

RESEARCH MONOGRAPH . COMPOUND PROFILE

SM-04554

A synthetic 1,4-diketone Wnt pathway activator developed by Samumed (Biosplice Therapeutics) as a topical treatment for androgenetic alopecia, distinguished by its mechanism of follicular Wnt/beta-catenin signaling restoration and hair follicle neogenesis capacity in preclinical models, advanced through Phase 3 clinical evaluation before discontinuation.

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ABSTRACT

SM-04554, also designated dalosirvat (International Nonproprietary Name), is a synthetic small-molecule activator of the canonical Wnt/beta-catenin signaling pathway developed by Samumed, LLC (subsequently renamed Biosplice Therapeutics, Inc.) as a topical treatment for androgenetic alopecia (AGA). The compound activates Wnt signaling with an EC₅₀ of approximately 28 to 29 nanomolar in cell-based reporter assays, producing increases in total and nuclear beta-catenin, versican expression, and Ki-67 proliferation marker specifically in hair follicle compartments. The molecular formula is C₁₈H₁₆O₄ with a molecular weight of 296.32 g/mol; the compound is a 1,4-diketone bearing a 2,3-dihydro-1,4-benzodioxin-6-yl moiety and a terminal phenyl group, conferring moderate lipophilicity (calculated XLogP 2.6) suitable for topical scalp formulation.

The mechanistic rationale for SM-04554 in androgenetic alopecia rests on the observation that Wnt/beta-catenin signaling is essential for the initiation and maintenance of the anagen (growth) phase of the hair cycle and that progressive reduction of Wnt pathway activity in the dermal papilla and hair bulge stem cell niche is a molecular correlate of follicular miniaturization in AGA. SM-04554 activates the pathway downstream of ligand-receptor interaction, increasing nuclear translocation of beta-catenin and transcription of Wnt target genes including those regulating dermal progenitor cell differentiation toward the hair follicle lineage. In preclinical models, topical SM-04554 induced hair follicle neogenesis in CD1 and C57BL/6 mice (2-fold increase in total follicle count after 4 days of treatment) and in Hanford

mini-pigs (significant increase in vellus follicle number sustained through 112 days of observation following a 42-day treatment course).

Clinical development proceeded through Phase 1 (29 subjects, 14-day topical application at 0.05%, 0.15%, and 0.45% concentrations), Phase 2 (two studies: a 49-subject biopsy-endpoint trial and a 300-subject efficacy trial, both 90-day treatment), and Phase 3 (625-subject registration trial initiated November 2018 and completed January 2021). The Phase 1 trial demonstrated safety with only one drug-related adverse event (eye irritation at the 0.45% concentration). The Phase 2 program demonstrated statistically significant increases in non-vellus hair count and density at the 0.15% concentration relative to vehicle, with an inverted-U dose-response in which the 0.15% concentration outperformed the higher 0.25% concentration. Adverse events across the Phase 2 program were mild (scalp redness, burning, stinging) and comparable in frequency to vehicle. No serious adverse events were reported in any treated patient across the Phase 2 program. The Phase 3 trial results were not publicly disclosed; Biosplice Therapeutics removed SM-04554 from its development pipeline in 2021, and a 2023 literature review confirmed cancellation of development based on Phase 3 outcomes. The compound is not approved by any regulatory authority.

SM-04554 is one component of a broader Wnt-modulating therapeutic platform developed by Samumed/Biosplice, which includes lorecivint (SM-04690, a CLK2/DYRK1A kinase inhibitor for knee osteoarthritis) and SM-04755 (a Wnt pathway inhibitor for tendinopathy). The compound is available from multiple research chemical suppliers as a white powder at greater

than 99% purity. This monograph reviews the chemistry, Wnt pathway pharmacology, preclinical hair growth models, the complete clinical evidence base across all trial phases, pharmacokinetic considerations for topical delivery, sourcing and handling, stack-interaction considerations, adverse-event profile, and a comparative assessment of five alternative androgenetic alopecia candidates against SM-04554 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Dalosirvat.

Development code: SM-04554 (Samumed, LLC). The development code SM-04554 is the canonical identifier throughout the clinical trial literature and is the identifier registered on ClinicalTrials.gov for all sponsored trials. The compound is also designated "Wnt pathway activator 1" in some research chemical supplier catalogs [1, 2].

Chemical Abstracts Service registry number: 1360540-81-3.

DrugBank identifier: DB18960.

PubChem compound identifier: 56837361.

Patent reference: Compound 1 in World Intellectual Property Organization patent WO2012024404A1, assigned to Samumed, LLC [3].

International Union of Pure and Applied Chemistry name: 1-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-phenylbutane-1,4-dione.

1.2 Structural class and chemistry

SM-04554 is a synthetic 1,4-diketone (1,4-diarylbutane-1,4-dione) characterized by two aromatic ketone termini connected by an ethylene bridge. The compound belongs to the structural class of diaryl diketones, a scaffold that has yielded bioactive compounds across multiple target classes in medicinal chemistry. The specific substitution pattern of SM-04554 places a 2,3-dihydro-1,4-benzodioxin-6-yl group (a catechol ether) at one terminus and an unsubstituted phenyl group at the other terminus [1, 2].

Molecular formula: C₁₈H₁₆O₄.

Molecular weight: 296.32 g/mol (monoisotopic mass 296.105 g/mol).

Physical properties: White to off-white crystalline powder. The compound has moderate lipophilicity (calculated XLogP 2.6) and low aqueous solubility consistent with its diaryl diketone structure. Topological polar surface area is 52.6 square angstroms. The compound has zero hydrogen bond donors and four hydrogen bond acceptors (two carbonyl oxygens and two dioxane ring oxygens). Rotatable bond count is 5. The compound satisfies all of Lipinski's rules for oral drug-likeness, although it was developed exclusively as a topical formulation [4].

Stereochemistry: SM-04554 contains no stereocenters and is achiral. No enantiomeric or diastereomeric considerations apply to sourcing or quality verification.

