

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Pyrilutamide

*A topical nonsteroidal antiandrogen developed by Kintor Pharmaceuticals as a first-in-class selective silent antagonist of the androgen receptor for the treatment of androgenetic alopecia and acne vulgaris, distinguished from oral 5-alpha-reductase inhibitors by receptor-level blockade with minimal systemic exposure.*

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## ABSTRACT

Pyrilutamide (developmental code KX-826) is a nonsteroidal antiandrogen of the thiohydantoin structural class under clinical development by Suzhou Kintor Pharmaceuticals for the topical treatment of androgenetic alopecia (AGA) and acne vulgaris. The compound acts as a selective, high-affinity silent antagonist of the androgen receptor (AR), competitively displacing dihydrotestosterone (DHT) and testosterone from the ligand-binding domain without inducing any agonist-mediated transcriptional activity. This mechanism distinguishes pyrilutamide from systemic 5- $\alpha$ -reductase inhibitors (finasteride, dutasteride) that reduce circulating DHT concentrations, and from first-generation nonsteroidal antiandrogens (bicalutamide, flutamide) that possess residual partial agonist activity and are administered systemically. In cell-based AR transactivation assays, pyrilutamide exhibits an IC<sub>50</sub> of approximately 0.28 nM, a K<sub>i</sub> of 24 nM in competitive AR binding assays (compared to 48 nM for enzalutamide), and an IC<sub>50</sub> of 264 nM for inhibition of prostate-specific antigen secretion in LNCaP prostate cancer cells, establishing it as one of the most potent topical antiandrogens characterized to date.

The compound was designed for topical delivery to the scalp and skin, with molecular properties selected to favor dermal retention and limit transdermal penetration. Preclinical pharmacokinetic evaluation in rats demonstrated rapid distribution to skin and adipose tissue following topical application, with low transdermal bioavailability and negligible plasma exposure. In human clinical studies, peak plasma concentrations following application of the

0.5% topical formulation remained below 0.5 ng/mL, with an estimated dermal half-life of approximately 2 hours. Toxicological assessments established no-observed-adverse-effect levels (NOAELs) of greater than 5000 mg/kg orally in rats and 90 mg/kg dermally in minipigs, yielding systemic safety margins of 168- to 222-fold over levels associated with therapeutic efficacy.

Clinical development of pyrilutamide has proceeded through multiple trials across China and the United States. A Phase I ascending-dose safety study in 40 men in the United States (0.3% to 9.6% concentrations) demonstrated tolerability with only mild contact dermatitis as the principal adverse event. A Phase II randomized, placebo-controlled trial in 120 Chinese men with androgenetic alopecia (Norwood grades 3V, 4, and 5) reported that 0.5% pyrilutamide applied twice daily for 24 weeks produced a mean increase of 22.73 hairs per square centimeter in target area hair count (TAHC) from baseline, representing a 15.34 hairs per square centimeter advantage over placebo. A Phase II trial in Chinese women with female-pattern hair loss met its primary endpoint. A subsequent pivotal Phase III trial in Chinese men, however, failed to demonstrate statistical significance on the primary TAHC endpoint versus placebo at 24 weeks (announced November 2023). Long-term safety extensions at 52 weeks reported that 46% of patients achieved at least a 10 hairs per square centimeter increase and 20% achieved at least a 20 hairs per square centimeter increase, with no drug-related sexual dysfunction and a favorable overall safety profile. A reformulated 1.0% tincture is now under evaluation in a Phase II/III pivotal trial initiated in 2025, with enrollment exceeding 750 participants at more than 20 hospital sites. A Phase II trial for acne vulgaris has completed enrollment in China. No regulatory approval has been granted in any jurisdiction as of the date of this monograph.

This monograph reviews the chemistry, structural class, and synthesis of pyrilutamide; the androgen receptor antagonist mechanism in molecular detail; the topical pharmacokinetic profile including systemic exposure characterization; the preclinical pharmacology in androgen-driven disease models; the clinical evidence base across androgenetic alopecia in men and women, acne vulgaris, and related dermatological indications; sourcing and quality verification considerations for research-grade material; reconstitution and handling; stack-interaction considerations with other dermatological and hormonal agents; the adverse-event and safety signal; and a comparative assessment of five alternative agents (finasteride, dutasteride, topilutamide, RU-58841, and minoxidil) against pyrilutamide on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name:** Ppyrilutamide (proposed; not yet formally assigned by the World Health Organization).

**Development code:** KX-826 (Kintor Pharmaceuticals). The development code is the canonical identifier in the clinical trial registrations, patent filings, and the entirety of the published pharmacological and clinical literature. The compound is referenced as KX-826 in all ClinicalTrials.gov entries and in Kintor corporate disclosures [1, 2].

**Chemical Abstracts Service registry number:** 1272719-00-2 (free base). This CAS number is used across all major chemical suppliers (Selleck Chemicals, MedChemExpress, Cayman Chemical, MedKoo Biosciences) and in patent databases [3].

**International Union of Pure and Applied Chemistry name:** 4-[3-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-1-imidazolidinyl]-2-fluoro-N-methylbenzamide.

**Other synonyms:** Ppyrilutamide, KX826, KX 826.

## 1.2 Structural class and chemistry

Ppyrilutamide is a nonsteroidal antiandrogen belonging to the thiohydantoin structural class. The core scaffold is a 2-thioxoimidazolidin-4-one (thiohydantoin) ring bearing two aromatic substituents: a 4-cyano-2-fluoro-3-(trifluoromethyl)phenyl group at the N3 position and a 2-fluoro-4-(N-methylcarboxamide)phenyl group at the N1 position, with 5,5-dimethyl substitution on the imidazolidine ring. The thiohydantoin core is a privileged scaffold in antiandrogen medicinal chemistry, shared with enzalutamide (4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-1-imidazolidinyl]-2-fluoro-N-methylbenzamide) and related second-generation AR antagonists developed from the diarylthiohydantoin series originally characterized at the University of California, Los Angeles [4, 5].

**Molecular formula:** C<sub>21</sub>H<sub>16</sub>F<sub>5</sub>N<sub>4</sub>O<sub>2</sub>S (calculated for the neutral free base; note that some databases list C<sub>21</sub>H<sub>15</sub>F<sub>5</sub>N<sub>4</sub>O<sub>2</sub>S, reflecting alternative hydrogen counting conventions for the thiohydantoin tautomer).

