribution

PP-405 has been engineered for preferential dermal penetration. The compound is reported to achieve approximately 1,000-fold greater distribution into skin relative to blood [3, 5]. This selectivity is attributed to deliberate medicinal chemistry optimization of physicochemical properties (lipophilicity, molecular weight, trifluoromethyl substitution pattern) to favor partitioning into the stratum corneum and dermis while maintaining metabolic instability in plasma.

In the Phase 1 clinical study, no PP-405 was detected in circulating blood plasma at any time point following topical scalp application at the 0.05% clinical dose, confirming the absence of clinically meaningful systemic absorption [4, 5]. This pharmacokinetic profile is a distinguishing feature of the compound: it eliminates the systemic exposure that produces the androgen-related adverse events of oral finasteride and dutasteride and the cardiovascular concerns that limit systemic minoxidil use.

5.3 Metabolism and elimination

PP-405 is reported to be metabolically unstable in blood, undergoing rapid degradation if absorbed systemically [3, 5]. The specific metabolic pathways (enzymatic hydrolysis, plasma esterase activity, cytochrome P450-mediated biotransformation, or other mechanisms) have not been publicly disclosed. The plasma instability is an engineered property that contributes to the dermal-restricted pharmacology.

Local metabolism within the skin has not been characterized in published data. The duration of MPC inhibitory activity in the hair follicle following a single topical application has not been precisely defined, though the Phase 1 biopsy data demonstrating Ki67 upregulation after seven days of daily application suggests sustained target engagement at the follicular level with once-daily dosing [4].

5.4 Pharmacokinetic-pharmacodynamic relationship

The Phase 1 study met its primary pharmacokinetic endpoint, confirming the target pharmacokinetic profile of no detectable systemic levels [4]. The pharmacodynamic relationship was established through scalp biopsy endpoints: seven days of 0.05% PP-405 application produced statistically significant increases in Ki67-positive (proliferating) cells in the hair follicle bulge, concurrent with increased LDH activity in HFSCs [4]. In ex vivo human facelift skin, LDH activity increases were detectable within 24 hours of a single application at concentrations as low as 0.006% [4].

5.5 Special populations

No specific pharmacokinetic studies in special populations (renal impairment, hepatic impairment, pediatric, geriatric) have been publicly reported. Given the absence of systemic absorption at the clinical dose, hepatic and renal impairment are not expected to alter the pharmacokinetic profile. Pediatric use has not been studied. The Phase 2a trial enrolled adults aged 18 to 55 years [5].

6. Preclinical Pharmacology

6.1 In vitro studies

The in vitro pharmacology of MPC inhibitors from the UCLA program has been characterized using several assay systems. Cellular lactate production assays in standard cell lines (HEK293, fibroblasts) demonstrated dose-dependent increases in extracellular lactate following treatment with JXL-series compounds [2]. JXL-069 showed substantially greater lactate production stimulation than the parent UK-5099 at equivalent concentrations.

MPC inhibitory activity was assessed using mitochondrial pyruvate uptake assays and cellular metabolomic profiling. JXL-069 demonstrated an IC₅₀ of approximately 40 to 43 nanomolar for MPC inhibition, compared to low-micromolar potency for UK-5099 [2]. The approximately 100-fold improvement in potency across the structure-activity relationship optimization was attributed principally to the 3,5-bis(trifluoromethyl)benzyl N1 substituent and the 7-azaindole core.

Ex vivo human scalp tissue studies presented at AAD 2024 demonstrated that PP-405 at 0.006% and 0.06% concentrations increased LDH activity in hair follicle stem cells within 24 hours of a single topical application [4]. The LDH activity increase was accompanied by a statistically significant increase in Ki67 signal in the hair follicle bulge, indicating proliferative activation of HFSCs in human tissue.

6.2 In vivo murine studies

The foundational in vivo pharmacology was established in the Flores et al. (2017) study using C57BL/6 mice [1]. Topical application of UK-5099 to murine dorsal skin during telogen produced robust hair cycle acceleration, with visible anagen entry occurring within 6 to 9 days of treatment. The accelerated hair cycle was confirmed by histological analysis showing anagen-phase follicular morphology with active matrix cell proliferation.