1.3 Synthesis

The published patent literature (WO2012024404A1) discloses SM-04554 as one of a series of 1,4-diarylbutanediones prepared by Samumed as Wnt pathway modulators [3]. The general synthetic approach for this structural class involves Friedel-Crafts acylation or transition-metal-catalyzed cross-coupling to install the aryl ketone functionalities on the central ethylene diketone scaffold. Specific synthetic details for SM-04554 have not been disclosed in the peer-reviewed literature; the compound is manufactured by Samumed/Biosplice Therapeutics and by multiple contract research organizations and fine chemical suppliers (MedChemExpress, InvivoChem, Xcess Biosciences, Aobious, MedKoo, Probechem) at greater than 99% purity by high-performance liquid chromatography. The synthesis is not considered complex by medicinal chemistry standards, and the compound is commercially available at moderate cost in milligram to gram quantities [1, 2, 5].

2. Abstract

SM-04554 (dalosirvat) is a small-molecule activator of the canonical Wnt/beta-catenin signaling pathway developed by Samumed, LLC (subsequently Biosplice Therapeutics, Inc., San Diego, California) as a topical treatment for androgenetic alopecia in males [6, 7]. The compound activates Wnt signaling with an EC50 of approximately 28 to 29 nanomolar, producing dose-dependent increases in nuclear beta-catenin accumulation, versican expression, and Ki-67 proliferation marker in hair follicle compartments in vitro and in vivo [8, 9].

The therapeutic rationale rests on the established role of Wnt/beta-catenin signaling in hair follicle morphogenesis and cycling. The Wnt pathway initiates and maintains the anagen (growth) phase of the hair cycle; Wnt ligands secreted by the dermal papilla activate beta-catenin-dependent transcription in matrix keratinocytes and in hair follicle stem cells in the bulge niche. Progressive attenuation of Wnt signaling in the dermal papilla is a molecular feature of androgenetic alopecia, contributing to follicular miniaturization and the transition from terminal to vellus hair production [10, 11]. SM-04554 restores Wnt pathway activity by increasing total and nuclear beta-catenin, thereby promoting dermal progenitor cell differentiation into the hair follicle lineage.

Preclinical studies demonstrated that topical SM-04554 induced de novo hair follicle formation (follicle neogenesis) in CD1 mice (2-fold increase in total follicle count after 4 days of treatment), hair growth induction in depilated C57BL/6 mice (visible growth after 10 days), and sustained increases in vellus follicle number in Hanford mini-pigs (significant increase maintained through 112 days after a 42-day treatment course) [8, 9].

Clinical development proceeded through a Phase 1 safety study (29 subjects, NCT02503137), two Phase 2 studies (a 49-subject biopsy study, NCT02275351; and a 300-subject efficacy study, NCT02503137), and a Phase 3 registration trial (625 subjects, NCT03742518) [6, 7, 12, 13]. The Phase 2 program demonstrated statistically significant increases in non-vellus hair count and non-vellus hair density at the 0.15% topical concentration relative to vehicle, with an inverted-U dose-response relationship in which the lower 0.15% concentration outperformed the higher 0.25% concentration. Biopsy endpoints confirmed increased follicle counts and

maintained anagen-phase status in treated subjects. The safety profile was favorable across all phases, with no serious adverse events reported in any treated patient; adverse events were limited to mild, self-resolving local scalp reactions (redness, burning, stinging) at rates comparable to vehicle [6, 12, 13].

The Phase 3 trial was initiated in November 2018, enrolled 625 subjects, and completed in January 2021. Results were not publicly disclosed. In the first half of 2021, Biosplice Therapeutics removed SM-04554 from its product pipeline, and a 2023 literature review confirmed that the company had cancelled development based on Phase 3 outcomes [14, 15]. The compound is not approved by any regulatory authority and is not in active commercial development. Research-grade material remains available from multiple chemical suppliers.

3. Discovery and Development History

3.1 Origin and platform context

SM-04554 was developed at Samumed, LLC, a private biopharmaceutical company founded in 2008 in San Diego, California, by Osman Kibar. The company was built around a proprietary technology platform targeting the Wnt signaling pathway, a fundamental developmental signaling cascade involved in embryogenesis, tissue homeostasis, stem cell maintenance, and regeneration. Samumed's thesis was that age-related deregulation of Wnt signaling contributes to degenerative diseases across multiple organ systems, and that small-molecule modulators of the pathway could restore tissue regeneration [16, 17].

The company operated in stealth mode for approximately eight years before publicly disclosing its pipeline in 2016, at which point it had raised approximately \$220 million in private capital from investors including IKEA's private venture firm and Vickers Venture Partners. In August 2018, Samumed raised an additional \$438 million, and the company carried a private valuation of approximately \$12 billion, the largest for a private biopharmaceutical company without an approved product at the time [17, 18].

3.2 SM-04554 in the Samumed pipeline

SM-04554 was one of several Wnt-modulating compounds in the Samumed pipeline. The lead program was lorecivivint (SM-04690), an intra-articular CLK2/DYRK1A kinase inhibitor that modulates Wnt signaling for knee osteoarthritis, which advanced to Phase 3 clinical trials [19]. Other pipeline compounds included SM-04755 (a Wnt pathway inhibitor for tendinopathy) and SM-04646 (a Wnt modulator for idiopathic pulmonary fibrosis, for which North American rights were licensed to United Therapeutics) [20].

SM-04554 occupied the dermatology position in the pipeline, developed as the first topical Wnt pathway activator for androgenetic alopecia. The compound was distinct from lorecivivint in both mechanism (direct Wnt activation rather than kinase inhibition) and route of administration (topical rather than intra-articular).

3.3 Clinical development timeline

The clinical development of SM-04554 proceeded on the following timeline:

2014 to 2015: Phase 1 safety, tolerability, and pharmacokinetic study (NCT02503137) in 29 male subjects with androgenetic alopecia (Norwood-Hamilton scale 4 to 7). The study tested three concentrations (0.05%, 0.15%, 0.45%) applied topically once daily for 14 days with a 28-day safety follow-up. Results demonstrated safety and tolerability with no clinically significant adverse events [6].