**Molecular weight:** 482.43 g/mol (free base).

**Physical properties:** White to off-white crystalline powder. Soluble in dimethyl sulfoxide (DMSO) at concentrations exceeding 50 mg/mL; sparingly soluble in ethanol and methanol; very poorly soluble in water (consistent with the high lipophilicity that favors dermal retention over systemic absorption). The compound is formulated for topical delivery in proprietary solvent systems containing ethanol and propylene glycol.

**LogP:** Estimated at approximately 3.5 to 4.0, consistent with favorable dermal partitioning and limited aqueous solubility. The lipophilicity is a deliberate design feature intended to maximize retention within the pilosebaceous unit and stratum corneum while minimizing transdermal flux into the systemic circulation.

## 1.3 Synthesis

The published patent literature from Kintor Pharmaceuticals describes the synthesis of pyrilutamide through a convergent approach involving: (a) construction of the 5,5-dimethylthiohydantoin core from 2-amino-2-methylpropanoic acid derivatives via cyclization with carbon disulfide or thiocarbonyl transfer reagents; (b) N-arylation at the N3 position with 4-bromo-2-fluoro-3-(trifluoromethyl)benzonitrile or equivalent electrophilic aromatic intermediate via copper- or palladium-catalyzed amination; and (c) N-arylation at the N1 position with 2-fluoro-4-(N-methylcarboxamide)halobenzene derivatives [6]. The synthesis is analogous to the established routes for enzalutamide and related diarylthiohydantoins, with modifications to accommodate the specific substitution pattern of pyrilutamide (notably the additional fluorine on the benzamide ring). Product purification is achieved by column chromatography followed by recrystallization. Analytical characterization employs nuclear magnetic resonance spectroscopy (<sup>1</sup>H and <sup>13</sup>C), high-resolution mass spectrometry, and high-performance liquid chromatography (HPLC). Research-grade material is supplied at greater than 98% purity by HPLC by multiple commercial vendors.

## 2. Abstract

Pyrilutamide (KX-826) is a selective, high-affinity, silent antagonist of the androgen receptor (AR), developed by Suzhou Kintor Pharmaceuticals as a topical treatment for androgen-dependent dermatological conditions, principally androgenetic alopecia (AGA) and acne vulgaris [1, 2]. The compound competitively binds the ligand-binding domain of the AR with nanomolar affinity, preventing dihydrotestosterone (DHT) and testosterone from activating AR-mediated transcriptional programs that drive hair follicle miniaturization in genetically susceptible scalp regions and sebaceous gland hyperactivity in acne-prone skin. As a "silent" antagonist, pyrilutamide induces no measurable agonist activity upon AR binding, distinguishing it from first-generation nonsteroidal antiandrogens (bicalutamide, flutamide, nilutamide) that exhibit residual partial agonist activity under certain cellular conditions [5, 7].

The clinical rationale for pyrilutamide rests on two principal advantages over existing androgenetic alopecia pharmacotherapy. First, unlike finasteride and dutasteride (systemic 5-alpha-reductase inhibitors that reduce circulating DHT but produce well-documented sexual adverse effects including erectile dysfunction, decreased libido, and ejaculation disorders), pyrilutamide blocks androgen signaling at the receptor level in the target tissue without reducing systemic androgen concentrations [8, 9]. Second, the topical route of administration and the molecular design (high lipophilicity, favorable dermal partitioning) produce negligible systemic exposure, with peak plasma concentrations below 0.5 ng/mL at the therapeutic 0.5% formulation, further reducing the risk of systemic antiandrogen effects [10].

The Phase II clinical program in China demonstrated statistically significant increases in target area hair count (TAHC) in both male and female androgenetic alopecia at 24 weeks of treatment [11, 12]. The subsequent Phase III pivotal trial in Chinese men, however, failed to reach statistical significance on the primary TAHC endpoint versus placebo at 24 weeks (announced November 2023), introducing uncertainty regarding the clinical translation of the Phase II efficacy signal [13]. A reformulated 1.0% tincture with enhanced scalp retention is currently under evaluation in a large Phase II/III pivotal trial initiated in 2025, and a long-term safety extension has demonstrated favorable tolerability through 52 weeks [14]. The com-

pound is not approved in any jurisdiction. It is sold as a research-grade preparation by multiple chemical suppliers; investigators should obtain analytical confirmation of identity and purity on every lot.

## 3. Discovery and Development History

### 3.1 Origin and rationale

Pyrilutamide was developed at Suzhou Kintor Pharmaceuticals, a Chinese biotechnology company founded in 2009 with a focus on treatments for androgen-driven diseases including androgenetic alopecia, acne vulgaris, and prostate cancer [1]. The founding scientific premise was that the limitations of existing AGA pharmacotherapy (systemic 5- $\alpha$ -reductase inhibitors with sexual side effects; minoxidil with a mechanism unrelated to the androgen axis) created an unmet need for a topical agent that could directly antagonize the androgen receptor at the follicular level without systemic hormonal disruption.

Development of pyrilutamide began approximately in 2010, building on the diarylthiohydantoin scaffold that had been extensively characterized in the prostate cancer antiandrogen literature, particularly the work of Tran et al. (2009) at UCLA that led to the discovery of enzalutamide [4]. Kintor's medicinal chemistry program sought to optimize the thiohydantoin series for topical dermatological application by selecting for high AR binding affinity, silent antagonist profile (zero agonist activity), high lipophilicity (to favor dermal retention), and rapid dermal metabolism or clearance (to limit systemic exposure). The resulting compound, designated KX-826, advanced through preclinical characterization in the mid-2010s.

### 3.2 Preclinical development

Preclinical pharmacology studies in androgen-sensitive cell lines and in animal models of androgen-driven conditions established the AR antagonist activity and the topical pharmacokinetic profile of pyrilutamide. In LNCaP prostate cancer cells (an AR-positive, androgen-responsive line), pyrilutamide inhibited DHT-stimulated prostate-specific antigen (PSA) secretion with an IC<sub>50</sub> of 264 nM and demonstrated competitive displacement of radiolabeled androgen from the AR ligand-binding domain with a K<sub>i</sub> of 24 nM [3, 5]. In AR transactivation reporter assays, the compound exhibited an IC<sub>50</sub> of 0.28 nM, making it approximately 10-fold more potent than bicalutamide (IC<sub>50</sub> 3.1 nM) in the same system [5].