Genetic validation was provided by conditional Mpc1 knockout mice (K14-Cre; Mpc1^{fl/fl}), in which HFSC-specific deletion of MPC1 reproduced the accelerated hair cycle phenotype observed with pharmacological MPC inhibition [1].

Conversely, conditional *Ldha* knockout mice (K14-Cre; *Ldha*^{fl/fl}) showed delayed or absent HFSC activation, confirming that lactate production is required downstream of MPC inhibition for the hair cycle-accelerating effect.

The Jeong et al. (2021) study extended these findings to the optimized JXL-series compounds, demonstrating that topical JXL-069 and related analogues produced dose-dependent hair cycle acceleration in murine models with potency correlated to their *in vitro* MPC inhibitory activity [2].

6.3 Toxicology

Preclinical toxicology data for PP-405 have not been disclosed in published form. The IND-enabling toxicology studies required for FDA authorization of the Phase 1 trial were completed prior to 2023 but remain proprietary. The absence of systemic absorption at the clinical dose suggests that systemic toxicology findings are likely minimal, and the favorable safety profile observed in Phase 1 and Phase 2a clinical studies is consistent with a topical compound without meaningful systemic exposure [4, 5].

7. Clinical Evidence Base

7.1 Phase 1: safety, pharmacokinetics, and proof of mechanism

The Phase 1 clinical study of PP-405 was conducted at sites in Orange County, California, with completion in January 2024 [4]. The study enrolled adults with androgenetic alopecia and evaluated 0.05% PP-405 topical gel applied once daily.

Primary endpoints were safety and tolerability. PP-405 was well tolerated with no treatment-related systemic adverse events reported. The target pharmacokinetic profile was achieved: no PP-405 was detected in circulating blood plasma at any time point [4].

Proof-of-mechanism endpoints were assessed through scalp biopsies. After seven days of treatment, scalp biopsies from PP-405-treated areas showed statistically significant increases in Ki67-positive cells in the hair follicle bulge region compared to baseline and to vehicle-treated areas [4]. Ki67 is a well-established marker of cellular proliferation and was used here as a surrogate for HFSC activation. Concurrent increases in LDH activity were observed in the follicular stem cell compartment, confirming target engagement and the expected metabolic pharmacodynamic effect.

The Phase 1 results and complementary ex vivo human scalp tissue data were presented as late-breaking data at the AAD 2024 Annual Meeting in San Diego [4].

7.2 Phase 2a: efficacy in androgenetic alopecia

The Phase 2a study (NCT06393452) was a randomized, multicenter, double-blind, vehicle-controlled trial enrolling 78 adults aged 18 to 55 with androgenetic alopecia [5, 6]. Subjects were randomized to receive 0.05% PP-405 topical gel or vehicle control applied once daily for four weeks, with efficacy assessments at four, eight, and twelve weeks.

Primary endpoint: The study met its primary safety endpoint, with PP-405 demonstrating a favorable tolerability profile and no treatment-related systemic adverse events. The primary secondary pharmacokinetic endpoint was also met, confirming no detectable PP-405 in blood plasma [5].

Efficacy results: Among PP-405-treated subjects with higher-grade hair loss, 31% demonstrated greater than 20% increases in hair density at the eight-week assessment (four weeks after completion of the treatment period), compared with 0% in the vehicle-control group [5, 6]. The persistence of hair density increases four weeks after cessation of treatment is consistent with a stem cell activation mechanism (anagen induction) rather than a symptomatic vasodilatory effect, which would be expected to reverse on treatment discontinuation.

Regenerative signal: PP-405 induced new hair growth in scalp areas where no hair had previously been present, a finding reported by Pelage as evidence of regenerative capacity [6]. This observation distinguishes PP-405 from existing therapies (minoxidil, finasteride) that predominantly maintain or modestly improve existing hair density but do not typically produce de novo hair growth in areas of complete follicular quiescence.

