



Attune Pharmaceuticals Announces Positive Data from Recent Pre-Clinical Studies for ATN-249, an Oral Plasma Kallikrein Inhibitor for the Treatment of HAE at C1-INH Deficiency Workshop

NEW YORK, NY. --(BUSINESS WIRE)-- May 22, 2017 — Attune Pharmaceuticals, a biotechnology company focused on the discovery and development of novel oral small molecule therapeutics for treatment of rare diseases, announced today positive results from preclinical safety studies evaluating ATN-249, a novel orally administered plasma kallikrein inhibitor for the treatment of Hereditary Angioedema (HAE). The data was presented in an oral presentation at the 10th C1-INH Deficiency Workshop (Budapest, Hungary) and can be found on the company's website [here](#). The strong safety, high potency, and high selectivity results suggest a wide therapeutic window with once-daily dosing potential of ATN-249.

In the preclinical toxicology and safety pharmacology studies, ATN-249 was generally safe and well tolerated. In addition, pharmacokinetic studies indicated high 24-hour exposure and comprehensive drug recovery after repeat oral doses of ATN-249. "This encouraging data, along with prior published potency and efficacy results, reinforce our belief that our lead drug candidate, ATN-249, has a favorable safety profile and once-a-day dosing regimen to address the unmet need for well-tolerated and safe oral therapies with improved patient quality life and prophylactic efficacy," said Dr. Andrew McDonald, CEO of Attune Pharmaceuticals, "These IND-enabling study results support commencing the Phase 1 clinical development of ATN-249 this summer."

The oral presentation outlined the results of several well-established preclinical assays. Studies included evaluation of potency of ATN-249 compared to C1INH via inhibition of plasma kallikrein, selectivity of ATN-249 on biochemical inhibition of plasma kallikrein relative to other closely related serine proteases, and ATN-249's pharmacokinetics, general toxicity, safety pharmacology, and genotoxicity profiles.

Study Results:

- SAFETY:
 - No-observed-adverse-effect-level (NOAEL) was established at 100 mg/kg/day, mid-dose level in monkeys
 - No mortality or adverse effects were observed on central nervous system, respiratory, and cardiovascular functions in safety pharmacology studies
 - No genotoxicity or coagulation issues were noted in a wide range of studies
- DMPK:
 - After repeat doses at the NOAEL dose of 100 mg/kg/day, ATN-249 provided C_{max} exposure >600-fold and 24-h exposure 20-fold higher than EC_{90} at day 28

- After single oral administration of 30 mg/kg, ATN-249 demonstrated >40% bioavailability in rats, dogs, and monkeys
- After single oral administration of 15 mg/kg in monkeys, ATN-249 provided C_{max} exposure 25-fold and 24-h exposure 4-fold higher than EC_{90}
- ATN-249 demonstrated 99% recovery in intact and bile duct cannulated rats after single oral dosing
- ATN-249 does not significantly inhibit P450 enzymes
- POTENCY: ATN-249 demonstrated ~10-fold greater plasma kallikrein inhibition relative to C1-INH in both biochemical inhibition and contact activation assays — an ex-vivo assay that closely represents clinical pharmacology
 - In biochemical inhibition, ATN-249 had an IC_{50} of 2.7nM and an IC_{90} of 16.2nM versus 25.4nM and 156.9nM, respectively for C1-INH
 - In contact activation assays, ATN-249 had an EC_{50} and EC_{90} of 8.2nM and 61.6nM versus 92.4nM and N/A, respectively for C1-INH
- SELECTIVITY: ATN-249 was >2000-fold more selective at inhibiting plasma kallikrein versus other closely related serine proteases, including tissue kallikrein 5, tissue kallikrein 7, tissue kallikrein 14, plasmin, Factor Xa, Factor VIIa, thrombin, and tissue plasminogen activator (tPA)

Based on the positive performance and excellent pre-clinical safety profile, Phase 1 clinical studies of ATN-249 are expected to start in the summer of this year to evaluate ATN-249's safety, tolerability and pharmacokinetic profile in healthy volunteers.

About Hereditary Angioedema

Hereditary angioedema (HAE) is a rare, potentially life-threatening disease characterized by acute skin and mucosal edema. It is caused by an autosomal dominant mutation of the SERPING1 or F12 genes, resulting in diminished C1 inhibitor levels and/or function. Dysregulation of the contact-kallikrein pathway mediated by dysfunctional C1 inhibitor causes upregulation of bradykinin production, leading to increased vascular permeability, recurrent abdominal pain, and mucosal swelling, which can be fatal with laryngeal involvement. Current treatments are limited by route of administration and adverse events, since all HAE drugs are administered intravenously or subcutaneously, and may be associated with drug-specific adverse effects.

About Attune Pharmaceuticals

Attune Pharmaceuticals is a pre-clinical stage biotechnology focused on the discovery and development of novel oral once-daily small molecule therapeutics for treatment of rare diseases. Attune Pharmaceuticals is currently developing 2 programs in rare diseases: Hereditary Angioedema (HAE) and complement-mediated diseases. Attune Pharmaceuticals has identified ATN-249 as a lead candidate to treat HAE and will begin clinical testing in 2017.



About ATN-249's Clinical Development Program

ATN-249 was designed as a novel, potent, selective, and orally-administered plasma kallikrein inhibitor for the treatment of Hereditary Angioedema (HAE) by blocking kallikrein-mediated production of bradykinin. Preclinical studies in both biochemical and contact activation assays have demonstrated that ATN-249 is highly selective and potent at plasma kallikrein inhibition. ATN-249 has been evaluated in several pharmacokinetic and toxicological studies in multiple species. Given its observed wide therapeutic window and once-daily dosing potential, these preclinical results suggest that ATN-249 may be a potent, safe, orally-administered plasma kallikrein inhibitor for the treatment of HAE.

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