Topical pharmacokinetic studies in rats demonstrated rapid distribution to skin and subcutaneous adipose tissue following dermal application, with low transdermal bioavailability and negligible plasma exposure. The estimated dermal half-life was approximately 2 hours, consistent with localized action at the androgen receptor within the pilosebaceous unit [10]. Toxicological studies established NOAELs of greater than 5000 mg/kg orally in rats and 90 mg/kg dermally in minipigs, with systemic exposure at these NOAEL doses being 168- to 222-fold higher than levels associated with therapeutic efficacy. Mutagenicity testing was negative across standard genotoxicity batteries [10].

### 3.3 Clinical development timeline

Kintor initiated Phase I clinical trials in the United States in 2018, evaluating the safety, tolerability, and pharmacokinetics of ascending topical doses (0.3%, 1.2%, 4.8%, and 9.6%) in 40 healthy men aged 18 to 60 with male-pattern hair loss [10]. The Phase I data supported advancement to Phase II.

Phase II trials were initiated in China in 2020, with the principal male AGA trial (120 subjects, Norwood grades 3V, 4, and 5) reporting topline results at the 6th National Hair Academic Conference in China in September 2022 [11]. A parallel Phase II trial in Chinese women with female-pattern hair loss met its primary endpoint in late 2022 [12]. A Phase II trial for acne vulgaris completed enrollment in China in 2022 [15].

A Phase III pivotal trial for male AGA in China completed enrollment of 416 subjects in 2023 and reported topline results in November 2023. The primary endpoint (change in TAHC versus placebo at 24 weeks) was not met [13]. Long-term safety and efficacy extensions continued through 52 weeks [14].

In response to the Phase III results, Kintor reformulated the product from a 0.5% solution to a 1.0% tincture with enhanced scalp retention properties and initiated a new Phase II/III pivotal trial in China in 2025, with planned enrollment exceeding 750 participants at more than 20 hospital sites [14, 16]. A Phase II trial in the United States demonstrated a 10 hairs per square centimeter increase with 0.5% pyrilitamide twice daily [17].

As of the date of this monograph, pyrilitamide has not received regulatory approval in any jurisdiction.

## 4. Mechanism of Action

### 4.1 Androgen receptor antagonism

The androgen receptor is a member of the nuclear receptor superfamily of ligand-activated transcription factors. In the canonical signaling pathway, binding of DHT (the principal androgen in hair follicle and sebaceous gland biology) or testosterone to the ligand-binding domain of the cytoplasmic AR induces a conformational change that releases heat shock proteins, promotes receptor dimerization, exposes the nuclear localization signal, and drives translocation to the nucleus where the AR dimer binds androgen response elements (AREs) in the promoter regions of target genes. In androgen-sensitive scalp hair follicles, this transcriptional program drives the progressive miniaturization of terminal hair follicles to vellus-like follicles that is the hallmark pathology of androgenetic alopecia. In sebaceous glands, AR-mediated transcription drives lipogenesis and glandular hypertrophy that contribute to acne pathogenesis [18, 19].

Pyrilutamide binds the ligand-binding domain of the AR in the same hydrophobic pocket occupied by DHT and testosterone, competing for ligand occupancy and preventing receptor activation [5]. The compound is classified as a "silent" antagonist: upon binding, it induces a conformational state of the AR that does not recruit transcriptional coactivators (SRC-1, SRC-3, p300/CBP) and does not promote nuclear translocation or ARE-dependent transcription [5, 7]. This distinguishes pyrilutamide from first-generation nonsteroidal antiandrogens (bicalutamide, flutamide, nilutamide) that, while predominantly antagonist, can exhibit partial agonist activity under conditions of AR overexpression, AR mutation, or coactivator dysregulation, as observed in the castration-resistant prostate cancer setting [20].

### 4.2 Binding pharmacology

In quantitative binding and functional assays, pyrilutamide demonstrates the following pharmacological profile:

AR competitive binding  $K_i$ : 24 nM (displacement of radiolabeled ligand from human AR ligand-binding domain), compared to 48 nM for enzalutamide and approximately 160 nM for bicalutamide in parallel assays [5].

AR transactivation IC<sub>50</sub>: 0.28 nM (inhibition of DHT-stimulated AR-dependent luciferase reporter activity), compared to 3.1 nM for bicalutamide [5].

PSA secretion IC<sub>50</sub>: 264 nM (inhibition of DHT-stimulated PSA secretion in LNCaP cells), a functional readout of AR-mediated gene expression in an endogenous androgen-responsive system [3, 5].

The binding affinity and functional potency place pyrilutamide in the same pharmacological range as the second-generation antiandrogens developed for castration-resistant prostate cancer (enzalutamide, apalutamide, darolutamide), though pyrilutamide is optimized for topical dermatological application rather than systemic oncology administration.

### 4.3 Selectivity

Pyrilutamide is reported to be selective for the androgen receptor over other nuclear hormone receptors, including the glucocorticoid receptor (GR), progesterone receptor (PR), mineralocorticoid receptor (MR), and estrogen receptors alpha and beta (ERa, ERb) [5]. The selectivity indices have not been published in full quantitative form in the peer-reviewed literature, but the absence of systemic hormonal adverse events in clinical trials (no gynecomastia, no menstrual disruption, no adrenal suppression) at topical doses is consistent with high AR selectivity and negligible systemic exposure at therapeutic concentrations [10, 11].

### 4.4 Downstream consequences for hair follicle biology

The blockade of AR-mediated transcription in dermal papilla cells of androgen-sensitive hair follicles is expected to interrupt the molecular cascade that drives follicular miniaturization. Key downstream targets of AR signaling in the dermal papilla include transforming growth factor beta-1 (TGF-beta-1), transforming growth factor beta-2 (TGF-beta-2), dickkopf-1 (DKK1), and interleukin-6 (IL-6), all of which are induced by DHT-AR signaling and contribute to catagen induction and follicular regression [18, 21]. By preventing AR activation at the receptor level, pyrilutamide is expected to reduce expression of these catabolic factors and to preserve or restore the anagen (growth) phase duration of affected follicles. The mechanistic parallel to systemic finasteride (which reduces DHT production rather than blocking receptor activation) is that both approaches converge on reducing AR-mediated transcriptional output in the follicle, but by different pharmacological nodes.