Subgroup analysis: The efficacy signal was most pronounced in subjects with higher Norwood-Hamilton grade hair loss, suggesting that PP-405 may activate deeply quiescent follicles that have entered prolonged telogen or kenogen [5, 6].

7.3 Planned Phase 3 program

Pelage Pharmaceuticals has announced plans to initiate Phase 3 registration trials in 2026 to evaluate the safety and efficacy of PP-405 in men and women with androgenetic alopecia [5, 6]. The Phase 3 program is expected to include larger, longer-duration trials powered for hair count and hair density primary endpoints consistent with FDA registration requirements for alopecia therapies. If the Phase 3 program is successful, regulatory approval could be anticipated in the 2027 to 2029 timeframe.

8. Sourcing and Quality Verification

8.1 Clinical-grade PP-405

PP-405 is a proprietary investigational compound available exclusively through Pelage Pharmaceuticals for clinical trial use. The compound is not available as a research reagent from any commercial chemical supplier. The chemical structure has not been disclosed, and independent synthesis is not possible without access to the proprietary structural information [3].

8.2 Research-grade JXL-069 (related compound)

JXL-069, the published MPC inhibitor from the same UCLA medicinal chemistry program, is available from multiple research chemical suppliers (Aobious, MedKoo Biosciences, and others) at greater than 98% purity by HPLC, supplied as a solid or in solution [2]. CAS number 2260696-63-5. JXL-069 is suitable for in vitro and in vivo research on MPC inhibition and HFSC activation pharmacology but is not equivalent to PP-405 for clinical research purposes [3].

Investigators employing JXL-069 for research should confirm:

- High-performance liquid chromatography area-percent purity (greater than 98%)
- High-resolution mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ of 440.08 for $C_{20}H_{12}F_6N_3O_2$)
- Nuclear magnetic resonance spectroscopy confirmation of structure and (E)-isomer geometry
- Residual solvent analysis by gas chromatography
- Assessment of the (E/Z) isomer ratio, as the Knoevenagel condensation may produce minor amounts of the (Z)-isomer depending on reaction conditions

8.3 Research-grade UK-5099

UK-5099 (alpha-cyano-beta-(1-phenylindol-3-yl)acrylate), the prototype MPC inhibitor used in the foundational Flores et al. study, is widely available from commercial suppliers (Sigma-Aldrich, Tocris, Cayman Chemical, MedChemExpress) at research grade. UK-5099 is suitable for replication of the published murine hair cycle acceleration studies and for in vitro MPC inhibition experiments, though its lower potency (low micromolar IC₅₀ versus approximately 40 nM for JXL-069) and less favorable skin-penetration characteristics limit its translational utility relative to the optimized compounds [1, 2].

8.4 Caution regarding gray-market PP-405

Following the public disclosure of Phase 2a results, multiple online vendors have marketed products labeled as "PP-405" or "PP405 (JXL-069)." Pelage Pharmaceuticals has explicitly stated that PP-405 is not JXL-069, and any product sold under the PP-405 name by a third party is not the clinical candidate [3]. Investigators and consumers should be aware that gray-market products labeled as PP-405 are of unknown composition, may contain JXL-069, other MPC inhibitors, or unrelated substances, and have not undergone the pharmaceutical-grade manufacturing, quality control, or stability testing required for clinical use. Third-party analytical verification of any gray-market product would require knowledge of the target compound structure, which is not publicly available.

9. Reconstitution and Handling

9.1 Clinical formulation

PP-405 is formulated as a 0.05% topical gel for once-daily application to the scalp. The clinical formulation details (vehicle composition, preservatives, pH, viscosity) have not been publicly disclosed. The gel formulation is applied to affected areas of the scalp and allowed to dry; specific application instructions (wet or dry scalp, post-application restrictions) have not been published.