2014 to 2016: Phase 2 biopsy study (NCT02275351) in 49 male subjects (Norwood-Hamilton scale 4 to 6). The study tested 0.15% and 0.25% SM-04554 concentrations versus vehicle applied topically once daily for 90 days with a 51-day follow-up. Biopsy endpoints demonstrated significantly increased total follicle counts in both treatment arms versus vehicle [12].

2015 to 2016: Phase 2 efficacy study in approximately 300 male subjects. The study tested 0.15% and 0.25% SM-04554 versus vehicle for 90 days with a 45-day follow-up. Results demonstrated significant increases in non-vellus hair count and density at the 0.15% concentration [13].

November 2018: Phase 2/3 registration trial (NCT03742518) initiated; first subject dosed. The trial enrolled 625 male subjects with androgenetic alopecia [7].

January 2021: Phase 3 trial completed per ClinicalTrials.gov listing.

Mid-2021: Biosplice Therapeutics (the renamed Samumed) removed SM-04554 from its product pipeline page and issued a statement indicating that the company was "not pursuing further independent development" and was "evaluating global out-licensing opportunities" [14, 15].

2023: A published literature review confirmed that Biosplice had cancelled SM-04554 development based on Phase 3 trial results [15].

3.4 Rebranding and company status

Samumed, LLC rebranded as Biosplice Therapeutics, Inc. in approximately 2021. The rebranding coincided with the pipeline restructuring that included removal of SM-04554. As of the most recent monograph revision, the Biosplice corporate entity

continues to exist, but no updates on SM-04554 development, out-licensing, or regulatory submissions have been publicly reported since the discontinuation announcement [14].

4. Mechanism of Action

4.1 The canonical Wnt/beta-catenin signaling pathway

The Wnt/beta-catenin pathway (canonical Wnt signaling) is a highly conserved signal transduction cascade that regulates cell proliferation, differentiation, migration, and polarity across virtually all metazoan tissues. In the absence of Wnt ligand stimulation, cytoplasmic beta-catenin is continuously phosphorylated by a destruction complex comprising axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3-beta (GSK3-beta), and casein kinase 1-alpha (CK1-alpha). Phosphorylated beta-catenin is ubiquitinated and degraded by the proteasome, maintaining low cytoplasmic and nuclear beta-catenin concentrations [10, 21].

When Wnt ligands (Wnt1, Wnt3a, Wnt7a, Wnt10b, and others) bind the Frizzled receptor and the LRP5/6 co-receptor complex, the destruction complex is inhibited. Beta-catenin accumulates in the cytoplasm, translocates to the nucleus, and forms transcriptional complexes with TCF/LEF family transcription factors. These complexes activate transcription of Wnt target genes, including those encoding cyclins (cell cycle progression), matrix metalloproteinases (tissue remodeling), Axin2 (negative feedback), and genes specific to the tissue context, including LEF1, versican, and hair keratin genes in the hair follicle [10, 21, 22].

4.2 Wnt signaling in hair follicle biology

Wnt/beta-catenin signaling is essential for hair follicle morphogenesis during embryonic development and for the regulation of the postnatal hair cycle. The hair cycle consists of three principal phases: anagen (active growth, in which the lower follicle regenerates and produces a hair shaft), catagen (regression, in which the lower follicle involutes), and telogen (rest, in which the follicle is quiescent). The transition from telogen to anagen is initiated by Wnt ligand secretion from the dermal papilla, which activates beta-catenin-dependent transcription in hair follicle stem cells residing in the bulge niche and in transit-amplifying matrix cells [10, 22, 23].

Genetic studies have demonstrated the essentiality of Wnt signaling for hair follicle formation and cycling. Conditional deletion of beta-catenin in skin epithelium prevents hair follicle formation in embryogenesis. Overexpression of the Wnt inhibitor Dickkopf-1 (DKK1) produces hair loss in transgenic mice. Conversely, constitutive activation of beta-catenin in skin epithelium produces de novo hair follicle formation (follicle neogenesis) in adult mice [22, 23].

4.3 Wnt pathway dysregulation in androgenetic alopecia

Androgenetic alopecia is characterized by progressive miniaturization of hair follicles in the frontotemporal and vertex scalp regions, driven by the action of dihydrotestosterone (DHT) on androgen receptors in the dermal papilla. A molecular consequence of chronic DHT signaling in the dermal papilla is reduced expression of Wnt ligands and increased expression of Wnt pathway inhibitors, including DKK1 and secreted frizzled-related proteins (SFRPs). The resulting attenuation of Wnt/beta-catenin signaling contributes to premature catagen entry, shortened anagen duration, and progressive follicular miniaturization [10, 11, 24].

The therapeutic rationale for SM-04554 is that exogenous activation of the Wnt/beta-catenin pathway in the hair follicle microenvironment can counteract the DHT-mediated suppression, restore anagen duration, and potentially induce follicle neogenesis by activating endogenous dermal progenitor cells.

4.4 SM-04554 mechanism: Wnt pathway activation

SM-04554 activates the canonical Wnt/beta-catenin pathway with an EC₅₀ of approximately 28 to 29 nanomolar in cell-based TCF/LEF reporter assays [1, 2, 8]. The compound increases total and nuclear beta-catenin protein levels, indicating stabilization of beta-catenin against proteasomal degradation. The precise molecular target through which SM-04554 activates the pathway has not been fully disclosed in the peer-reviewed literature. The compound is classified as a direct Wnt pathway activator (distinct from the kinase inhibition mechanism used by lorecivivint, which inhibits CLK2 and DYRK1A to modulate Wnt signaling indirectly) [8, 19].

In hair follicle-relevant cell systems, SM-04554 produces the following downstream effects:

- Increased total and nuclear beta-catenin protein (immunofluorescence and western blot) [8, 9]

- Increased expression of versican, a Wnt target gene and dermal papilla marker associated with anagen induction [8, 9]
- Increased Ki-67 proliferation marker expression specifically in hair follicle compartments [8, 9]
- Induction of dermal progenitor cell differentiation toward the hair follicle lineage [8]

The specificity of these effects for hair follicle compartments (rather than interfollicular epidermis) in the preclinical models suggests a degree of cellular context dependence that may reflect the particular sensitivity of dermal papilla cells and bulge stem cells to Wnt pathway activation.

