# 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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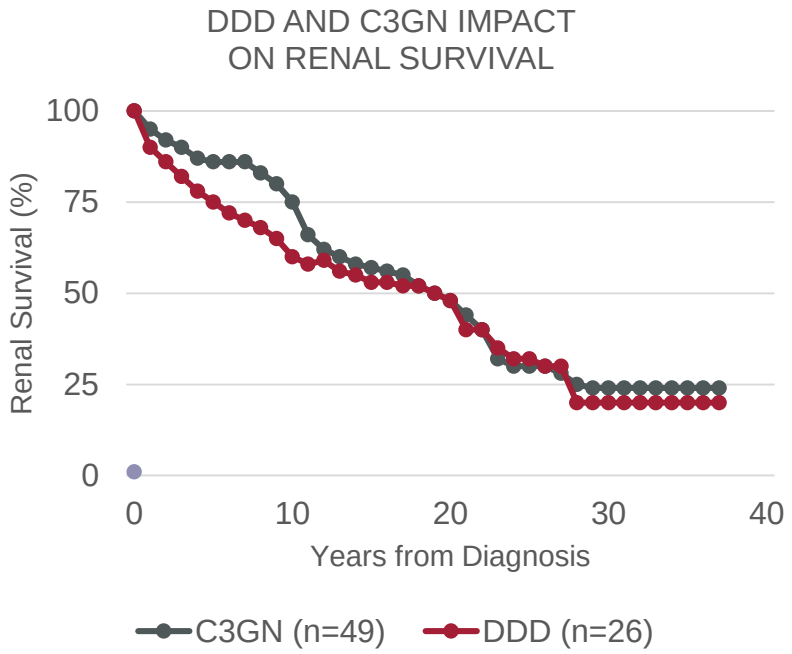
# C3 Glomerulopathy (C3G)

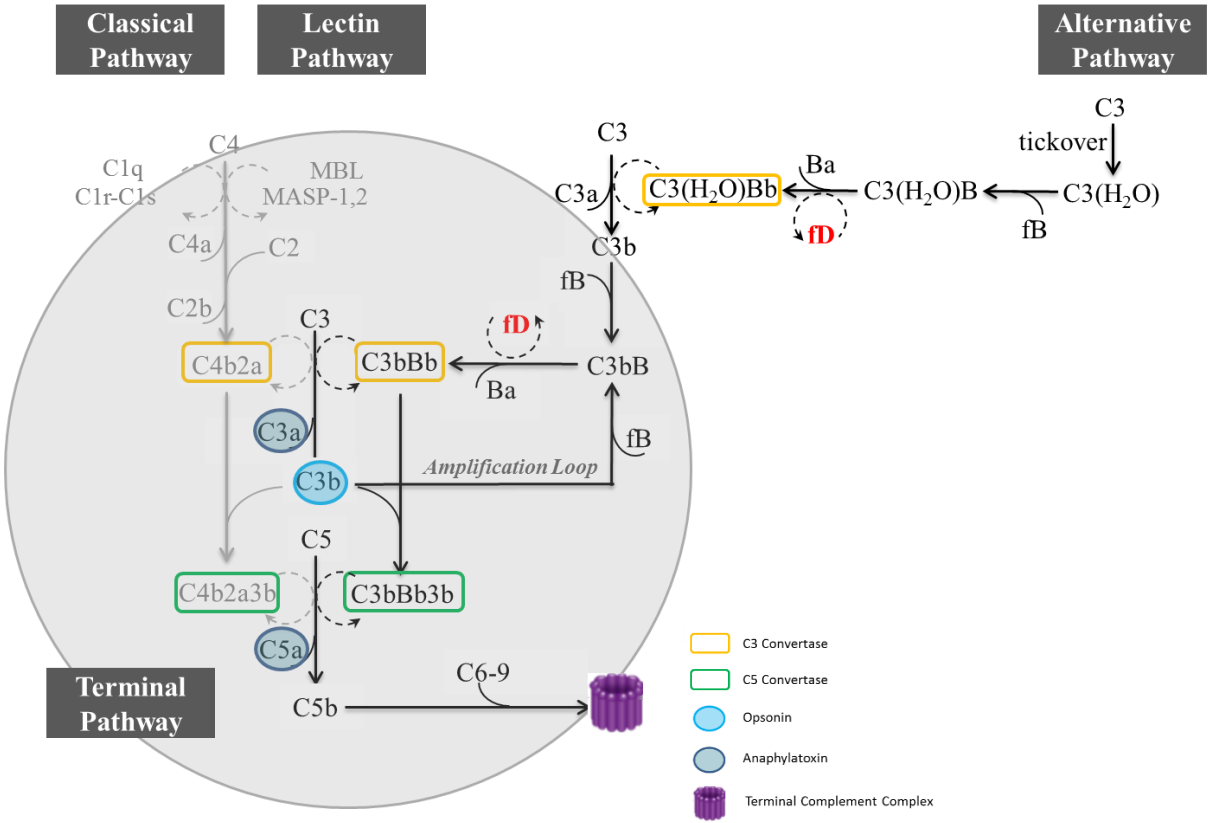
- C3G
  - Dense deposit disease (DDD)
  - C3 glomerulonephritis (C3GN)
- Estimated prevalence of 8–12 people affected per million in major markets
  - Incidence rate of 1–2 per million patients diagnosed with C3G on an annual basis
- There are no approved treatments indicated for patients with C3G
  - 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