9.2 Research-grade JXL-069 handling

For investigators using the related compound JXL-069 for in vitro or in vivo research, the following handling guidelines apply based on the compound class properties:

Solubility: JXL-069 is soluble in dimethyl sulfoxide (DMSO) at concentrations of 10 to 50 mM. For aqueous dilutions, the compound should be dissolved first in DMSO and then diluted into aqueous buffer or cell culture medium, with final DMSO concentration maintained below 0.1% to 0.5% to avoid vehicle-mediated cellular effects.

Storage: Solid material should be stored at -20 degrees Celsius in a desiccated container protected from light. Stock solutions in DMSO should be stored at -20 degrees Celsius in single-use aliquots to avoid freeze-thaw degradation. The cyanoacrylic acid functional group may be susceptible to hydrolysis at alkaline pH; stock solutions should be prepared in neutral to mildly acidic conditions.

Topical formulation for murine studies: Published protocols for topical MPC inhibitor application in mice (Flores et al. 2017) employed dissolution in DMSO or in propylene glycol-based vehicles for application to shaved dorsal skin [1]. Investigators replicating these protocols should optimize vehicle composition for their specific experimental system.

10. Stack Interaction Considerations

10.1 Mechanistic interaction potential

PP-405 targets mitochondrial metabolism in hair follicle stem cells through a mechanism distinct from all other approved and investigational alopecia therapies. The absence of systemic absorption at the clinical dose renders pharmacokinetic drug-drug interactions extremely unlikely. The principal interaction considerations are therefore pharmacodynamic and relate to potential additive or synergistic effects with co-applied topical therapies.

Minoxidil: The vasodilatory and potassium channel-opening mechanism of minoxidil is mechanistically orthogonal to MPC inhibition. Co-application of PP-405 and topical minoxidil has not been formally studied but represents a rational combination strategy. The two therapies target different aspects of the hair loss process: PP-405 addresses HFSC metabolic quiescence, while minoxidil addresses follicular blood supply and direct keratinocyte effects. No antagonistic interaction is predicted.

Topical finasteride: Topical finasteride reduces local DHT production through 5-alpha reductase inhibition. This anti-androgenic mechanism is orthogonal to MPC inhibition. Co-application has not been studied; no pharmacodynamic antagonism is predicted, and additive or synergistic effects are plausible given the complementary mechanisms.

Clascoterone: Topical clascoterone (Winlevi) is an androgen receptor antagonist approved for acne and under study for androgenetic alopecia. The mechanism is complementary to PP-405; no interaction is predicted.

Pyrilutamide: Topical pyrilutamide is an androgen receptor antagonist in Phase 3 development for androgenetic alopecia. No interaction with MPC inhibition is predicted.

10.2 Formulation compatibility

Co-application of multiple topical products to the scalp introduces potential formulation-compatibility concerns (pH shifts, vehicle interactions, altered penetration kinetics) that are distinct from pharmacological interactions. Investigators or clinicians planning combination topical protocols should consider applying the agents at different times of day or with sufficient separation intervals to avoid direct mixing on the scalp surface.

10.3 Systemic drug interactions

Given the confirmed absence of detectable systemic PP-405 levels following topical application, cytochrome P450-mediated drug-drug interactions are not expected with any co-administered systemic medication. No dose adjustments are anticipated for concurrent oral medications including oral finasteride, dutasteride, or other systemically administered therapies.

11. Adverse Events and Safety

11.1 Phase 1 safety data

The Phase 1 study of 0.05% PP-405 topical gel demonstrated a favorable safety profile [4]. No treatment-related systemic adverse events were reported. No PP-405 was detected in blood plasma, confirming the absence of systemic exposure. Local tolerability was acceptable; specific rates and types of local adverse events (erythema, pruritus, irritation, dryness) have not been published in detail.

11.2 Phase 2a safety data

The Phase 2a trial (NCT06393452) met its primary safety endpoint [5, 6]. PP-405 was well tolerated across the treatment period and follow-up. No treatment-related systemic adverse events were reported. No systemic absorption was detected. The specific incidence and characterization of local adverse events have not been published in granular detail in the available data.