4.5 Theoretical safety considerations of Wnt activation

The Wnt/beta-catenin pathway is a known oncogenic signaling axis. Activating mutations in beta-catenin and loss-of-function mutations in the destruction complex component APC are driver events in colorectal carcinoma and other malignancies [21]. Sustained, systemic Wnt pathway activation therefore carries a theoretical risk of promoting neoplastic transformation. The SM-04554 development program addressed this concern through topical (rather than systemic) administration, which limits drug exposure to the scalp and minimizes systemic bioavailability. The Phase 1, 2, and 3 clinical trials monitored for neoplastic events and did not report any such findings [6, 12, 13, 7].

5. Pharmacokinetics and Routes of Administration

5.1 Route of administration

SM-04554 was developed exclusively as a topical formulation applied once daily to the scalp. The formulation vehicle was a polyethylene glycol (PEG)-based solution designed to deliver the compound to the hair follicle infundibulum and dermal papilla region while minimizing systemic absorption [6, 8].

5.2 Topical absorption and systemic exposure

Detailed pharmacokinetic data for SM-04554 have not been published in the peer-reviewed literature. The Phase 1 study (NCT02503137) included systemic pharmacokinetic assessments as a safety measure [6]. The study design (topical application to a limited scalp area at low concentrations of 0.05% to 0.45%) and the physicochemical properties of the compound (molecular weight 296.32, moderate lipophilicity with XLogP 2.6, topological polar surface area 52.6) are consistent with limited transcutaneous absorption and low systemic exposure.

The absence of systemic adverse events across the Phase 1 and Phase 2 programs, the absence of clinically significant changes in ECGs, laboratory values, or vital signs, and the absence of any reported systemic pharmacologic effect are indirect evidence of low systemic bioavailability following topical scalp application [6, 12, 13].

5.3 Local distribution

The compound is designed to distribute through the stratum corneum and through the hair follicle infundibulum into the perifollicular dermis, where the dermal papilla and hair bulge stem cell niche are located. The PEG-based vehicle and the moderate lipophilicity of the compound support partitioning into the follicular microenvironment. Research into nanoparticle delivery systems for SM-04554 has been reported, aimed at enhancing local bioavailability at the target site [25].

5.4 Metabolism and elimination

Specific metabolic and elimination data for SM-04554 have not been published. The 1,4-diketone structure and the benzodioxin ring are susceptible to hepatic cytochrome P450-mediated oxidation and to glucuronide or sulfate conjugation if systemic exposure occurs. Given the topical route and the evidence for limited systemic absorption, hepatic metabolism is not expected to be a principal determinant of the pharmacokinetic profile at clinical doses.

5.5 Concentrations studied

Three topical concentrations were evaluated in clinical development:

- **0.05%:** Phase 1 only; safety assessment dose [6]
- **0.15%:** Phase 1, Phase 2, and Phase 3; the concentration demonstrating optimal efficacy in the Phase 2 program [6, 12, 13]
- **0.25%:** Phase 2; demonstrated lower efficacy than 0.15%, suggesting an inverted-U dose-response [12, 13]
- **0.45%:** Phase 1 only; highest safety assessment dose [6]

The inverted-U dose-response relationship is consistent with the biology of Wnt pathway activation, in which supraphysiological Wnt signaling can paradoxically inhibit hair follicle cycling through premature catagen induction or through activation of negative feedback mechanisms (Axin2, Naked cuticle homolog) [22].

6. Preclinical Pharmacology

6.1 In vitro Wnt pathway activation

SM-04554 activated canonical Wnt signaling with an EC₅₀ of approximately 28 to 29 nanomolar in TCF/LEF luciferase reporter cell lines [1, 2, 8]. The compound increased total beta-catenin protein levels and promoted nuclear translocation of beta-catenin in treated cells. Downstream transcriptional targets of the Wnt pathway, including versican and cyclin D1, were upregulated in response to SM-04554 treatment [8].

6.2 Mouse hair growth models

In CD1 mice, topical SM-04554 induced hair growth following a 4-day treatment period. Total hair follicle counts increased approximately 2-fold compared to vehicle-treated controls [8, 9]. The increase included both terminal and vellus follicle populations, suggesting de novo follicle formation (follicle neogenesis) rather than simple conversion of existing vellus follicles to terminal status.

In depilated C57BL/6 mice (a standard model for anagen induction in which hair regrowth can be quantified visually and histologically), SM-04554 induced visible hair growth after 10 days of topical treatment, compared to minimal regrowth in vehicle-treated controls [8, 9].

Histological analysis of treated skin in both mouse strains confirmed increased expression of Wnt pathway markers (beta-catenin, versican) and the proliferation marker Ki-67 specifically within hair follicle structures, with minimal change in interfollicular epidermis [8, 9].

6.3 Mini-pig model

In Hanford mini-pigs (a large-animal model with skin architecture and hair follicle biology more similar to humans than rodent models), topical SM-04554 applied for 42 days produced a significant increase in vellus follicle numbers [8, 9]. The increase was sustained through day 112 (70 days after cessation of treatment), compared to controls in which follicle numbers returned to baseline. The sustained ef-

fect after treatment cessation is consistent with a disease-modifying (follicle neogenesis) mechanism rather than a purely pharmacologic (anagen maintenance) effect.

6.4 Preclinical safety

Published preclinical safety data for SM-04554 are limited in the public domain. The compound was advanced to Phase 1 human studies, which requires satisfactory completion of good laboratory practice (GLP) toxicology studies including dermal toxicity, dermal sensitization, and systemic toxicity assessments. The absence of any reported safety signal in the preclinical or clinical programs is indirect evidence of an acceptable preclinical safety profile for topical application at the studied concentrations [6].

7. Clinical Evidence Base

7.1 Phase 1 study

Trial registration: NCT02503137 (ClinicalTrials.gov).

Design: Single-center, open-label, ascending-dose safety and tolerability study.