## 4.5 Distinction from 5-alpha-reductase inhibition

The mechanistic distinction between AR antagonism (pyrilutamide) and 5-alpha-reductase inhibition (finasteride, dutasteride) is clinically consequential. 5-alpha-reductase inhibitors reduce the conversion of testosterone to DHT systemically, producing a 60 to 70% reduction in serum DHT (finasteride) or a greater than 90% reduction (dutasteride) [8, 9]. This systemic DHT reduction produces the well-documented sexual adverse effects (erectile dysfunction, decreased libido, ejaculation disorders) reported in 2 to 8% of patients in registration trials, and the persistent post-finasteride syndrome reported in case series and cohort studies [22]. Pylilutamide, by contrast, blocks AR signaling only at the site of topical application without reducing circulating DHT or testosterone concentrations, and the negligible systemic absorption further limits the potential for systemic antiandrogen effects. No drug-related sexual dysfunction has been reported in any completed pyrilutamide clinical trial [10, 11, 14].

# 5. Pharmacokinetics and Routes of Administration

## 5.1 Absorption and dermal pharmacokinetics

Pyrilutamide is administered topically to the scalp as a solution or tincture. The compound's high lipophilicity (estimated LogP 3.5 to 4.0) and molecular weight (482.43 g/mol) favor partitioning into the lipid-rich stratum corneum and dermal compartments while limiting transdermal flux into the systemic circulation. Preclinical pharmacokinetic studies in rats demonstrated rapid distribution to skin and subcutaneous adipose tissue following topical application, with the majority of the applied dose retained in the dermal and follicular compartments [10].

In human pharmacokinetic studies from the Phase I ascending-dose trial, peak plasma concentrations following application of the 0.5% formulation were below 0.5 ng/mL (approximately 1 nM), representing a systemic exposure approximately 25-fold below the AR competitive binding  $K_i$  of 24 nM and approximately 4-fold below the functional transactivation  $IC_{50}$  of 0.28 nM [10]. This negligible systemic exposure confirms that the compound operates as a locally-acting topical agent with minimal potential for systemic pharmacological activity at the AR.

The estimated dermal half-life is approximately 2 hours, suggesting that twice-daily application is required to maintain sustained AR occupancy in the pilosebaceous unit. The 1.0% tincture formulation under evaluation in the current Phase II/III trial is designed to increase the dermal retention time and local drug concentration at the follicular target relative to the earlier 0.5% solution formulation [16].

## 5.2 Distribution

Systemic distribution of pyrilutamide following topical application is negligible. The low plasma concentrations (below 0.5 ng/mL) preclude meaningful distribution to distant organs. The compound is expected to be highly protein-bound in plasma based on its lipophilicity, though formal plasma protein binding data have not been published.

## 5.3 Metabolism

The metabolic fate of topically applied pyrilutamide has not been fully characterized in published literature. The thiohydantoin core is subject to hepatic oxidation and glucuronidation when systemically bioavailable, as characterized for the structurally related enzalutamide (metabolized primarily by CYP2C8 and CYP3A4). Given the negligible systemic exposure of topically applied pyrilutamide, hepatic metabolism is expected to play a minimal role in the elimination of the therapeutically relevant dermal drug pool. Local cutaneous metabolism by esterases and oxidases within the skin may contribute to the 2-hour dermal half-life, though this has not been formally characterized.

## 5.4 Elimination

Preclinical studies in rats indicated primary excretion via urine following topical application, consistent with the small fraction of drug that reaches the systemic circulation being metabolized hepatically and eliminated renally [10]. The principal route of drug removal from the application site is expected to be physical (washing, desquamation) rather than metabolic.

## 5.5 Routes of administration

Topical application to the scalp is the only route studied in clinical trials. The 0.5% solution was applied twice daily (BID) in the Phase I, Phase II, and initial Phase III trials. The reformulated 1.0% tincture is applied per the protocol of the current Phase II/III trial. Oral and parenteral routes have not been studied in human clinical trials and are not contemplated for the dermatological indications.

## 5.6 Special populations

Specific pharmacokinetic data in hepatic or renal impairment populations have not been published. Given the negligible systemic exposure, dose adjustment for hepatic or renal impairment is not expected to be required. Pediatric pharmacokinetics have not been characterized. The compound has been studied in adult men and women aged 18 to 60 in clinical trials [10, 11, 12].

## 6. Preclinical Pharmacology

### 6.1 In vitro pharmacology

In vitro characterization of pyrilutamide encompasses AR binding, transactivation, and functional cell-based assays. The compound demonstrates competitive displacement of radiolabeled androgens from the human AR ligand-binding domain ( $K_i$  24 nM), potent inhibition of DHT-stimulated AR-dependent transcription ( $IC_{50}$  0.28 nM in luciferase reporter systems), and dose-dependent inhibition of PSA secretion in LNCaP prostate cancer cells ( $IC_{50}$  264 nM) [3, 5]. The "silent" antagonist profile has been confirmed by the absence of AR-dependent reporter activation at any tested concentration in the absence of androgen, distinguishing pyrilutamide from partial agonist antiandrogens [5, 7].

### 6.2 In vivo pharmacology

Preclinical in vivo studies have been conducted in androgen-driven disease models, though detailed published reports are limited relative to the clinical data. Topical application of pyrilutamide in rodent models demonstrated suppression of androgen-dependent endpoints in skin, including sebaceous gland size reduction and reversal of androgen-stimulated follicular regression, consistent with local AR blockade [10]. The NOAEL determinations (greater than 5000 mg/kg oral in rats, 90 mg/kg dermal in minipigs) established wide safety margins, with the dermal NOAEL producing systemic exposure 168- to 222-fold above therapeutic levels [10].

### 6.3 Toxicology

Standard regulatory toxicology assessments have been conducted. Genotoxicity testing, including bacterial reverse mutation (Ames) assays and in vitro chromosomal aberration assays, was negative. Repeat-dose dermal toxicity studies in minipigs at doses up to 90 mg/kg demonstrated no treatment-related findings. Reproductive toxicology data have not been published. Phototoxicity and dermal sensitization studies have been conducted as part of the topical formulation development program, with results supporting the clinical safety profile [10].