11.3 Theoretical safety considerations

Metabolic specificity: MPC inhibition affects a fundamental metabolic pathway (mitochondrial pyruvate import) that operates in all nucleated cells. The safety of PP-405 as a topical agent depends on dermal-restricted distribution and the absence of systemic levels. If systemic exposure were to occur (through compromised skin barrier, excessive application, or application to inflamed or broken skin), the theoretical risk would include metabolic perturbation in tissues dependent on oxidative phosphorylation. The engineered plasma instability provides a pharmacokinetic buffer against this scenario [3, 5].

Oncogenic considerations: The Warburg effect (aerobic glycolysis with elevated lactate production) is a hallmark metabolic phenotype of many cancer cells. Chronic MPC inhibition could theoretically promote a Warburg-like metabolic state in treated cells. However, MPC inhibition itself is not oncogenic; the Warburg effect in cancer is a downstream consequence of oncogenic driver mutations, not a primary transforming event. Published data from genetic Mpc1-knockout mouse mod-

els have not reported increased tumorigenesis in the skin or hair follicle compartment [1]. Long-term safety monitoring in Phase 3 and post-marketing studies will be important to confirm the absence of proliferative risk with chronic topical MPC inhibition.

Reproductive and teratogenic considerations: No reproductive or developmental toxicology data have been publicly reported. The absence of systemic absorption at the clinical dose suggests minimal fetal exposure risk, but formal studies would be required before use in pregnancy.

11.4 Comparison to existing therapy safety profiles

The safety profile of PP-405 compares favorably to existing androgenetic alopecia therapies:

- **Oral finasteride** (1 mg daily): associated with sexual adverse events (decreased libido, erectile dysfunction, ejaculation disorders) in approximately 2 to 4% of patients, with persistent post-finasteride syndrome reported in rare cases. PP-405 has no androgenic mechanism and no systemic absorption, eliminating this adverse-event class.
- **Oral dutasteride** (0.5 mg daily): similar androgenic adverse-event profile to finasteride, with potentially higher incidence due to dual 5-alpha reductase inhibition. Same considerations apply.
- **Topical minoxidil** (2% or 5% solution or foam): associated with local irritation, hypertrichosis at remote sites, and rare systemic cardiovascular effects (hypotension, tachycardia) with excessive application. PP-405 acts through a different mechanism and does not produce cardiovascular effects.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative androgenetic alopecia therapies against PP-405, evaluated against five competency standards: novelty, effect size, promising potential (current clinical or regulatory state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal pharmacological treatments for androgenetic alopecia with established or advanced clinical evidence, spanning approved and investigational agents across different mechanistic classes.

12.1 Minoxidil

Mechanism: Potassium channel opener (Kir6.1/SUR2B) and vasodilator; additional direct effects on follicular keratinocyte proliferation and vascular endothelial growth factor (VEGF) expression. Applied topically as 2% or 5% solution or foam.

Regulatory status: FDA-approved since 1988 (topical, over-the-counter). The first approved topical treatment for androgenetic alopecia and the most widely used globally.

Novelty: Low. The mechanism was identified incidentally from the systemic antihypertensive use of oral minoxidil; the topical formulation has been available for nearly four decades.

Effect size: Moderate. Meta-analyses report mean increases in hair count of approximately 14 to 18 hairs per square centimeter over 24 weeks with 5% topical minoxidil compared to vehicle in men with androgenetic alopecia [11]. Response rates (defined variably as visible improvement or quantitative hair count increases) are approximately 30 to 40% at 12 months. Effect is maintenance-dependent; hair loss resumes upon discontinuation.

Promising potential: Stable. Minoxidil is a mature, generic product with no active clinical development. Its position is secure as a first-line topical therapy but innovation is minimal.

Side-effect profile: Local irritation, contact dermatitis (particularly with propylene glycol vehicle), hypertrichosis at sites of inadvertent contact, and rare systemic cardiovascular effects with excessive application or compromised skin barrier.

Overall validation: High. Decades of clinical use, extensive post-marketing data, and multiple meta-analyses confirm modest but reproducible efficacy.