Population: 29 male subjects with androgenetic alopecia, Norwood-Hamilton scale 4 to 7, ages 18 to 55 years.

Treatment: Topical SM-04554 solution applied once daily to the scalp at concentrations of 0.05%, 0.15%, or 0.45%, with 10 subjects per concentration cohort. Treatment duration was 14 days with a 28-day post-treatment safety follow-up [6].

Safety results: Fifteen adverse events were reported by 11 subjects (38%), but 4 of these events occurred in the vehicle group. Investigators determined that only one adverse event (eye irritation in a subject receiving the 0.45% concentration) was related to the study drug. Electrocardiograms, clinical laboratory values, and vital signs showed no clinically significant changes from baseline. Scalp dermatological assessments demonstrated no safety concerns at any concentration [6].

Conclusions: SM-04554 applied topically to the scalp once daily for 14 days was safe and well tolerated at concentrations up to 0.45%. No systemic pharmacologic effects were observed.

7.2 Phase 2 biopsy study

Trial registration: NCT02275351 (ClinicalTrials.gov).

Design: Multi-center, randomized, double-blind, vehicle-controlled trial with biopsy endpoints.

Population: 49 male subjects with androgenetic alopecia, Norwood-Hamilton scale 4 to 6.

Treatment: Topical SM-04554 solution at 0.15% or 0.25% versus vehicle applied once daily for 90 days with a 51-day post-treatment follow-up [12].

Efficacy results: Both SM-04554 concentration groups demonstrated significant increases in total follicle count on scalp biopsy compared to vehicle. The 0.15% concentration showed superior results for terminal (non-vellus) hair follicle counts compared to the 0.25% concentration, establishing the inverted-U dose-response. Both treatment groups maintained anagen-phase follicle proportions while the vehicle group showed declining anagen-phase representation over the treatment period [12].

Safety results: The study reported safety and tolerability consistent with the Phase 1 findings. No serious adverse events were reported. Adverse events were mild and local [12].

Publication: Results were presented at the American Academy of Dermatology annual meeting (2017) and published as an abstract in the Journal of the American Academy of Dermatology [12].

7.3 Phase 2 efficacy study

Trial registration: Part of the NCT02503137 program.

Design: Multi-center, randomized, double-blind, vehicle-controlled efficacy trial.

Population: Approximately 300 male subjects with androgenetic alopecia, Norwood-Hamilton scale 4 to 6.

Treatment: Topical SM-04554 solution at 0.15% or 0.25% versus vehicle applied once daily for 90 days with a 45-day post-treatment follow-up [13].

Efficacy results: The 0.15% SM-04554 concentration demonstrated statistically significant increases in non-vellus hair count (target area hair count, or TAHC) and non-vellus hair density compared to vehicle at days 45, 90, and 135 (the post-treatment follow-up assessment). The 0.25% concentration produced numerically smaller improvements that did not consistently reach statistical significance versus vehicle, confirming the inverted-U dose-response [13].

Safety results: A total of 48 adverse events were reported by 29 subjects across all groups: 14 in the 0.15% SM-04554 group, 16 in the 0.25% SM-04554 group, and 18 in the vehicle group. No serious adverse events were reported in any treatment group.

The adverse-event distribution, with the vehicle group showing a comparable or higher rate than the active treatment groups, supports the interpretation that SM-04554 does not produce dose-dependent toxicity at the studied concentrations [13].

Conclusions: The Phase 2 program identified 0.15% as the optimal topical concentration, demonstrated statistically significant hair count and density improvements, and confirmed a favorable safety profile. These results supported advancement to Phase 3 [7].

7.4 Phase 3 registration trial

Trial registration: NCT03742518 (ClinicalTrials.gov).

Design: Multi-center, randomized, double-blind, vehicle-controlled efficacy and safety study.

Population: 625 male subjects with androgenetic alopecia.

Treatment: SM-04554 topical solution versus vehicle. Specific concentrations and treatment duration have not been publicly disclosed [7].

Timeline: First subject dosed November 19, 2018 (as announced by Samumed via press release). Trial completed January 2021 per ClinicalTrials.gov listing [7].

Results: Phase 3 results were not publicly disclosed. Biosplice Therapeutics did not publish, present, or announce efficacy or safety outcomes from the Phase 3 trial. In the first half of 2021, the company removed SM-04554 from its product pipeline page and issued a statement indicating that it was "not pursuing further independent development" and was "evaluating global out-licensing opportunities" [14, 15].

Interpretation: The absence of public disclosure of Phase 3 results, combined with the removal of the compound from the development pipeline, is consistent with a negative efficacy outcome (failure to meet the primary efficacy endpoint). No safety concerns were publicly reported from the Phase 3 trial. The compound did not advance to regulatory submission in any jurisdiction [14, 15].

7.5 Phase 2/3 study in Turkey

A Phase 2/3 clinical trial of SM-04554 was reported to be underway in Turkey as of April 2021 [15]. Outcomes from this trial have not been publicly reported, and the status of the trial in relation to the overall program discontinuation is unclear.

8. Sourcing and Quality Verification

SM-04554 (dalosirvat) is available as a research-grade chemical from multiple suppliers, including MedChemExpress, InvivoChem, Xcess Biosciences, Aobious, MedKoo Biosciences, Probechem Biochemicals, and NINGBO INNO PHARMCHEM [1, 2, 5, 25]. The compound is supplied as a white powder at greater than 99% purity by high-performance liquid chromatography. Pricing is moderate for research-grade material, in the range typical of patent-expired or non-marketed small molecules.

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

- High-performance liquid chromatography area-percent purity (target: greater than 98%, ideally greater than 99%)
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 297.11 for the protonated molecular ion)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) consistent with the 1,4-diarylbutanedione structure and the benzodioxin substitution pattern
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

As SM-04554 is achiral, chiral purity assessment is not required. The compound has no polymorphism concerns reported in the literature, and the crystalline form supplied by commercial vendors is expected to be consistent across lots.

Third-party analytical verification is recommended for any investigation where dose-response precision is important, particularly for in vivo studies where formulation concentration accuracy directly determines the pharmacologic outcome.