## 7. Clinical Evidence Base

### 7.1 Phase I: United States ascending-dose safety study

A Phase I clinical trial was conducted in the United States to evaluate the safety, tolerability, and pharmacokinetics of topically applied pyrilitamide in 40 men aged 18 to 60 with male-pattern hair loss (Hamilton-Norwood classification). Ascending dose cohorts received 0.3%, 1.2%, 4.8%, and 9.6% concentrations applied to the scalp. The trial confirmed that peak plasma concentrations remained below 0.5 ng/mL at the 0.5% formulation concentration, consistent with the targeted negligible systemic exposure profile. The only reported adverse events were mild contact dermatitis at the application site, with no systemic adverse events, no changes in serum testosterone or DHT, and no sexual function complaints [10].

### 7.2 Phase II: Chinese male androgenetic alopecia

The principal Phase II efficacy trial enrolled 120 Chinese men with androgenetic alopecia (Norwood grades 3V, 4, and 5) and randomized them to four treatment arms: KX-826 2.5 mg BID, KX-826 5 mg QD (once daily), KX-826 5 mg BID, and placebo applied QD and BID. The primary endpoint was change in non-vellus target area hair count (TAHC) from baseline to week 24 [11].

The 5 mg BID (0.5% concentration, twice daily) arm produced the most favorable results: a mean increase of 22.73 hairs per square centimeter from baseline, representing a 15.34 hairs per square centimeter advantage over placebo. This effect size was statistically significant and was considered clinically meaningful. The 2.5 mg BID and 5 mg QD arms produced intermediate effects. The incidence of adverse drug reactions was 16.1%, with the most common being pruritus (itching) at the application site. No serious adverse events or serious adverse drug reactions were reported [11].

These results were presented at the 6th National Hair Academic Conference in China in September 2022 and subsequently at the 28th Annual Meeting of the Chinese Society of Dermatology.

## 7.3 Phase II: Chinese female androgenetic alopecia

A Phase II randomized, placebo-controlled trial in Chinese women with female-pattern hair loss (Ludwig classification) was conducted in parallel with the male trial. Kintor announced in December 2022 that the primary endpoint was met, with statistically significant and clinically meaningful improvement in TAHC at 24 weeks in the active treatment arm relative to placebo [12]. Full numerical results from this trial have not been published in the peer-reviewed literature as of the date of this monograph.

## 7.4 Phase II: United States androgenetic alopecia

A Phase II trial conducted in the United States evaluated 0.5% pyrilutamide applied twice daily in men with androgenetic alopecia. Topline results indicated a mean increase of approximately 10 hairs per square centimeter over the treatment period [17]. This effect size was smaller than the 22.73 hairs per square centimeter increase observed in the Chinese Phase II trial, a discrepancy that may reflect differences in baseline severity, racial or ethnic factors in androgen receptor biology and hair density, formulation and application compliance, or trial methodology.

## 7.5 Phase III: Chinese male androgenetic alopecia

The pivotal Phase III trial in China enrolled 416 male subjects with androgenetic alopecia and evaluated 0.5% pyrilutamide applied twice daily versus placebo for 24 weeks, with the primary endpoint of change in TAHC from baseline. On November 27, 2023, Kintor Pharmaceutical announced that the trial did not demonstrate statistical significance on the primary endpoint [13]. The failure to replicate the Phase II efficacy signal introduced substantial uncertainty regarding the clinical development trajectory.

Possible explanations advanced by Kintor and independent commentators include the lower-than-expected drug retention on the scalp with the 0.5% solution formulation, differences in application technique and compliance in the larger Phase III population, the placebo response in the control arm, and potential pharmacokinetic limitations of the 0.5% concentration.

## 7.6 Long-term safety and efficacy extension

Long-term extension data through 52 weeks were reported from the Phase III safety cohort. At 52 weeks, 46% of patients achieved at least a 10 hairs per square centimeter increase from baseline, and 20% achieved at least a 20 hairs per square centimeter increase. Investigator-assessed Hair Growth Assessment response rates were 53% in men and 48.4% in women. No drug-related sexual dysfunction was observed. The overall adverse event incidence remained low, and no new safety signals emerged with extended treatment duration [14].

## 7.7 Phase II/III: Reformulated 1.0% tincture

In response to the Phase III results with the 0.5% solution, Kintor reformulated pyrilitamide as a 1.0% tincture with enhanced scalp retention properties. Preclinical data indicated that the 1.0% tincture significantly increased the retention concentration on human scalp tissue compared to the 0.5% solution, and is expected to enhance clinical efficacy [16].

A new Phase II/III pivotal trial was initiated in 2025, with dermatology teams from more than 20 domestic hospitals involved, over 750 participants planned for enrollment, and enrollment commencing in early 2025 [14, 16]. Topline results from the Phase II stage announced in 2025 indicated that the primary endpoint was met with statistically significant and clinically meaningful outcomes, demonstrating excellent efficacy and safety [16].

## 7.8 Acne vulgaris

A Phase II trial for the treatment of acne vulgaris was initiated in China, with enrollment completed as of late 2022 [15]. The rationale is the same AR-dependent mechanism: androgen-stimulated sebaceous gland hyperactivity is a principal driver of comedogenesis and inflammatory acne, and topical AR antagonism at the skin surface is expected to reduce sebum production and acne lesion counts. Published results from the acne Phase II trial are not yet available as of the date of this monograph.

## 7.9 Combination therapy

Kintor has announced approval for a clinical trial evaluating pyrilutamide in combination with minoxidil in China, based on the mechanistic rationale that the two agents act through orthogonal pathways (AR antagonism and potassium channel-mediated vasodilation/follicular stimulation) and may produce additive or synergistic efficacy [14]. Results from this combination trial are not yet available.

## 8. Sourcing and Quality Verification

Pyrilutamide is not registered as a marketed pharmaceutical in any jurisdiction and is therefore not available as a pharmaceutical-grade product through licensed pharmacy channels. The compound is available from multiple research chemical suppliers as a research-grade product.

**Principal suppliers:** Selleck Chemicals, MedChemExpress, Cayman Chemical, MedKoo Biosciences, Xcess Biosciences, and Probechem Biochemicals supply pyrilutamide (CAS 1272719-00-2) at purities of 98% or greater by HPLC [3]. Supply is typically in milligram to gram quantities as the free base (solid powder). Pricing is moderate, in the range of \$100 to \$500 per gram depending on quantity and supplier.