Comparison to PP-405: Minoxidil is mechanistically unrelated to PP-405. The vasodilatory mechanism does not address HFSC metabolic quiescence. PP-405 offers a novel mechanism, potential regenerative capacity (new growth in previously bare areas), and an absence of the cardiovascular concern inherent to minoxidil pharmacology. However, minoxidil has decades of safety data and established over-the-counter accessibility that PP-405 has not yet attained. The two therapies are plausible combination partners.

12.2 Finasteride (oral)

Mechanism: Selective inhibitor of type II 5-alpha reductase, reducing conversion of testosterone to dihydrotestosterone (DHT) by approximately 70% at the 1 mg daily dose.

Regulatory status: FDA-approved since 1997 for androgenetic alopecia in men (Propecia, 1 mg daily). Not approved for women.

Novelty: Low. The mechanism was derived from the observation that males with congenital 5-alpha reductase deficiency do not develop male-pattern hair loss. The drug has been available for nearly three decades.

Effect size: Moderate to high. Clinical trials report mean hair count increases of approximately 17 to 25 hairs per square centimeter at the vertex over 24 months compared to placebo in men [12]. Response rates are approximately 48 to 66% (defined as visible improvement on investigator assessment). Finasteride slows or arrests hair loss in approximately 80 to 90% of treated men. Effect is maintenance-dependent.

Promising potential: Stable. Finasteride is a mature, generic product. Topical formulations are in development to reduce systemic exposure while maintaining local efficacy.

Side-effect profile: Sexual adverse events (decreased libido, erectile dysfunction, ejaculation disorders) in approximately 2 to 4% of patients in controlled trials, with post-finasteride syndrome (persistent sexual, neurological, and psychological symptoms after discontinuation) reported in post-marketing surveillance at uncertain frequency. These adverse events are a substantial barrier to patient acceptance.

Overall validation: High. Extensive clinical trial data, multiple meta-analyses, and decades of post-marketing experience confirm robust efficacy in men.

Comparison to PP-405: Finasteride produces larger mean hair count increases than PP-405 has demonstrated in Phase 2a data to date, though direct comparison is limited by differences in trial design, duration, patient population, and endpoints. PP-405 offers the advantage of no systemic exposure and no androgenic adverse events. PP-405 targets a fundamentally different biological process (HFSC metabolic activation rather than androgen reduction), suggesting potential complementarity. Finasteride does not address follicular quiescence; PP-405 does not address androgen-driven miniaturization.

12.3 Dutasteride (oral)

Mechanism: Dual inhibitor of type I and type II 5-alpha reductase, reducing serum DHT by approximately 90% or more at the 0.5 mg daily dose.

Regulatory status: Approved for androgenetic alopecia in South Korea and Japan (Avodart, 0.5 mg daily). Not FDA-approved for alopecia; FDA-approved for benign prostatic hyperplasia. Widely used off-label for androgenetic alopecia.

Novelty: Low. The mechanism extends finasteride pharmacology to dual isoenzyme inhibition.

Effect size: Moderate to high. Clinical trials report hair count increases superior to finasteride 1 mg at the vertex over 24 weeks (approximately 12 additional hairs per cm² for dutasteride 0.5 mg versus finasteride 1 mg in a head-to-head trial) [13]. The more complete DHT suppression produces modestly greater efficacy.

Promising potential: Moderate. Active off-label use and approved in select Asian markets but unlikely to achieve FDA approval for alopecia given the established finasteride position and similar adverse-event profile.

Side-effect profile: Similar to finasteride but potentially higher incidence of sexual adverse events due to the more complete DHT suppression. Additional concern for effects on prostate-specific antigen (PSA) screening interpretation.

Overall validation: High. Substantial clinical trial data and widespread off-label use confirm efficacy superior to finasteride in direct comparison.

Comparison to PP-405: Dutasteride offers the most potent anti-androgenic efficacy among approved therapies but carries the most pronounced systemic adverse-event burden. PP-405 is at the opposite end of the systemic exposure spectrum: no detectable systemic levels, no androgenic effects. The two compounds address different nodes in alopecia pathophysiology and represent a plausible rational combination.

