BACKGROUND

ACH-4471 is a novel, highly potent and specific orally-administered small molecule inhibitor of factor D (fD), a serine protease within the complement alternative pathway (AP).

**Proposed mechanism of action**
- Prevents factor B cleavage into Ba and Bb in the AP, leading to:
  - Blockade of C3 convertase production and its subsequent amplification
  - Prevention of C3 fragment deposition on paroxysmal nocturnal hemoglobinuria (PNH) cells, which is associated with the development of extravascular hemolysis in the setting of C5 blockade.

**Structural biology**
- Achieved high resolution (0.8 Å), three dimensional x-ray structure of ACH-4471 complexed with fD.

**Preclinical**
- Binding affinity to human fD: Kᵢ = 0.54 nM
- Inhibition of catalytic activity of fD against factor B: Kᵢ = 5.7 nM
- Inhibition of AP activity in vitro:
  - IC₅₀ = 27 nM for rabbit erythrocyte hemolysis
  - IC₅₀ = 14 nM for PNH erythrocyte hemolysis
- IC₅₀ = 26 nM by Wieslab assay
- Low potential for off-target inhibition of other serine proteases
- Well-tolerated in non-clinical toxicology studies

OBJECTIVES

- Assess safety and tolerability of single ascending oral doses in healthy volunteers
- Evaluate pharmacokinetic (PK) and pharmacodynamic (PD) profiles and PK/PD relationship as measured by serum AP activity ex vivo

METHODS

**Phase 1a Healthy Volunteer Study (evaluated for 28 days after dosing)**
- **Group 1**: 200 mg, single dose (6 active + 6 placebo subjects)
- **Group 2**: 600 mg, single dose (6 active + 2 placebo subjects)
- **Group 3**: 1200 mg, single dose (6 active + 2 placebo subjects)
- **Group 4**: 1200 mg x 2 doses (Q12H) (6 active + 2 placebo subjects)

**All Groups**
- Inhibition of serum AP activity evaluated by AP Wieslab assay and hemolysis assays
- 36 subjects dosed and evaluated (35 males + 1 female)
- Median age of 24.2 years (range 21.0 - 54.2)
- Followed for AEs/SAEs through the last scheduled visit at Day 28
- Blood samples collected at predefined time points from Day 1 to Day 7 to determine plasma concentrations

RESULTS

**Demographics**

**Inhibition of AP Hemolysis**

**Pharmacodynamics**

**Pharmacokinetics**

**Safety**

**CONCLUSIONS**

ACH-4471 was well-tolerated at all evaluated dose levels, without evidence for drug-related safety issues, and achieved up to 100% inhibition of AP complement activity.

- **PD**: 1200 mg x 2 doses (Q12H) achieved median 99.5% inhibition of AP hemolysis at 24 hours.
- **PK/PD modeling**: Predicts that a dosing regimen of 750 mg (Q12H) dosing regimen could achieve greater than 90% sustained inhibition of AP activity.

ACH-4471 may prevent both intravascular and extravascular hemolysis in PNH patients based on its unique mechanism of action.

- Formulation optimization is being evaluated for potential QD dosing.

**REFERENCES**