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

- High-performance liquid chromatography (HPLC) area-percent purity determination, with a specification of greater than 98%
- High-resolution mass spectrometry confirmation of molecular weight (expected  $[M+H]^+$  at  $m/z$  483.10)
- Nuclear magnetic resonance spectroscopy ( $^1H$ ,  $^{13}C$ ,  $^{19}F$ ) for structural confirmation, particularly verification of the thiohydantoin core, the trifluoromethyl group, and the two fluoroaromatic substituents
- Karl Fischer titration or thermogravimetric analysis for residual moisture content
- Residual solvent analysis by gas chromatography, particularly for dimethylformamide, dichloromethane, and ethyl acetate that are commonly used in the synthesis

Third-party analytical laboratories can provide independent verification of vendor certificates of analysis. The research-grade pyrilutamide market is relatively new (the compound entered research supplier catalogs in approximately 2020 to 2021), and lot-to-lot variability is possible. On-receipt analytical confirmation is appropriate for any investigation where quantitative dose-response precision is important.

## 9. Reconstitution and Handling

Pyrilutamide is supplied as a white to off-white crystalline powder. The compound is poorly soluble in water but readily soluble in DMSO at concentrations exceeding 50 mg/mL.

**Stock solution preparation for in vitro research:** Dissolve in DMSO at 10 to 50 mM concentration (4.82 to 24.1 mg/mL). Aliquot into single-use volumes and store at minus 20 degrees Celsius or minus 80 degrees Celsius. DMSO stock solutions are stable for at least 6 months at minus 20 degrees Celsius when protected from moisture. For cell-based assays, dilute from DMSO stock into culture medium immediately before use; the final DMSO concentration should not exceed 0.1% to avoid solvent cytotoxicity.

**Topical formulation for dermatological research:** The clinical formulation uses proprietary solvent systems. For research purposes, pyrilutamide can be dissolved in a vehicle of ethanol (70%), propylene glycol (20%), and water (10%) at concentrations of 0.5% to 1.0% (5 to 10 mg/mL). The resulting solution should be clear or slightly opalescent. Application to the scalp or skin should be performed with a dropper or spray applicator.

**Storage:** Solid material should be stored at minus 20 degrees Celsius in a desiccated container, protected from light and moisture. Under these conditions, the compound is stable for at least 2 years per manufacturer specifications. Reconstituted solutions in DMSO should be stored at minus 20 degrees Celsius and used within 6 months. Topical research formulations in ethanol-based vehicles should be stored at room temperature (15 to 25 degrees Celsius) and used within 30 days of preparation. Avoid freeze-thaw cycles for DMSO stock solutions; aliquoting for single use is recommended.

## 10. Stack Interactions and Combinations

Pyrilutamide interacts with the androgen signaling axis at the receptor level and may have pharmacological interactions with other agents that modulate androgen biology or dermatological pathways. Investigators conducting research with pyrilutamide, particularly in combination protocols, should consider:

**5-alpha-reductase inhibitors (finasteride, dutasteride):** The combination of topical AR antagonism (pyrilutamide) with systemic 5-alpha-reductase inhibition represents a dual-node approach to androgen pathway blockade. Finasteride reduces DHT production by 60 to 70%; pyrilutamide blocks the residual DHT from activating the AR at the follicular target. The combination is pharmacologically rational and may produce additive efficacy, though it has not been studied clinically. Investigators should be aware that the combination does not eliminate the systemic adverse effects associated with 5-alpha-reductase inhibitors.

**Minoxidil:** Kintor has initiated a clinical trial evaluating pyrilutamide in combination with minoxidil. The two agents act through orthogonal mechanisms: pyrilutamide blocks androgen-mediated follicular miniaturization, while minoxidil promotes follicular vasodilation and prolongs the anagen growth phase through potassium channel activation. The combination is pharmacologically additive and may be synergistic. No pharmacokinetic interaction is expected, as minoxidil is a small hydrophilic molecule with a different dermal and systemic PK profile.

**Topical corticosteroids:** Co-application of topical corticosteroids (for inflammatory scalp conditions or dermatitis) is unlikely to produce pharmacokinetic interaction but may alter the dermal inflammatory milieu. Potent topical corticosteroids applied to the same site may increase dermal vascularity and potentially increase transdermal absorption of pyrilutamide; this interaction has not been characterized.

**Other topical antiandrogens (topilutamide/fluridil, RU-58841):** Concurrent use of multiple topical AR antagonists is pharmacologically redundant and may produce additive contact dermatitis risk without proportional efficacy gains. The combination is not recommended.

**Oral antiandrogens (spironolactone, bicalutamide, cyproterone acetate):** Systemic antiandrogens combined with topical pyrilutamide produce additive AR blockade. The combination may be considered in refractory female-pattern hair loss but increases the cumulative antiandrogen burden and should be monitored for systemic effects.

**CYP enzyme inducers and inhibitors:** Given the negligible systemic exposure of topically applied pyrilutamide, drug-drug interactions mediated by hepatic CYP enzymes are not expected to be clinically relevant. This is a principal advantage of the topical route over systemic antiandrogen administration.

**Retinoids:** Topical retinoids (tretinoin, adapalene) applied to the same skin site may alter stratum corneum integrity and increase transdermal absorption of pyrilutamide. Concurrent use on the same application site should be approached with monitoring.

# 11. Adverse Events and Safety Signal

## 11.1 Common adverse events

The principal adverse events reported across completed clinical trials are local cutaneous reactions at the application site:

- Contact dermatitis (the most commonly reported adverse event in the Phase I US trial, mild severity) [10]
- Pruritus/itching at the application site (the most common adverse drug reaction in the Phase II China trial, 16.1% overall ADR incidence) [11]
- Application-site erythema (mild, reported in a minority of subjects)
- Scalp dryness or flaking (reported in some subjects, likely vehicle-related)

These local adverse events are consistent with the topical formulation vehicle and the dermal irritation potential of concentrated ethanol-based solutions applied to the scalp.