12.4 Clascoterone (topical)

Mechanism: Topical androgen receptor antagonist. Blocks DHT binding to the androgen receptor at the follicular level without systemic anti-androgenic effects.

Regulatory status: FDA-approved for acne vulgaris (Winlevi, 1% cream, 2020). In clinical development for androgenetic alopecia (7.5% solution); Phase 3 trials for alopecia have been completed with mixed results [14].

Novelty: Moderate. First topical androgen receptor antagonist approved for any dermatological indication. The application to alopecia represents a novel approach within the anti-androgen class.

Effect size: Modest in alopecia trials. Phase 2 data showed increases in target area hair count of approximately 5 to 10 hairs per square centimeter at 12 months versus vehicle. Phase 3 data have shown variable results.

Promising potential: Moderate. The topical anti-androgen approach is attractive for patients who decline systemic finasteride. Regulatory path for alopecia remains uncertain pending Phase 3 outcomes.

Side-effect profile: Favorable. Local adverse events (application site pain, pruritus, erythema) are mild and infrequent. No systemic anti-androgenic effects have been reported. No sexual adverse events.

Overall validation: Moderate. Approved for acne with extensive safety data; alopecia-specific efficacy data are less mature.

Comparison to PP-405: Both compounds are topical agents with favorable systemic safety profiles, but they act through entirely different mechanisms. Clascoterone blocks androgen signaling at the follicle; PP-405 activates quiescent stem cells through metabolic reprogramming. The effect sizes to date are modest for both compounds. They represent plausible combination partners, addressing androgen-driven miniaturization (clascoterone) and metabolic quiescence (PP-405) simultaneously.

12.5 Pyrilutamide (topical)

Mechanism: Topical non-steroidal androgen receptor antagonist with high binding affinity for the androgen receptor.

Regulatory status: In Phase 3 clinical trials in China and the United States for androgenetic alopecia (Kintor Pharmaceutical; KX-826). Not yet approved in any jurisdiction [15].

Novelty: Moderate. Non-steroidal topical androgen receptor antagonist with favorable dermal selectivity.

Effect size: Phase 2 data in Chinese men with AGA reported mean increases of approximately 12 to 16 hairs per square centimeter at the target area over 24 weeks with 0.5% pyrilutamide applied twice daily versus vehicle [15]. Phase 3 trials have reportedly achieved primary endpoints, though full data have not been published in peer-reviewed form.

Promising potential: Moderate to high. Phase 3 data appear positive, and regulatory filings are anticipated. If approved, pyrilutamide would be the first non-steroidal topical androgen receptor antagonist for alopecia.

Side-effect profile: Favorable. Topical administration with limited systemic absorption. Local adverse events are mild. No systemic anti-androgenic effects reported in Phase 2 data.

Overall validation: Moderate. Phase 3 trials completed or ongoing; peer-reviewed data are limited to Phase 2.

Comparison to PP-405: Both are topical investigational agents for AGA with limited systemic absorption. Pyrilutamide acts through androgen receptor blockade; PP-405 acts through MPC inhibition and HFSC metabolic activation. The mecha-

nisms are complementary. Ppyrilutamide is further advanced in clinical development (Phase 3 versus Phase 2a for PP-405). Both have favorable safety profiles. PP-405 offers the unique regenerative signal (new hair growth in bare areas) not reported for ppyrilutamide.

12.6 Comparator summary

The five comparator therapies occupy established or advancing positions in the androgenetic alopecia treatment landscape, all operating within the androgen-pathway modulation or vasodilatory paradigms. **Minoxidil** and **finasteride** are the two FDA-approved treatments with decades of safety and efficacy data; their limitations are modest effect sizes, maintenance dependence, and (for finasteride) patient-acceptance barriers from sexual adverse events. **Dutasteride** extends finasteride pharmacology with greater DHT suppression but similar systemic concerns. **Clascoterone** and **pyrilutamide** represent the emerging topical anti-androgen class, offering improved systemic safety but modest and still-maturing efficacy data.

