Factor D Inhibition with ACH-4471 Reduces Complement Alternative Pathway Hyperactivity and Proteinuria in C3 Glomerulopathy: Preliminary Proof-of-Concept Data

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C3 Glomerulopathy (C3G)

- **C3G**
  - Dense deposit disease (DDD)
  - C3 glomerulonephritis (C3GN)
- Estimated prevalence of 8–12 people affected per million in major markets
  - Incidence rate of 1–2 per million patients diagnosed with C3G on an annual basis
- There are no approved treatments indicated for patients with C3G
  - Non-specific treatment approaches include blood pressure control and broad immunosuppression
- ACH-4471: First-in-class, selective, oral complement alternative pathway (AP) inhibitor targeting factor D serine protease


Factor D Inhibitor for the Treatment of C3G
Factor D Inhibitor for the Treatment of C3G

C3G: A Disease of Alternative Pathway (AP) Hyperactivity
- Increased consumption of intact C3
- Excess production of C3 fragments
- C3 fragments deposited in glomeruli
Factor D Inhibitor for the Treatment of C3G

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ACH-4471: An AP Inhibitor

ACH-4471 is the first drug designed to target the underlying pathophysiology of C3G
- ACH-4471 inhibits factor D, selectively reducing AP activity
- Reduction of AP hyperactivity should prevent further glomerular C3 deposition
Factor D Inhibitor for the Treatment of C3G

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Key Biomarkers
- Intact C3
- C3 fragments
- Bb/Ba
ACH-4471: First-in-Class Oral Factor D Inhibitor

ACH-4471
• Potent and specific modulator of AP
• More than 150 healthy volunteers exposed with acceptable safety profile at target exposures

C3G CLINICAL DEVELOPMENT STUDIES
• Ongoing 14-day Phase 2a study (data presented today)
• Two ongoing Phase 2b proof-of-concept (POC) studies
  • 6-month, randomized, placebo-controlled trial
  • 12-month, open-label POC trial

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) CLINICAL DEVELOPMENT
• Patients have received drug for more than one year with an acceptable safety profile
• POC established in PNH based on improvement in hemoglobin, lactase dehydrogenase, PNH clone size and FACIT scores

ACH-4471 inhibits AP by blocking cleavage of complement factor B
C3 GLOMERULOPATHY (C3G)
Phase 2 14-day Trial in Patients with C3G or IC-MPGN

SCREENING
CRITERIA
Must have diagnosis of C3G or IC-MPGN based on central review of historical biopsy
Low C3 with normal/near-normal C4

TREATMENT
14 DAYS
GROUP 1
2 patients received ACH-4471 100mg TID x 14 days followed by 7-day taper

GROUP 2
Up to 8 additional patients to receive ACH-4471 at doses up to 200mg TID x 14 days followed by 7-day taper

CLINICAL TRIAL DESIGN

TAPER
7 DAYS
FOLLOW UP
28 DAYS

OUTCOME MEASURES

- Changes in AP biomarkers:
  - Intact C3 levels
  - C3 fragments
  - Bb/Ba
- Clinical manifestations of disease: albumin to creatinine ratio (ACR), BP, eGFR
- Safety and tolerability
- Pharmacokinetic profile

https://www.clinicaltrials.gov/ct2/show/NCT03124368

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Key Baseline Patient Characteristics

- Concomitant medication doses were stable for at least one month prior to the first dose of study drug, and included mycophenolate mofetil (n=2), prednisone (n=2), ACE/ARB (n=4), atorvastatin (n=2), and spironolactone (n = 3)
- eGFR > 60 ml/min/1.73m² in all patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>Age (Y)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Urine dipstick for protein</th>
<th>ACR (0-2.5 mg/mmol) Day 1 Pre-dose</th>
<th>BP (mmHg)</th>
<th>Renal Biopsy Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>30</td>
<td>M</td>
<td>67</td>
<td>3+</td>
<td>259.3</td>
<td>126/72</td>
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<tr>
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<td>B</td>
<td>19</td>
<td>M</td>
<td>68</td>
<td>3+</td>
<td>580.3</td>
<td>123/80</td>
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<td>2</td>
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<td>27</td>
<td>M</td>
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<tr>
<td></td>
<td>D</td>
<td>22</td>
<td>M</td>
<td>39</td>
<td>3+</td>
<td>276.3</td>
<td>119/74</td>
<td>C3GN</td>
</tr>
</tbody>
</table>

* Final review by central pathologist confirmed that the historical biopsy met criteria for IC-MPGN

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Trends in AP Activity with 14-Day ACH-4471 Treatment

- Trends in AP biomarkers show reduction in AP hyperactivity with ACH-4471 treatment
- Data suggest that further improvements in AP hyperactivity may be observed with longer treatment durations

**Mean Serum C3 (g/L)**
- Range: 0.78–1.82
- n=4

**Mean Fragment C3 (% of total C3)**
- Range: 1.4520–5.4054
- n=4

**Mean Complement Bb (μg/ml)**
- Range: 0.4900–1.420
- n=4

**Mean Ba Production, ex vivo† (ng/ml)**
- † Ex vivo Ba production assay is non-GLP
- Day 1 predose: 0.3
- Day 15: 0.35
- Day 28: 0.4
- Day 35: 0.45

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## Evidence of fD Inhibition and the AP Response

### Table: Baseline Biomarker Data

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<tr>
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<th>BASELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Serum C3</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Fragment C3(^*) (% of total)</td>
<td>High</td>
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<tr>
<td></td>
<td>Bb</td>
<td>Normal</td>
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<tr>
<td></td>
<td>Fragment C3(^*) (% of total)</td>
<td>Fragment undetectable</td>
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Red, in the baseline and post-treatment columns, represents a value that is consistent with AP hyperactivity. Green in the on-treatment column indicates evidence for AP inhibition. 

\(^*\) Fragment C3 (% of total) normal range is derived from normal ranges of components.
Evidence of fD Inhibition and the AP Response

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<tr>
<td></td>
<td>Fragment C3* (% of total)</td>
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<td>Decreased to baseline</td>
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**ON-TARGET EFFECT WITH REDUCED AP HYPERACTIVITY**

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Reduction in ACR with 14-Day ACH-4471 Treatment

- Stable eGFR and blood pressure observed
- Patients A, B, & C had approximately 50% reduction in ACR
- Patient D had highly variable ACR values; as a result, two 24 hr urinary proteins were collected on days 14 (0.7g/day) and 17 (2.44 g/day)
ACH-4471: A Potential Innovative Treatment for C3G

- C3G is a disease of AP hyperactivity with C3 fragment deposition in glomeruli

- ACH-4471 is an oral, potent, factor D inhibitor that reduces AP activity
  - Data presented today demonstrate ACH-4471 can mitigate the AP hyperactivity in C3G
  - Short-term treatment with ACH-4471 was associated with approximately 50% reduction in ACR
  - Acceptable safety profile in C3G to date (no treatment-emergent serious adverse events or discontinuations due to adverse events)

- Ongoing studies include
  - Proof-of-mechanism study (ACH471-201) — recruiting
  - 6-month, randomized, placebo-controlled, proof-of-concept study (ACH471-204) — recruiting
  - 12 month, open-label, proof-of-concept study (ACH471-205) — recruiting

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ACHILION TEAM MEMBERS
• Clinical, Regulatory, CMC, Project Management
• Chemistry, DMPK, Toxicology, and Complement biology
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