Poster #03

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

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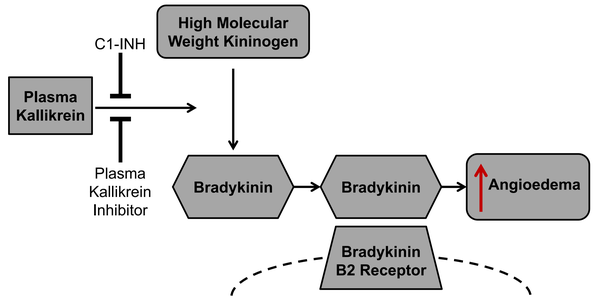
BACKGROUND

- Hereditary angioedema (HAE) is a rare, potentially life-threatening disease characterized by acute skin and mucosal edema[1]
- HAE may result in recurrent skin swelling, abdominal pain, laryngeal edema, nonerythematous rash, tingling sensations, anxiety, mood changes, or exhaustion[1]
- HAE is caused by a deficiency in C1 inhibitor (C1-INH), which leads to increased levels of plasma kallikrein[2]
- Increased levels of plasma kallikrein lead to elevated levels of bradykinin, which causes vasodilation, inflammation, and edema[2]
- Currently, there is an unmet need for well tolerated, orally-administered therapies that control plasma kallikrein activity and prevent HAE attacks
- ATN-249 is a novel, orally-administered plasma kallikrein inhibitor that potentially treats HAE by blocking kallikrein-mediated production of bradykinin

Figure 1: Overview of Hereditary Angioedema and C1-INH Pathway-Specific Treatment Options*



* Adapted from Ameratunga R, et al. Front Immunol. 2016.

OBJECTIVES

Assess the safety, tolerability, and pharmacokinetics (PK) (including food effect) of ATN-249 in healthy male participants in a single-ascending-dose (SAD) study

MATERIALS & METHODS

- 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 mg, 100 mg, 150 mg, 200 mg, 400 mg, 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 (AUC_{inf}), maximum concentration (C_{max}), time of maximum concentration (T_{max}), and half-life
- Safety measures including treatment-emergent adverse events (TEAEs) were assessed

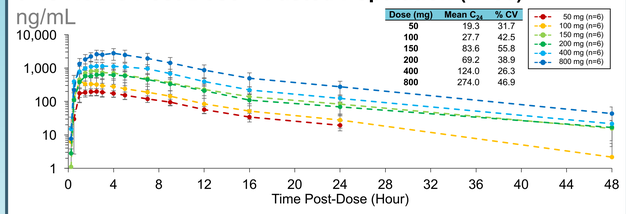
RESULTS

- Participant demographics were well balanced by cohort **(Table 1)**
- AUC and C_{max} increased proportionally with dose **(Figure 3 and 4)**
- 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

Table 1: Participant Demographics (n=48)

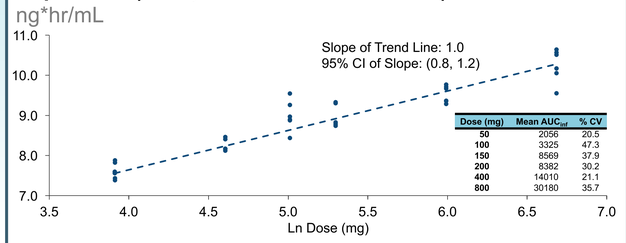
Characteristics		Dose (mg) 50	100	150	200	400	800	All
Age, Years	Mean (SD)	27(5)	26(5)	25(4)	17(11)	27(6)	28(11)	25(8)
Race, % (n)	Caucasian	38(3)	88(7)	63(5)	50(4)	75(6)	50(4)	60(29)
	Others	63(5)	13(1)	38(3)	50(4)	25(2)	50(4)	40(19)

Figure 2: Mean (±SD) Plasma Concentration of ATN-249 0-48 Hours Post Dose – Fasted Population (n=36)



Concentrations increased in a dose-dependent manner

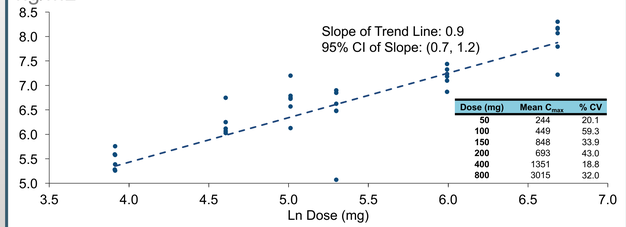
Figure 3: Ln AUC_{inf} of ATN-249 by Ln Dose – Fasted Population (n=36, 6 in Each Dose Cohort*)



* 5 subjects in 200 mg cohort had AUC_{inf} data

AUC_{inf} increased proportionally with dose

Figure 4: Ln C_{max} of ATN-249 by Ln Dose – Fasted Population (n=36, 6 in Each Dose Cohort)



C_{max} increased proportionally with dose

Table 2: Mean (% CV) PK Parameters of ATN-249 by Dose – Fasted Population (n=36, 6 in Each Dose Cohort)

Parameter	Dose (mg) 50	100	150	200*	400	800
AUC_{inf} (ng*hr/mL)	2056 (20.5)	3325 (47.3)	8569 (37.9)	8382 (30.2)	14010 (21.1)	30180 (35.7)
C_{max} (ng/mL)	244 (20.1)	449 (59.3)	848 (33.9)	693 (43.0)	1351 (18.8)	3015 (32.0)
T_{max} (Hours)	1.8 (43.3)	2.8 (109.7)	1.9 (19.6)	2.3 (50.2)	2.4 (57.7)	2.9 (33.3)
Half-Life (Hours)	6.5 (24.1)	8.0 (33.0)	9.7 (15.4)	9.8 (11.3)	9.5 (9.9)	9.0 (9.9)

* 5 subjects in 200 mg cohort had data for AUC_{inf} and half-life

Table 3: Geometric Mean (Geometric % CV) AUC_{inf} and C_{max} Following ATN-249 100 mg – Fasted vs. Fed Conditions (n=6 Under Each Condition)

Parameter	Fasted	Fed	% Ratio*
AUC_{inf} (ng*hr/mL)	2573 (135.1)	3866 (16.1)	150.3
C_{max} (ng/mL)	297 (236.1)	382 (35.8)	128.5

* Percent geometric mean ratio calculated by 100*(Fed/Fasted)

Minimal food effect was observed

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:
1. Bork K, et al. J Allergy Clin Immunol. 2012.
2. Ameratunga R, et al. Front Immunol. 2016.

Presented at WSAAI, January 20-24, 2019, Maui, Hawaii