9. Reconstitution and Handling

SM-04554 has limited aqueous solubility consistent with its diaryl diketone structure and moderate lipophilicity. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (10 to 100 millimolar). Working concentrations for cell-based Wnt reporter assays are in the nanomolar to low-micromolar range (EC50 approximately 29 nM), and dilution from DMSO stock into culture medium should maintain the final DMSO concentration below 0.1% to avoid solvent-related cytotoxicity [1, 2].

For topical in vivo applications in animal models, the compound is formulated in polyethylene glycol-based vehicles, ethanol-containing solutions, or other dermal delivery vehicles. The clinical formulation used by Samumed was a PEG-based topical solution; the specific excipient composition has not been publicly disclosed [6, 8].

Storage recommendations for the solid compound include:

- Temperature: minus 20 degrees Celsius for long-term storage; 2 to 8 degrees Celsius for short-term storage
- Protection from light and moisture
- Inert atmosphere (nitrogen or argon) for long-term storage is recommended but not strictly required

DMSO stock solutions should be aliquoted to avoid repeated freeze-thaw cycles and should be stored at minus 20 degrees Celsius. Stability data specific to SM-04554 in solution have not been published; general guidance for 1,4-diketones suggests stability for at least 6 months at minus 20 degrees Celsius in anhydrous DMSO.

10. Stack Interaction Considerations

SM-04554 was developed as a topical formulation with limited systemic bioavailability. Pharmacokinetic drug-drug interactions through hepatic cytochrome P450 enzymes are therefore not expected to be clinically relevant at the studied topical concentrations [6]. However, several pharmacologic and formulation-level interaction considerations are relevant for research applications:

Other Wnt pathway modulators: Concurrent use of SM-04554 with other Wnt pathway activators (lithium chloride, CHIR99021, Wnt3a recombinant protein, other GSK3-beta inhibitors) would be expected to produce additive or synergistic Wnt pathway activation. This combination may be useful in research settings to achieve maximal pathway activation but carries the theoretical risk of supraphysiological Wnt signaling and potential oncogenic transformation in long-term studies [21].

Wnt pathway inhibitors: Concurrent use with Wnt pathway inhibitors (IWP-2, IWR-1-endo, XAV939, DKK1 recombinant protein, tankyrase inhibitors) would be expected to attenuate or abolish SM-04554 efficacy. Such combinations may be useful for mechanistic studies confirming that SM-04554 effects are Wnt-dependent.

Topical minoxidil: Concurrent topical application of SM-04554 and minoxidil has not been studied. The two compounds operate through distinct mechanisms (Wnt activation versus vasodilation and potassium channel opening). Formulation compatibility and potential for altered dermal absorption when co-applied have not been characterized.

Topical finasteride or dutasteride: Topical 5-alpha-reductase inhibitors reduce local DHT production, which may complement SM-04554 by reducing the upstream androgenic suppression of Wnt signaling. No formal combination studies have been reported.

Systemic finasteride or dutasteride: Oral 5-alpha-reductase inhibitors reduce circulating and tissue DHT levels systemically. No pharmacokinetic interaction with topical SM-04554 is expected, and the mechanistic complementarity (androgen axis suppression plus Wnt pathway activation) provides a theoretical rationale for combination research.

Dermal penetration enhancers: Co-formulation or co-application with dermal penetration enhancers (transcutol, oleic acid, dimethyl isosorbide) could increase SM-04554 delivery to the dermal papilla but could also increase systemic absorption. This interaction has not been characterized and should be approached with caution given the oncogenic potential of systemic Wnt pathway activation.

11. Adverse Events and Safety

11.1 Common adverse events

The clinical trial program for SM-04554 demonstrated a favorable safety profile across all phases. The following adverse events were reported at the studied topical concentrations [6, 12, 13]:

- Scalp redness (erythema) at the application site: mild, self-resolving, severity rated 1 to 2 on a 5-point scale
- Scalp burning or stinging at the application site: mild, transient, typically resolving within minutes to hours of application
- Scalp pruritus (itching): mild, intermittent
- Eye irritation: reported in one subject at the 0.45% concentration in Phase 1; classified as the only drug-related adverse event in that study

Adverse-event rates in the Phase 2 efficacy study were comparable across treatment and vehicle groups (14 events in the 0.15% group, 16 in the 0.25% group, and 18 in the vehicle group across a total of approximately 300 subjects), indicating that the local irritation signal is largely attributable to the vehicle formulation rather than the active compound [13].

11.2 Serious adverse events

No serious adverse events were reported in any treated patient across the Phase 1, Phase 2, or (to the extent publicly disclosed) Phase 3 clinical programs [6, 12, 13, 7]. Specifically:

- No neoplastic events were reported
- No systemic pharmacologic effects (cardiac, hepatic, renal, hematologic) were reported
- No discontinuations due to adverse events were reported in the Phase 1 or Phase 2 programs

11.3 Theoretical safety considerations

The principal theoretical safety concern for any Wnt pathway activator is oncogenic potential, given the role of constitutive Wnt/beta-catenin signaling in colorectal carcinoma, hepatocellular carcinoma, and other malignancies [21]. This concern is mitigated for SM-04554 by:

- Topical route of administration with limited systemic bioavailability
- Low drug concentrations (0.05% to 0.45%) applied to a limited body surface area
- Self-limiting duration of treatment in the clinical trial designs (90 days in Phase 2)
- Absence of neoplastic events in the clinical program

Long-term safety data (beyond the clinical trial durations) for topical Wnt pathway activation are not available. Investigators conducting extended preclinical studies with SM-04554 should monitor treated tissue for dysplastic or neoplastic changes.

11.4 Dermal safety

Scalp dermatological assessments in the Phase 1 study, including erythema scoring, edema assessment, and clinical examination, showed no clinically significant changes at any concentration [6]. The compound does not appear to be a dermal sensitizer or a significant irritant at the studied concentrations, although formal sensitization testing data have not been published in the peer-reviewed literature.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative androgenetic alopecia treatment candidates against SM-04554, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal pharmacologic approaches to AGA treatment, spanning anti-androgen, vasodilatory, prostaglandin, and novel targeted mechanisms.

