



Research Overview

Development of Fluridil, a Topical Suppressor of the Androgen Receptor in Androgenetic Alopecia

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Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Nonsteroidal antiandrogens (AA) cannot be topically used for androgenetic alopecia (AGA) because of systemic resorption. A new class of androgen receptor (AR) suppressors designed for safe topical treatment of AGA was synthesized from (3-amino-2-hydroxy-2-methyl-N-(4-nitro-3-trifluoromethyl)phenyl) propanamide (BP-34), to contain perfluoroalkyl moieties. The trifluoromethyl derivative (fluridil) at 10 μM decreased expression of the AR in LNCaP human cells by 95%, its serum half-life was 6 h; it decomposes hydrolytically to BP-34 and trifluoroacetic acid. Acute intraperitoneal maximum tolerated dose (MTD) of fluridil in mice is 270–300 mg/kg/d and the subacute MTD is 450 mg/kg/d. The oral LD₅₀ in mice was 2,872 mg/kg in males, 2,232 mg/kg in females, and >2,500 mg/kg in rats. Fluridil solution in isopropanol was not cutaneously absorbed in rabbits, did not sensitize or show any phototoxic or photoallergic effects on guinea pig skin, and demonstrated no skin irritation potential in rabbits and humans. Fluridil solid induced only slight and reversible eye irritancy in rabbits and displayed no cytotoxicity to rabbit corneal fibroblasts *in vitro*. Fluridil demonstrated no significant mutagenicity potential by Ames method. In a double-blind study, 43 males with AGA, Norwood grade II to Va, used topical 2% fluridil in isopropanol or the vehicle daily for 12 months. Anagens (growing hairs) increased in the fluridil group from 76 to 89%. All hematological and biochemistry values remained within normal range, including testosterone, which varied but seasonally. No fluridil or its decomposition product (BP-34) was detected in serum. No adverse side effects were reported. **58:000–000, 2003.**

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Key words: fluridil; androgenetic alopecia; androgen receptor; hair growth; topical antiandrogen

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M. Sovak, A. L. Seligson, Brian K. Campion, and Jason W. Brown are inventors of fluridil and Biophysica, Inc. holds the patent rights.

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