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Short Communication

PP405 in Alopecia: An Emerging Molecule worth Investigating

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Abstract

Androgenetic alopecia (AA) is the most common form of hair loss globally and, despite minimal physical health effects, frequently causes psychological distress. Current FDA-approved therapies, such as topical minoxidil and oral finasteride, offer limited efficacy and are associated with side effects, highlighting the need for safer, more effective options. Recent clinical evidence suggests that PP405, a novel non-hormonal topical agent, may stimulate dormant hair follicle stem cells by modulating cellular metabolism, offering a potentially regenerative approach to AA. Human studies in the early stages demonstrated favorable tolerability of topical PP405 with low systemic absorption. In the Phase 1 trial, daily application of 0.05% gel was well tolerated and caused increases in markers of early hair regeneration. In a subsequent Phase 2a study, PP405 treatment was associated with a > 20% increase in hair density in a subset of men with advanced hair loss compared with placebo by week 8, although there have been no reports of significant adverse events. These preliminary results are promising, but confirmatory efficacy, optimal dosing, and safety need to be determined through large-scale, long-term clinical trials on diverse populations. PP405 may represent a novel therapeutic avenue in AA management if phase 3 outcomes are favorable.

Introduction

Alopecia refers to a condition involving the loss of hair, which can be due to several causes, including genetics, autoimmune disease, and hormonal imbalance. The most common alopecia worldwide is Androgenetic Alopecia (AA) [1]. Despite having little effect on physical health, it can have a significant effect on mental health, which may lead to anxiety, depression & loss of confidence [2]. Alopecia at an early stage is being treated through FDA-approved drugs like topical minoxidil 2%, preferably for females & 5% for men, and finasteride orally, but both drugs show minor side effects [3]. Recent studies have shown that PP405, a novel non-hormonal topical molecule, is demonstrating positive results in regenerating dormant hair follicles in AA by stimulating stem cell activity.

However, PP405 is not yet FDA-approved and remains an investigational therapy currently in clinical trials, not available for routine clinical use. The drug has completed phase 2a trial & the pharmaceutical company, Pelage Pharmaceuticals, is planning for phase 3 in 2026. The purpose of writing this article is to explore the emerging therapeutic potential of PP405 in the management of AA, critically examining current evidence, clinical trial data, and future research needs. This article does not present original clinical or experimental data but provides a narrative overview of existing evidence on PP405 and other alopecia therapies.

Current therapeutic landscape in alopecia

AA thins hair over time, which may eventually lead to the loss of hair follicles. Androgenetic alopecia is a genetically influenced hair-loss disorder characterized by progressive miniaturization of hair follicles and patterned thinning due to androgen sensitivity [4]. In contrast, alopecia areata is an autoimmune condition in which the immune system attacks hair follicles, leading to sudden, non-scarring patchy hair loss that can affect the scalp and other body areas [5]. These two forms differ in underlying cause and clinical presentation, and they respond differently to therapy — with AA managed

primarily through hormonal and regenerative strategies, and alopecia areata targeted with immune-modulating interventions.

Other types include trichotillomania, chemotherapy-induced alopecia, traction alopecia, and effluvium forms. Numerous therapeutic approaches are available; despite extensive testing, the majority of them fail due to side effects or inconsistent outcomes. Another choice apart from medications is hair transplantation, which is expensive, requires skilled workers, and has risks like infection, bleeding, pain, and follicle loss. These difficulties highlight the need for safer, easier-to-access, and more effective treatments. Promising approaches for the future include stem cell therapy, gene therapy, active hypertrichotic phytochemicals, dermal penetration enhancers, and blended medications [6].

Mechanism of action

Pelage Pharmaceuticals created PP405, a novel non-hormonal topical treatment, to revitalize dormant hair follicle stem cells and treat AA. It was discovered by researchers at the University of California that reviving hair growth could be achieved by altering the energy source of the cells from oxidative phosphorylation to glycolysis. This is accomplished by PP405, which flips that metabolic switch by blocking the mitochondrial pyruvate carrier (MPC). With structural similarities to well-known mitochondrial inhibitors like UK-5099, it has an electrophilic group and a substituted aromatic ring that are specifically made for localized, safe use with little bloodstream absorption [7].

Clinical trial evidence

In 20 men participating in a Phase 1 clinical trial, using a 0.05% gel once daily for a week produced no systemic absorption, better tolerability, and a noticeable rise in Ki67, a protein associated with early hair regeneration and cell growth [8]. 78 adults between the ages of 18 and 55 participated in a larger Phase 2a trial, which found no significant adverse effects. Surprisingly, when compared to the placebo group, 31% of men with more severe hair loss saw a rise in hair density of more than 20% by week eight. These early results suggest that PP405 is a promising treatment for regenerative hair loss [9].

