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An Orally Administered Small Molecule Factor D Inhibitor (ACH-4471) For Treatment of PNH, C3G and Complement – Mediated Diseases: Interim Phase 1 Results In Healthy Volunteers

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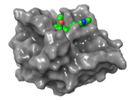
BACKGROUND

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[1], which is associated with the development of extravascular hemolysis in the setting of C5 blockade[2,3]
- **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: K_D = 0.54 nM
  - Inhibition of catalytic activity of fD against factor B: Ki = 5.7 nM
  - Inhibition of AP activity in vitro:
    - IC_{50} = 27 nM for rabbit erythrocyte hemolysis
    - IC_{50} = 14 nM for PNH erythrocyte hemolysis
    - IC_{50} = 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* 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

*Tests in the presence of potent activator: LPS, a bacterial endotoxin (Wieslab®) or rabbit erythrocytes (hemolysis)

RESULTS

Demographics

	Group 1	Group 2	Group 3	Group 4	Placebo
	200 mg QD (N = 6)	600 mg QD (N = 6)	1200 mg QD (N = 6)	1200 mg x 2 doses (Q12H) (N = 6)	0 mg (N = 12)
Mean Age (years)	26.4	22.3	26.2	24.9	30.3
Gender					
Male, n (%)	6 (100)	6 (100)	6 (100)	6 (100)	11 (91.7)
Female, n (%)	0	0	0	0	1 (8.3)
Race					
White, n (%)	5 (83.3)	5 (83.3)	2 (33.3)	2 (33.3)	10 (83.3)
Asian, n (%)	0	1 (16.7)	4 (66.7)	3 (50.0)	0
Other, n (%)	1 (16.7)[a]	0	0	1 (16.7)[b]	2 (16.7)[c]
Mean BMI (kg/m²)	24.7	24.7	23.5	23.2	24.4

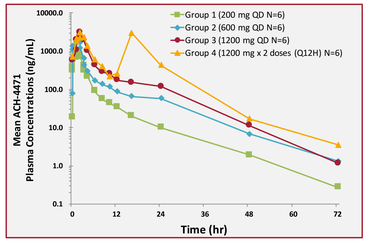
[a] Mixed; White and Pacific Islander, [b]Maori/Tongan, [c]One subject identifies as Maori. One subject identifies as New Zealand Maori.

Safety

- No treatment emergent adverse events (TEAEs) leading to discontinuation
- No drug-related serious adverse events or drug-related Grade 3/4 TEAEs

Pharmacokinetics

Fig 1: *Mean Plasma PK*



- Peak plasma concentrations (C_{max}) achieved by 1 to 2.5 hours for all dose groups
- Majority of exposure (measured as AUC) occurred over first 24 hours
- Terminal phase begins 16 hours post dose
- Mean terminal half-life ~ 9 hours

Pharmacodynamics

Fig 2: *AP Wieslab Activity vs AP Hemolysis Activity*

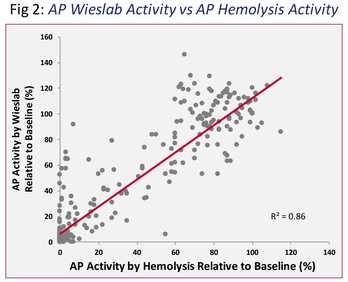
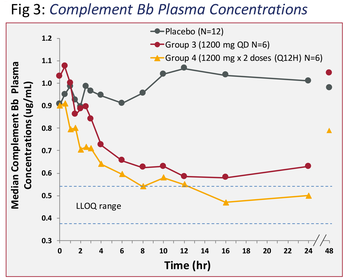


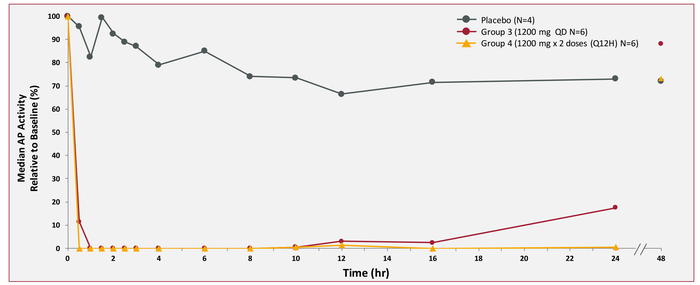
Fig 3: *Complement Bb Plasma Concentrations*



- Up to 100% inhibition of AP complement activity was achieved in all dose groups, and duration of inhibition was dose-dependent
- Mean plasma concentrations necessary to achieve AP Wieslab inhibition:
  - > 80% ~ 180 ng/mL and > 90% ~ 230 ng/mL
- AP Wieslab and AP hemolysis assays are well correlated (R^2 = 0.86) (Fig 2) (all data for groups 1-4 up to 48 hours)
- Plasma Bb concentration decreased in a dose-dependent fashion with a nadir at 16 hours post dose and gradual recovery to original levels by 48 hours (Groups 3 and 4) (Fig3)
- No significant change in serum fD concentration as well as complement C3, C4, and classical pathway function CH50 compared to baseline in all Groups (data not shown)

Inhibition of AP Hemolysis

Fig 4: *AP Activity as Measured by Hemolysis*



- Median Inhibition of AP hemolysis at 24 hour time point in Group 4 is 99.5% (Range 96-100%) (Fig 4)
- Regimen modeling: PK/PD modeling indicates that a 750 mg (Q12H) dosing regimen could achieve greater than 90% sustained inhibition of AP activity

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 administered every 12 hours would deliver sustained suppression of AP activity
- **Bb and Ba levels (cleavage products of factor B) are potentially useful as *in vivo* biomarkers of fD inhibition**
  - Bb declined after dosing, reaching a nadir by 16 hours in Groups 3 and 4
  - Bb gradually returned to baseline by 48 hours post dose
- **Ongoing development program**
  - 14-day multiple ascending dose study planned for 2Q2016
  - Plans to initiate dosing in PNH and C3G patients by year end 2016
  - 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

[1]**Gavriilaki E., et al.** Small molecule factor D inhibitors block complement activation in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. *Blood. 2015 Dec; 126 (23):275*

[2]**Risitano AM, et al.** Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. *Blood. 2009;113(17):4094-100*

[3]**Hill A, et al.** Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization. *Haematologica. 2010 Apr;95(4):567-73*

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