Poster L11

Selectivity, Potency, and Exposure Evaluation of ATN-249, A New Oral Kallikrein Inhibitor for Hereditary Angioedema

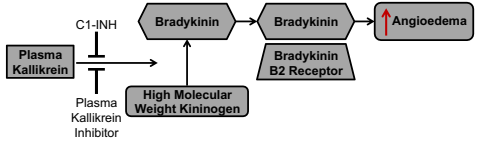
Ira Kalfus[1]; Andrew McDonald[1]; Shawn Qian[1]
[1]Attune Pharmaceuticals, LLC, New York City, NY

Attune Pharmaceuticals

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 of 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 orally-administered therapies that control plasma kallikrein activity, prevent HAE attacks, and are well-tolerated

Figure 1: Overview of Hereditary Angioedema and C1-INH Pathway-Specific Treatment Options[2]



2: Adapted from Ameratunga R, et al. Front Immunol. 2016

- ATN-249 is a novel, orally-administered plasma kallikrein inhibitor that potentially treats HAE by blocking kallikrein-mediated production of bradykinin

OBJECTIVES

The objective of this preclinical study was to evaluate the selectivity of ATN-249, as well as the potency, pharmacokinetic exposure, and safety of ATN-249 as compared to C1 inhibitor (C1-INH)

MATERIALS & METHODS

- Selectivity was evaluated by biochemical inhibition on plasma kallikrein relative to other serine proteases, including tissue kallikrein 5, plasmin, Factor Xa, Factor VIIa, thrombin, and tissue plasminogen activator (tPA)
- Potency was evaluated by biochemical inhibition and contact activation assays in human plasma
- Pharmacokinetic exposure was evaluated in monkeys after a single oral administration of ATN-249 at 15mg/kg
- The no-observed-adverse-effect-level (NOAEL) was evaluated in 14-day non-GLP rat and monkey toxicology studies; animals were given daily doses of 100 or 300mg/kg

RESULTS

- ATN-249 was >2000-fold more selective at inhibiting plasma kallikrein versus other closely related serine proteases (**Table 1**)
- In biochemical inhibition, ATN-249 had an IC_{50} of 2.7nM vs 25.4nM for C1-INH; in contact activation assays, the EC_{50} was 8.2nM vs 92.4nM, respectively (**Figure 2**)
- A single oral dose of ATN-249 at 15mg/kg provided 24-hour exposure (C_{24}) 30-fold greater than EC_{50} (**Figure 3**)
- No adverse events were observed at the highest dose (300mg/kg), setting the no-observed-adverse-effect-level (NOAEL) at 300mg/kg

Table 1: Selectivity of ATN-249

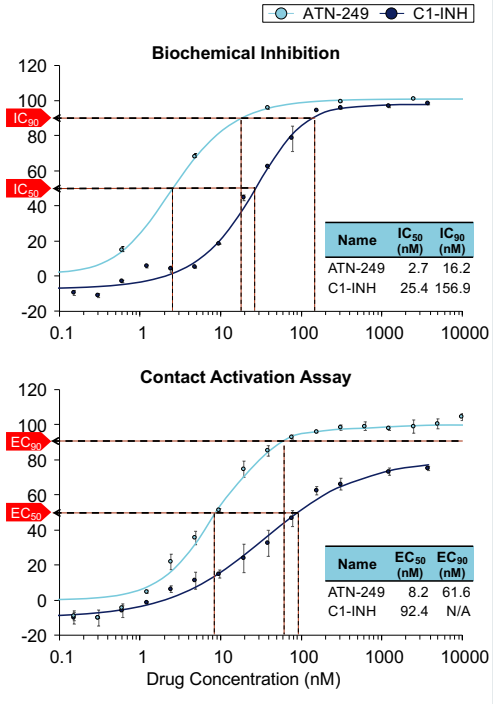
IC_{50} (nM)

Serine Protease	IC_{50}
Plasma Kallikrein	2.7
Tissue Kallikrein 5	>20,000
Plasmin	>7,000
Factor Xa	>50,000
Factor VIIa	>50,000
Thrombin	>100,000
Tissue Plasminogen Activator (tPA)	>100,000

ATN-249 demonstrated >2000-fold selectivity at inhibiting plasma kallikrein versus other serine proteases

Figure 2: Potency of ATN-249 and C1-INH

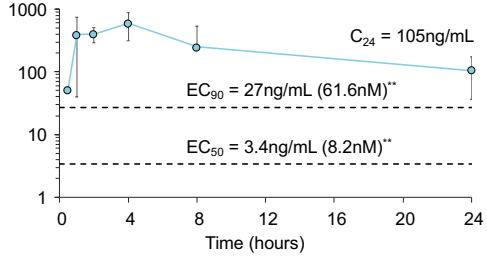
Plasma Kallikrein Inhibition (Percent)



ATN-249 was 9- to 11- fold more potent than C1-INH at inhibiting plasma kallikrein in both biochemical inhibition and contact activation assays

Figure 3: Pharmacokinetic Exposure of ATN-249 After a Single Oral Dosing at 15 mg/kg* in Monkeys

Plasma Concentration (ng/mL)



* Approximately 50 mg/animal (400 mg human equivalent dose)
** EC_{50} and EC_{90} derived from contact activation assay inhibition

A single oral dosing of ATN-249 at 15mg/kg provided 24-hour exposure (C_{24}) 30-fold greater than EC_{50} in monkeys

CONCLUSIONS/DISCUSSIONS

- ATN-249 was highly selective at plasma kallikrein inhibition compared to other closely related serine proteases
- 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
- After a single dose, ATN-249 at 15mg/kg provided 24-hour exposure 30-fold greater than EC_{50} and 20-fold below the NOAEL
- These results suggest a wide therapeutic window and once-daily dosing potential
- ATN-249 may be a potent, safe, orally-administered plasma kallikrein inhibitor for treatment of HAE

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

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