Although detailed gender-specific efficacy data for PP405 are not yet available, differences in tolerability and adverse event profiles between men and women have been reported for other alopecia treatments. For example, in a retrospective analysis of low-dose oral minoxidil use in androgenetic alopecia, females experienced a higher overall incidence of adverse events than males, and other pooled data suggest that women may report side effects more frequently at comparable doses.

Limitations and ongoing needs

While early clinical results for PP405 are encouraging, there are important limitations that must be acknowledged before it can be regarded as a reliable treatment. The Phase 2a trial enrolled only 78 participants, which is typical for early safety studies, but is still a relatively small sample size that limits confidence in efficacy signals and makes it harder to generalize findings broadly across different patient groups. Additionally, the duration of treatment and follow-up was short relative to hair biology: participants applied PP405 once daily for four weeks and were monitored out to 12 weeks. Such a short duration does not really capture the full hair growth cycle, which usually takes several months, and therefore, it's challenging to judge whether early improvements are maintained over the longer term.

Another important limitation is that, so far, the trial only investigated one dose (0.05%), so that dose-response relationships and optimal dosing strategies have not been established. Without the exploration of multiple concentrations, it is unclear whether efficacy could be enhanced or side effects reduced at other doses. These limitations, such as small sample size, short duration, and single-dose evaluation, indicate larger, longer, more detailed studies. Planned Phase 3 trials beginning in 2026 will be critical for confirming the initial findings, determining long-term safety, and establishing whether PP405 can meaningfully benefit a broader range of people with androgenetic alopecia.

Future perspectives

To advance PP405 toward clinical use, larger and more rigorous clinical trials are needed. Owing to the positive results from the Phase 2a clinical trials, Pelage Pharmaceuticals is set to conduct Phase 3 studies in 2026, which will prove to be pivotal for assessing the safety and efficacy of PP405 in both men and women diagnosed with androgenetic alopecia. The clinical trials are expected to involve more participants, which would help identify the treatment effect on the various demographic groups based on sex, age, and the level of hair loss.

Key Phase 3 endpoints will likely encompass:

- Efficacy measures such as change in hair density (e.g., hairs per cm^2), global photographic assessment by blinded reviewers, and patient-reported outcomes on hair growth and satisfaction. These endpoints are standard in alopecia trials and will provide a more robust evaluation of clinical benefit than exploratory measures alone.
- Safety outcomes, such as treatment-related adverse events with a longer exposure period, the evaluation of any local irritation of the scalp, and any systemic effects. A longer follow-up is essential to ensure that the benefit is sustained without any emerging safety concerns.
- Durability of response, with follow-up extending well

beyond the usual 12 weeks of early trials, possibly to 12 months or longer, to measure sustained regrowth through one or more hair growth cycles.

The Phase 3 trials are also expected to examine differing doses to identify an optimal level of concentration to apply, fixing a weakness of the initial trials that only trialed one form of treatment. Extensive examination of combination treatment approaches like PP405 combined with platelet-rich plasma (PRP) therapy, microneedling, and/or low-level laser therapy may be considered within the scope of an exploratory portion of trials to assess if a combination of treatments can improve outcomes.

Importantly, future research should incorporate broadly inclusive eligibility criteria to ensure representation of different ethnicities, hair types, and genders, improving generalizability. Attention to patient-reported quality-of-life outcomes in these trials will further contextualize the clinical relevance of any observed regrowth. If these Phase 3 trials meet their primary endpoints and demonstrate a favorable risk-benefit profile, PP405 could be positioned for regulatory submission and potential approval in 2028 or beyond, providing a much-needed regenerative option for individuals affected by hair loss

Emerging evidence from immunology research suggests that innate immune mechanisms such as neutrophil extracellular traps (NETs) may modulate inflammatory responses in chronic inflammatory and autoimmune disorders. NETs are web-like structures released by activated neutrophils that trap pathogens but can also drive sterile inflammation through the release of cytotoxic components and activation of pro-inflammatory pathways [1,2]. Though best described in autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis, where uncontrolled NET formation contributes to tissue inflammation and disease progression, the function of NETs has not yet been characterized in hair follicle-associated inflammation. The present line of investigation may point to new inflammatory modulators that alter treatment efficiency or suggest targeted strategies aimed at mitigating injurious immune activation [10].

Conclusion

In conclusion, hair loss remains a significant clinical challenge, and current therapies such as minoxidil and finasteride are often limited by modest efficacy, slow onset, and side effects, leaving many patients dissatisfied. PP405 represents a potentially transformative approach by directly targeting hair follicle stem cells to promote regeneration rather than merely slowing hair thinning. Phase 2a results showed early signs of meaningful hair density increases and a robust safety profile, suggesting that PP405 could offer advantages over existing options in both speed and biological effect. While larger, longer Phase 3 trials are needed to confirm these findings and establish long-term outcomes, PP405 has the potential to broaden the therapeutic landscape for androgenetic alopecia and address an unmet need for more effective, regenerative treatments.

Data availability statement

Data sharing does not apply to this article as no new data were created or analyzed in this study.

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