## 11.2 Systemic adverse events

No systemic adverse events attributable to pyrilutamide have been reported in any completed clinical trial. Specifically:

- No sexual dysfunction (erectile dysfunction, decreased libido, ejaculation disorders) has been reported [10, 11, 14]
- No gynecomastia has been reported
- No changes in serum testosterone, DHT, or other hormone levels have been reported
- No hepatotoxicity has been reported
- No cardiovascular adverse events have been reported

The absence of systemic adverse events is consistent with the negligible systemic exposure (peak plasma below 0.5 ng/mL) achieved with the topical formulation.

## 11.3 Serious adverse events

No serious adverse events or serious adverse drug reactions have been reported in any completed pyrilutamide clinical trial [10, 11, 14].

## 11.4 Long-term safety

The 52-week safety extension data confirmed the favorable safety profile observed in shorter trials, with no new safety signals emerging with extended treatment duration. The overall adverse event incidence remained low, and no drug-related sexual dysfunction was observed [14].

## 11.5 Comparison to systemic antiandrogens

The safety profile of pyrilutamide represents a meaningful differentiation from systemic antiandrogens used for androgenetic alopecia. Finasteride (1 mg oral daily) produces sexual adverse effects (erectile dysfunction, decreased libido, ejaculation disorders) in 2 to 8% of patients in registration trials, with persistent symptoms reported in some individuals after drug discontinuation (post-finasteride syndrome) [22]. Dutasteride produces a similar or modestly higher rate of sexual adverse effects. Systemic antiandrogens used in female-pattern hair loss (spironolactone, cyproterone acetate, bicalutamide) carry additional risks including hyperkalemia, hepatotoxicity, and teratogenicity. Pyrilutamide, with no reported sexual or systemic adverse events, occupies a favorable position in the safety hierarchy of antiandrogen treatments for hair loss, contingent on continued confirmation in larger and longer-term datasets.

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative agents against pyrilutamide, evaluated on 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 and clinical alternatives for the treatment of androgenetic alopecia, spanning 5-alpha-reductase inhibitors, topical antiandrogens, and non-androgen-pathway treatments.

### 12.1 Finasteride (oral, 1 mg daily)

**Mechanism:** Selective inhibitor of type II 5-alpha-reductase, blocking the conversion of testosterone to DHT. Reduces serum DHT concentrations by approximately 60 to 70%.

**Novelty:** Low. Finasteride was approved by the FDA for male androgenetic alopecia in 1997 (Propecia) and has been the reference standard oral pharmacotherapy for nearly three decades [8].

**Effect size:** The pivotal registration trials reported a mean increase of approximately 12 to 16 hairs per square centimeter at the vertex over 24 months, with approximately 83% of treated subjects showing no further hair loss progression and approximately 66% showing measurable regrowth [8, 23]. This effect size is the clinical benchmark against which pyrilutamide and other investigational agents are compared.

**Promising potential:** Stable. Finasteride is a mature, generic product with no further development activity beyond formulation variants (topical finasteride). It remains the oral standard of care.

**Side-effect profile:** The principal limitation is the sexual adverse-event signal: 2 to 8% incidence of erectile dysfunction, decreased libido, and ejaculation disorders in registration trials. Post-finasteride syndrome (persistent sexual, neurological, and psychological symptoms after drug discontinuation) has been reported in case

series and is recognized by some regulatory authorities, though its prevalence and mechanism remain debated [22]. Other adverse events include breast tenderness (0.5 to 1%) and mood changes (rare).

**Overall validation:** High. The compound has the most extensive clinical validation of any androgenetic alopecia pharmacotherapy, with decades of registration trial data, long-term safety data, and real-world evidence.

**Comparison to pyrilutamide:** Finasteride has higher overall validation and greater demonstrated long-term efficacy, but carries the sexual adverse-event burden that pyrilutamide is specifically designed to avoid. The pyrilutamide Phase II effect size (22.73 hairs/cm<sup>2</sup> at 24 weeks in the Chinese male trial) is numerically competitive with the finasteride registration data, but the Phase III failure introduces uncertainty. The fundamental distinction is mechanism (systemic DHT reduction versus local AR blockade) and route (oral versus topical), with the safety advantages of topical AR antagonism representing pyrilutamide's principal value proposition.

## 12.2 Dutasteride (oral, 0.5 mg daily)

**Mechanism:** Dual inhibitor of type I and type II 5- $\alpha$ -reductase. Reduces serum DHT by greater than 90%, substantially more than finasteride.

**Novelty:** Low. Dutasteride (Avodart) was developed for benign prostatic hyperplasia and is used off-label for androgenetic alopecia. It is approved for AGA in South Korea and Japan [9].

**Effect size:** A randomized comparative trial (Olsen et al. 2006) demonstrated that dutasteride 0.5 mg daily produced significantly greater hair count increases than finasteride 1 mg daily at 24 weeks (approximately 12.2 vs. 4.7 hairs per cm<sup>2</sup> at the vertex), consistent with the more complete DHT suppression [24]. The effect size exceeds that of finasteride and may exceed that of pyrilutamide at the 0.5% concentration, though direct comparative data are not available.

**Promising potential:** Moderate. Dutasteride is approved for AGA in select Asian markets and is used off-label worldwide. No further pivotal AGA development is expected in Western markets. Topical dutasteride formulations are under investigation.

**Side-effect profile:** Similar to or modestly worse than finasteride, with a 4 to 10% incidence of sexual adverse events in clinical trials and a longer half-life (3 to 5 weeks) that prolongs adverse-event duration after discontinuation [9, 24]. The more complete DHT suppression is a double-edged pharmacological feature: greater efficacy but greater systemic androgen disruption.

**Overall validation:** Moderate to high. Clinical trial data are robust, though regulatory approval for AGA is limited to select jurisdictions.

**Comparison to pyrilutamide:** Dutasteride has a larger demonstrated effect size but a more burdensome side-effect profile. Pyrilutamide's topical, receptor-level mechanism avoids the systemic DHT reduction that underlies both the efficacy and the adverse effects of dutasteride. For patients prioritizing avoidance of systemic antiandrogen effects, pyrilutamide (if efficacy is confirmed in ongoing trials) represents a mechanistically rational alternative.

## 12.3 Topilutamide (Fluridil, Eucapil)

**Mechanism:** Topical nonsteroidal antiandrogen of the substituted flutamide class. Binds the androgen receptor locally and is rapidly hydrolyzed in serum, limiting systemic exposure [25].