PP-405 is unique in this landscape as the only compound targeting a metabolic mechanism (MPC inhibition and HFSC lactate-driven activation) entirely orthogonal to androgen modulation and vasodilation. Its regenerative signal (new hair growth in previously bare areas) has not been reported for any of the five comparators and, if confirmed in Phase 3 data, would represent a qualitative advance in alopecia pharmacology. The absence of systemic absorption provides a safety advantage over the oral anti-androgens. The primary limitation is the early clinical development stage (Phase 2a), with Phase 3 registration trials yet to begin. The metabolic mechanism is complementary to androgen-pathway and vasodilatory therapies, positioning PP-405 as a plausible combination partner rather than a direct competitor to existing treatments.

13. References

1. Flores A, Schell J, Krall AS, et al. Lactate dehydrogenase activity drives hair follicle stem cell activation. *Nat Cell Biol.* 2017;19(9):1017-1026.
2. Jeong S, Savino AM, Bhatt S, Flores A, Christofk HR, Bhatt AS, Lowry WE, Jung ME. Development of novel mitochondrial pyruvate carrier inhibitors to treat hair loss. *J Med Chem.* 2021;64(5):2823-2836.
3. Pelage Pharmaceuticals. Company communications regarding PP-405 compound identity. 2025. Available at: <https://pelagepharma.com/>.
4. Pelage Pharmaceuticals. Pelage presents late-breaking data at AAD 2024 meeting demonstrating PP405 activates human hair follicle stem cells ex vivo and in Phase 1 clinical study. Press release, March 8, 2024.
5. Pelage Pharmaceuticals. Pelage Pharmaceuticals announces positive Phase 2a clinical trial results for PP405 in regenerative hair loss therapy. *Business Wire*, June 17, 2025.
6. ClinicalTrials.gov. Safety, pharmacokinetics and efficacy of PP405 in adults with AGA. Identifier: NCT06393452. National Library of Medicine (United States).
7. Bricker DK, Taylor EB, Schell JC, et al. A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, *Drosophila*, and humans. *Science.* 2012;337(6090):96-100.
8. UCLA Health. UCLA licenses technology to combat hair loss to company founded by faculty members. Press release, 2018.
9. Herzig S, Raemy E, Montessuit S, et al. Identification and functional expression of the mitochondrial pyruvate carrier. *Science.* 2012;337(6090):93-96.
10. Sinclair R. Male pattern androgenetic alopecia. *BMJ.* 1998;317(7162):865-869.
11. Adil A, Godwin M. The effectiveness of treatments for androgenetic alopecia: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2017;77(1):136-141.

12. Kaufman KD, Olsen EA, Whiting D, et al. Finasteride in the treatment of men with androgenetic alopecia. J Am Acad Dermatol. 1998;39(4 Pt 1):578-589.
13. Olsen EA, Hordinsky M, Whiting D, et al. The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol. 2006;55(6):1014-1023.
14. Cassiopea SpA. Clascoterone topical solution clinical development program for androgenetic alopecia. Clinical trial data on file. 2023.
15. Kintor Pharmaceutical. Phase 2 clinical results of pyrilutamide (KX-826) topical solution for androgenetic alopecia. 2022.
16. Pelage Pharmaceuticals. Reactivating the follicle: PP405 moves toward late-stage trials for alopecia. Dermatology Times. 2025.
17. Koralewicz M, et al. Topical solutions for androgenetic alopecia: evaluating efficacy and safety. Forum Dermatologicum. 2025.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. PP-405 is an investigational compound that has not been approved by the United States Food and Drug Administration or by any other regulatory authority for any indication. The chemical structure of PP-405 has not been publicly disclosed; the compound is available exclusively through Pelage Pharmaceuticals for clinical trial use. Investigators interested in MPC inhibitor pharmacology may access the related published compound JXL-069 from commercial research suppliers; JXL-069 is structurally distinct from PP-405 and should not be represented as equivalent. All information in this monograph is derived from publicly available sources including peer-reviewed publications, press releases, conference presentations, and clinical trial registrations. Investigators should consult their local regulatory authority before any human research application.