Pharmacokinetics and Safety of ATN-249, a Novel Oral Plasma Kallikrein Inhibitor for Hereditary Angioedema

Ira Kalfus1; Elliot Offman2; Andrew McDonald1
1Attune Pharmaceuticals, Inc., New York City, NY; 2Cetara Strategic Consulting, Toronto, ON, Canada

**BACKGROUND**

- Hereditary angioedema (HAE) is a rare, potentially life-threatening disease characterized by acute skin and mucosal edema.
- HAE may result in recurrent skin swelling, abdominal pain, laryngeal edema, non-meningeval rash, tingling sensations, anxiety, mood changes, or exhaustion.
- HAE is caused by a deficiency in C1 inhibitor (C1-INH), which leads to increased levels of plasma kallikrein
- Increased levels of plasma kallikrein lead to elevated levels of bradykinin, which causes vasoconstriction, inflammation, and edema.
- Currently, there is no cure for this need for well tolerated, orally-administered therapies that control plasma kallikrein activity and prevent HAE attacks.

**OBJECTIVES**

- ATN-249 is a novel, orally-administered plasma kallikrein inhibitor that potentially treats HAE by blocking kallikrein-mediated production of bradykinin
- A randomized, double-blind, placebo-controlled single ascending dose and crossover food effect study
- 48 healthy male participants (6 active:2 placebo in each of the 6 dose cohorts) received a single daily dose of ATN-249: 50, 100, 150, 200, 400, or 800 mg
- Subjects in the 100 mg dose cohort received first dose of ATN-249 under fasted condition in period 1 and after a 7-day washout, a second dose 30 minutes after the start of a high fat, high caloric meal in period 2.
- Serial blood draws were collected to calculate PK parameters, including area under the curve (AUC) from time zero to infinity (AUCinf), maximum concentration (Cmax), time of maximum concentration (Tmax), and half-life.
- Safety measures including treatment-emergent adverse events (TEAEs) were assessed

**RESULTS**

- Participant demographics were well balanced by cohort Table 1
- Minimal food effect was observed following 100 mg dosing (Table 3)
- ATN-249 was generally safe and well tolerated across all 6 dose cohorts:
  - 29 TEAEs were observed, all TEAEs were mild (grade 1)
  - Top 3 most common TEAEs were headache, upper respiratory tract infection, and lightheadedness (2 incidences for each TEAE, respectively)
  - No drug-related TEAEs and no serious AEs (SAEs)
  - TEAEs were equally distributed across all cohorts

**CONCLUSIONS/DISCUSSION**

- ATN-249 systemic exposure increased in a dose-dependent manner and was largely proportional to dose
- PK results showed low to moderate between-subject variability
- ATN-249 PK after a high fat, high caloric meal was similar to fasting conditions
- Once-daily dosing of ATN-249 was generally well tolerated with no moderate or severe TEAEs, no drug-related TEAEs, no SAEs, and no dose limiting toxicity
- Results demonstrate predictable PK and support further development of ATN-249 as a potent, safe, oral plasma kallikrein inhibitor for the prophylactic treatment of hereditary angioedema (HAE)

**ACKNOWLEDGMENTS**

Writing support was provided by Xelay Acumen Group, Inc. Study was funded by Attune Pharmaceuticals, Inc.

**REFERENCES**