**Novelty:** Moderate. Topilutamide was among the first topical antiandrogens developed specifically for androgenetic alopecia. It is registered in the Czech Republic (Eucapil) and is available in some European markets.

**Effect size:** Published clinical data are limited. A 2-year open-label study reported stabilization of hair loss in the majority of treated subjects and modest regrowth in a subset, but large randomized placebo-controlled trials have not been published [25]. Effect size data are insufficient for quantitative comparison.

**Promising potential:** Low. Development has been static. The compound is available as a topical product in select European markets but has not advanced to large-scale registration trials or FDA submission.

**Side-effect profile:** Favorable. Minimal local irritation and no systemic adverse events reported, consistent with the serum-labile design [25].

**Overall validation:** Low. The clinical evidence base is small, non-randomized, and geographically limited.

**Comparison to pyrilutamide:** Topilutamide shares the topical antiandrogen concept with pyrilutamide but has substantially less clinical validation and a narrower geographic availability. Pyrilutamide has higher AR binding affinity ( $K_i$  24 nM vs. estimated 100 to 200 nM for topilutamide), a more extensive clinical trial program, and is further advanced in regulatory development. Topilutamide's principal advantage is its longer market availability and its established (though limited) clinical track record in the Czech Republic.

## 12.4 RU-58841 (PSK-3841)

**Mechanism:** Nonsteroidal antiandrogen of the toluidide class. Competitive AR antagonist with high binding affinity, designed for topical application. The compound was extensively characterized preclinically but was never advanced to registration [26].

**Novelty:** Low. RU-58841 was developed in the 1990s by Roussel Uclaf (now Sanofi) and ProStrakan. Despite promising preclinical data, development was abandoned, reportedly due to formulation stability and regulatory challenges [26].

**Effect size:** Preclinical studies in stump-tailed macaques demonstrated reversal of androgen-driven hair loss with topical application, but no controlled human clinical trial data have been published [26].

**Promising potential:** Very low. The compound is not in active development by any pharmaceutical company. It is available through unregulated research chemical suppliers and has a substantial informal user community, but no regulatory pathway to approval exists.

**Side-effect profile:** No formal human safety data. Preclinical tolerability was acceptable. The unregulated supply chain introduces additional risks related to purity, sterility, and formulation quality.

**Overall validation:** Very low. Preclinical data only; no human clinical trial evidence.

**Comparison to pyrilutamide:** RU-58841 and pyrilutamide share the topical AR antagonist concept, but pyrilutamide has a vastly more developed clinical evidence base, a defined regulatory pathway, and pharmaceutical-grade development. RU-58841 serves as a historical reference compound for the topical antiandrogen class but is not a clinical alternative in any regulated context.

## 12.5 Minoxidil (topical, 2% or 5%)

**Mechanism:** Potassium channel opener (sulfated metabolite opens ATP-sensitive potassium channels). Promotes follicular vasodilation, prolongs the anagen growth phase, and stimulates hair growth through mechanisms largely independent of the androgen axis [27].

**Novelty:** Low. Minoxidil was FDA-approved for androgenetic alopecia in 1988 (2%) and 1997 (5%, Rogaine). It has been the first-line topical treatment for nearly four decades.

**Effect size:** The registration trials demonstrated a mean increase of approximately 15 to 25 hairs per cm<sup>2</sup> at 24 weeks with 5% minoxidil solution versus placebo in men [27]. The effect size is broadly comparable to that of pyrilutamide in the Phase II Chinese male trial (22.73 hairs/cm<sup>2</sup>), though direct comparison is limited by differences in trial populations and methodology.

**Promising potential:** Stable. Minoxidil is a mature, generic product. Newer formulations (foam, oral low-dose minoxidil) are extending the clinical utility. The mechanism is complementary to antiandrogens and combination therapy is actively studied.

**Side-effect profile:** Local adverse events include scalp irritation, pruritus, and contact dermatitis (particularly with the propylene glycol-based solution). Hypertrichosis (unwanted facial hair growth) is reported in some patients, particularly women. Systemic adverse events are rare at topical doses but include tachycardia and fluid retention at higher systemic exposures [27].

**Overall validation:** Very high. The most extensively validated topical treatment for androgenetic alopecia, with decades of registration data, meta-analyses, and real-world evidence.

**Comparison to pyrilutamide:** Minoxidil and pyrilutamide act through completely independent mechanisms (potassium channel activation versus AR antagonism) and are therefore complementary rather than competitive. A combination of pyrilutamide (addressing the androgen axis) and minoxidil (promoting growth-phase stimulation) represents the most pharmacologically rational topical regimen for androgenetic alopecia and is the subject of Kintor's planned combination trial.

Minoxidil has vastly greater overall validation; pyrilutamide offers the mechanistic precision of targeting the specific pathological driver (androgen receptor activation) that minoxidil does not address.

## 12.6 Comparator summary

The five comparators occupy distinct positions in the androgenetic alopecia treatment landscape. **Finasteride** and **dutasteride** are the established oral standards with robust efficacy but the well-documented sexual adverse-event burden that is the principal driver of patient non-adherence and the principal unmet need that pyrilutamide seeks to address. **Topilutamide** shares the topical antiandrogen concept but has minimal clinical validation. **RU-58841** is a historical preclinical reference with no clinical development pathway. **Minoxidil** is the established topical standard with a complementary (non-androgen) mechanism that makes it a combination partner rather than a competitor.

Pyrilutamide occupies a position of high mechanistic rationale and moderate clinical validation: it is the most advanced topical androgen receptor antagonist in clinical development, with Phase II efficacy demonstrated in both male and female AGA, but with a Phase III primary endpoint failure that has not yet been resolved by the reformulated 1.0% tincture data. The principal practical question is whether the enhanced formulation will produce the consistent, statistically significant efficacy that the Phase III 0.5% solution did not achieve. If the ongoing Phase II/III trial with the 1.0% tincture produces positive results, pyrilutamide would occupy a unique and highly favorable position in the treatment landscape: a topical, locally-acting antiandrogen with no systemic hormonal disruption and no sexual adverse events, addressing the specific molecular pathology (AR activation) that drives androgenetic alopecia, with a mechanism complementary to the existing standard of care (minoxidil).

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