12.1 Minoxidil

Mechanism: Vasodilator; potassium channel opener. Minoxidil sulfate, the active metabolite, opens ATP-sensitive potassium channels in vascular smooth muscle cells surrounding the hair follicle, increasing perifollicular blood flow and nutrient delivery. Additional mechanisms include stimulation of vascular endothelial growth factor (VEGF) expression and prolongation of the anagen phase through incompletely characterized intracellular signaling [26, 27].

Development trajectory: Minoxidil was originally developed as an oral antihypertensive agent. The observation of hypertrichosis as a side effect led to development of topical formulations for AGA. Topical minoxidil (2% and 5% solutions and 5% foam) received FDA approval for AGA in 1988 (2%) and 2006 (5% foam) and is available over the counter in most jurisdictions [26].

Novelty: Low. Minoxidil has been in clinical use for AGA for over 35 years and is the reference standard for topical AGA treatment.

Effect size: Moderate. Meta-analyses of randomized controlled trials report mean increases in non-vellus hair count of approximately 15 to 25 hairs per square centimeter over 24 to 48 weeks of treatment with 5% minoxidil, compared to approximately 5 to 10 hairs per square centimeter for SM-04554 at 0.15% over 90 days [26, 27]. Direct comparison is complicated by differences in treatment duration, assessment methodology, and patient populations.

Promising potential: Established. Minoxidil is FDA-approved, widely available, and the first-line topical treatment for AGA in current clinical practice guidelines.

Side-effect profile: Local adverse events include scalp irritation, dryness, and allergic contact dermatitis (more common with the propylene glycol vehicle in solution formulations). Systemic adverse events are rare with topical application but include hypotension, tachycardia, and fluid retention at high systemic exposures. Hypertrichosis on non-scalp body surfaces is reported in a minority of users [26].

Overall validation: High. Minoxidil is the most extensively validated topical AGA treatment, with decades of clinical use, multiple large randomized controlled trials, and regulatory approval in multiple jurisdictions.

Comparison to SM-04554: Minoxidil operates through a fundamentally different mechanism (vasodilation) than SM-04554 (Wnt pathway activation). Minoxidil has substantially greater clinical validation, longer treatment history, and regulatory approval. SM-04554 offered a mechanistically novel approach (Wnt activation) but failed to demonstrate sufficient efficacy in Phase 3 to support registration. The two agents are mechanistically complementary and could theoretically be combined, though this combination has not been studied.

12.2 Finasteride

Mechanism: Type II 5-alpha-reductase inhibitor. Finasteride inhibits the conversion of testosterone to dihydrotestosterone (DHT) in the hair follicle dermal papilla and in other androgen-sensitive tissues. Reduced DHT levels decrease androgen receptor-mediated suppression of Wnt signaling and other growth-promoting pathways in the dermal papilla [28, 29].

Development trajectory: Finasteride received FDA approval for AGA at 1 mg daily oral dose in 1997. It was previously approved at 5 mg daily for benign prostatic hyperplasia. The compound is the standard oral treatment for male AGA.

Novelty: Low to moderate. The 5-alpha-reductase inhibition mechanism was novel at the time of AGA approval. Topical finasteride formulations represent a more recent development aimed at reducing systemic exposure and associated sexual side effects.

Effect size: Moderate to large. Clinical trials demonstrate mean increases of 10 to 15% in hair count over 12 to 24 months of treatment at 1 mg daily, with prevention of further hair loss in approximately 80 to 90% of treated men [28, 29]. The effect size exceeds that reported for SM-04554 in Phase 2 trials.

Promising potential: Established. Finasteride is FDA-approved, widely prescribed, and a first-line oral treatment for male AGA.

Side-effect profile: The principal safety concern is sexual adverse effects (decreased libido, erectile dysfunction, decreased ejaculate volume), reported in approximately 2 to 4% of treated men in registration trials and in a larger proportion in some observational studies. Post-finasteride syndrome (persistent sexual, neurological, and psychological symptoms after discontinuation) has been reported but remains controversial and incompletely characterized. Depression and anxiety have been reported in postmarketing surveillance [28, 29].

Overall validation: High. Finasteride is one of the two FDA-approved pharmacologic treatments for AGA (along with minoxidil) and has extensive long-term efficacy and safety data.

Comparison to SM-04554: Finasteride addresses the upstream androgenic cause of Wnt pathway suppression in AGA, while SM-04554 directly activates the Wnt pathway downstream. Finasteride has substantially greater efficacy, longer clinical track record, and regulatory approval. SM-04554 offered the theoretical advantage of a topical, non-hormonal mechanism without sexual side effects, but Phase 3 failure terminated this advantage.

12.3 Dutasteride

Mechanism: Dual type I and type II 5-alpha-reductase inhibitor. Dutasteride inhibits both isoforms of 5-alpha-reductase, producing greater suppression of serum and tissue DHT levels than finasteride (approximately 90% versus 70% suppression) [30].

Development trajectory: Dutasteride is approved for benign prostatic hyperplasia at 0.5 mg daily. It is approved for AGA in Japan and South Korea but not in the United States or the European Union for this indication. Off-label use for AGA is common.

Novelty: Low. The mechanism is an extension of finasteride pharmacology with broader isoform coverage.

Effect size: Moderate to large, and numerically superior to finasteride in head-to-head trials. A 24-week randomized trial demonstrated that dutasteride 0.5 mg daily produced significantly greater increases in hair count than finasteride 1 mg daily [30].

Promising potential: Moderate. The compound is established for benign prostatic hyperplasia and is used off-label for AGA. Regulatory approval for AGA in additional jurisdictions has not been pursued.

Side-effect profile: Similar to finasteride but with potentially higher rates of sexual adverse events due to greater DHT suppression. The long elimination half-life (approximately 5 weeks) means that adverse effects persist longer after discontinuation [30].

Overall validation: Moderate to high. The compound has regulatory approval for AGA in two jurisdictions and extensive clinical data supporting efficacy.

Comparison to SM-04554: Dutasteride offers greater DHT suppression and numerically superior hair count outcomes compared to SM-04554. Like finasteride, it addresses the upstream androgenic cause of AGA, while SM-04554 targets the downstream Wnt pathway. The hormonal mechanism and associated sexual side-effect profile are the principal disadvantages relative to the SM-04554 approach, but SM-04554's Phase 3 failure renders this comparison academic.

12.4 Pyrilitamide (KX-826)

Mechanism: Topical androgen receptor antagonist. Pyrilitamide binds and blocks the androgen receptor in skin, preventing DHT from activating androgen-dependent gene transcription in the dermal papilla. Unlike oral anti-androgens, topical application is designed to limit systemic anti-androgen exposure [31, 32].

Development trajectory: Developed by Kintor Pharmaceutical (Suzhou, China). Phase 2 trials in male and female AGA have been completed in China, with Phase 3 trials ongoing. Phase 2 results demonstrated significant improvements in non-velus target area hair count (TAHC) after 24 weeks of treatment [31, 32].

Novelty: High. Pyrilutamide represents a first-in-class topical androgen receptor antagonist for AGA, addressing the androgen signaling axis through a mechanism distinct from 5-alpha-reductase inhibition.

Effect size: Phase 2 data demonstrate significant improvements in hair count, though published effect sizes are not directly comparable to SM-04554 Phase 2 data due to differences in trial design, duration, and assessment methodology.

Promising potential: Moderate to high. The compound is in active Phase 3 development, which is further advanced in the regulatory trajectory than SM-04554 at the time of its discontinuation.

Side-effect profile: Phase 2 data report a favorable safety profile with adverse events comparable to vehicle. Systemic anti-androgen effects have not been reported, consistent with the topical route and local mechanism of action [31, 32].

Overall validation: Low to moderate. Phase 2 data are encouraging but Phase 3 results have not been reported. The compound has not received regulatory approval in any jurisdiction.

Comparison to SM-04554: Pyrilutamide targets the androgen receptor directly (the upstream driver of AGA pathology), while SM-04554 targets the downstream Wnt pathway. Both are topical, non-systemic approaches. Pyrilutamide is further in active development than SM-04554, which has been discontinued. The mechanistic comparison favors pyrilutamide in targeting the primary disease driver, while SM-04554's Wnt activation approach represented a more novel but ultimately less validated strategy.

12.5 GT20029

Mechanism: Androgen receptor degrader using proteolysis-targeting chimera (PROTAC) technology. GT20029 recruits the E3 ubiquitin ligase to the androgen receptor, promoting its proteasomal degradation rather than simply blocking ligand binding. This mechanism achieves more complete suppression of androgen receptor signaling than receptor antagonism [33, 34].

Development trajectory: Developed by Kintor Pharmaceutical. Phase 2 trials in male AGA have been completed, demonstrating efficacy at 0.5% once daily and 1.0% twice weekly concentrations. The twice-weekly dosing regimen achieved effi-

cacy comparable to daily application, which may improve patient adherence [33, 34].

Novelty: Very high. GT20029 is the first PROTAC-based therapeutic candidate for AGA and represents a fundamentally new pharmacologic modality (targeted protein degradation) in dermatology.

Effect size: Phase 2 data demonstrate significant improvements in non-vellus TAHC relative to placebo controls. The twice-weekly regimen achieving comparable efficacy to daily application is a noteworthy finding [33, 34].

Promising potential: Moderate. Phase 2 results are promising, but Phase 3 data and regulatory review are pending. The PROTAC modality is validated in oncology (ARV-110, ARV-471) but is novel in dermatology.

Side-effect profile: Phase 2 data report favorable safety and tolerability, with adverse events comparable to placebo. Systemic androgen receptor degradation has not been reported, consistent with the topical route [33, 34].

Overall validation: Low to moderate. Phase 2 data are available; Phase 3 and regulatory evaluation are pending.

Comparison to SM-04554: GT20029 targets the androgen receptor for degradation (upstream disease driver), while SM-04554 activates the downstream Wnt pathway. GT20029 represents a more novel pharmacologic modality (PROTAC technology) and is in active development, whereas SM-04554 development has been discontinued. Both compounds share the advantage of topical, non-systemic administration.

12.6 Comparator summary

The five comparator compounds span the principal pharmacologic strategies for androgenetic alopecia: vasodilation (minoxidil), systemic anti-androgen therapy (finasteride, dutasteride), topical anti-androgen therapy (pyrilutamide), and targeted protein degradation (GT20029). SM-04554 occupies a unique mechanistic position as the only Wnt/beta-catenin pathway activator to have reached Phase 3 clinical evaluation for AGA.

Minoxidil and **finasteride** are the established reference standards with regulatory approval and extensive clinical validation; both demonstrate effect sizes that appear to meet or exceed SM-04554's Phase 2 outcomes. **Dutasteride** offers greater

anti-androgen efficacy than finasteride with a correspondingly greater side-effect burden. **Pyrilutamide** and **GT20029** represent the most active current development programs in AGA, both targeting the androgen receptor through novel topical approaches.

SM-04554's principal contribution to the AGA therapeutic landscape is the demonstration that topical Wnt pathway activation can produce measurable hair growth improvements in Phase 2 with an acceptable safety profile. The Phase 3 failure terminated the compound's clinical trajectory but does not invalidate the mechanistic approach; the inverted-U dose-response relationship and the apparent difficulty in optimizing Wnt pathway activation for hair growth without triggering negative feedback suggest that the pharmacology is achievable but that the therapeutic window is narrow. Future Wnt-modulating approaches for AGA may benefit from the SM-04554 clinical experience, particularly the dose-response characterization and the demonstration that topical Wnt activation does not produce safety signals in human scalp tissue at the studied concentrations and durations.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. SM-04554 (dalosirvat) is not approved by any regulatory authority for any indication. The compound was discontinued from clinical development following Phase 3 trial completion. Research-grade material is available from multiple chemical suppliers; investigators should obtain analytical confirmation of identity and purity on every lot. Wnt pathway activation carries a theoretical oncogenic risk; investigators conducting in vivo stud-

ies should monitor treated tissues for dysplastic changes. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.