Barbour et al. (2015); NICE C3G Evidence Summary (2015).

Sources: Servais et al (2013); Medjeral-Thomas et al (2014); Data on File. Achillion Pharmaceuticals. 2016.

# Factor D Inhibitor for the Treatment of C3G



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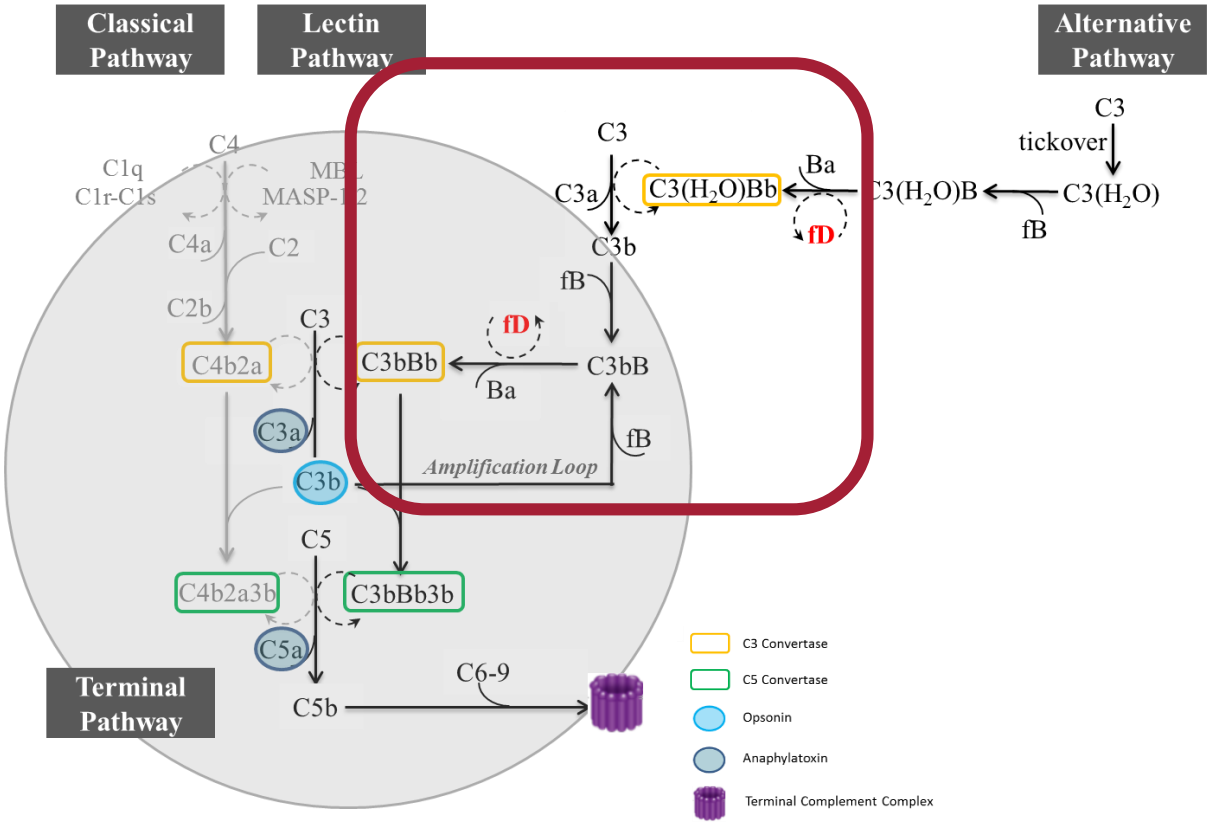
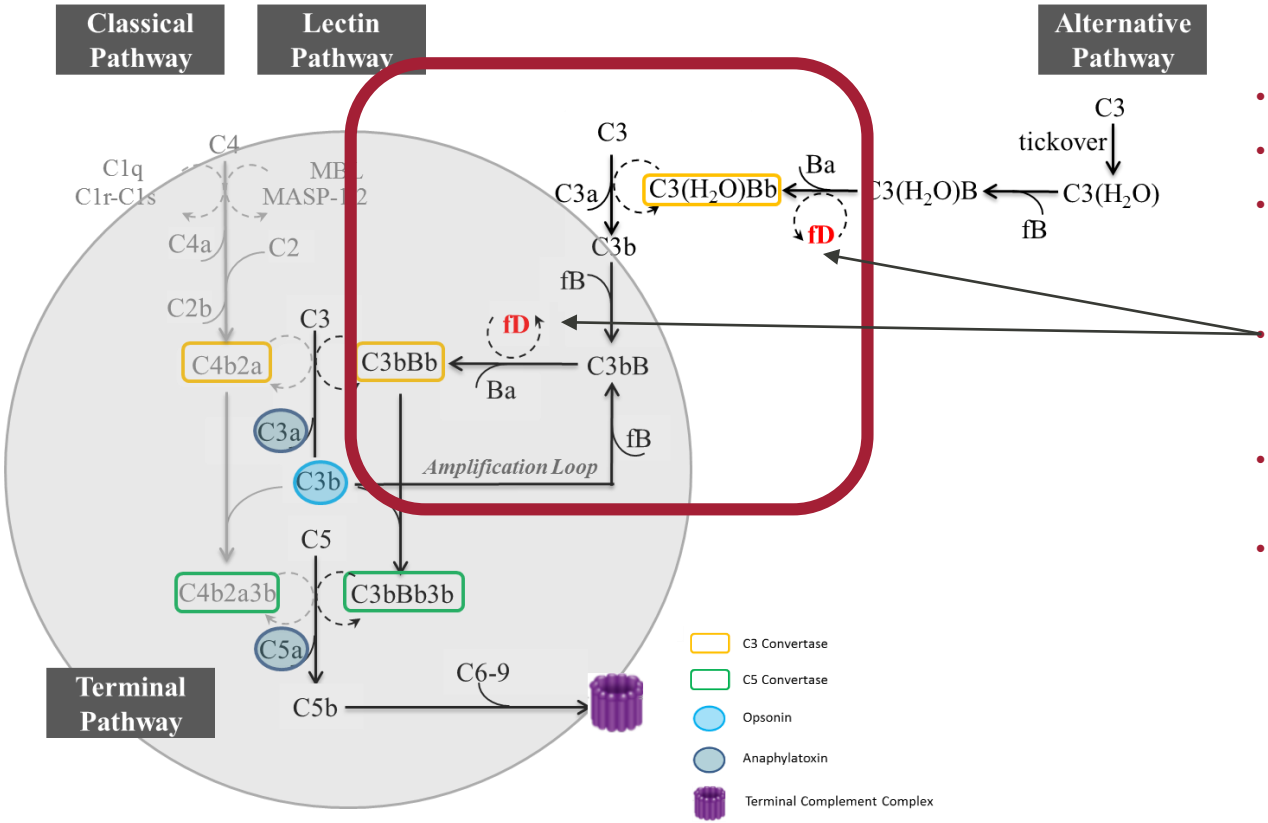



## C3G: A Disease of Alternative Pathway (AP) Hyperactivity

- 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

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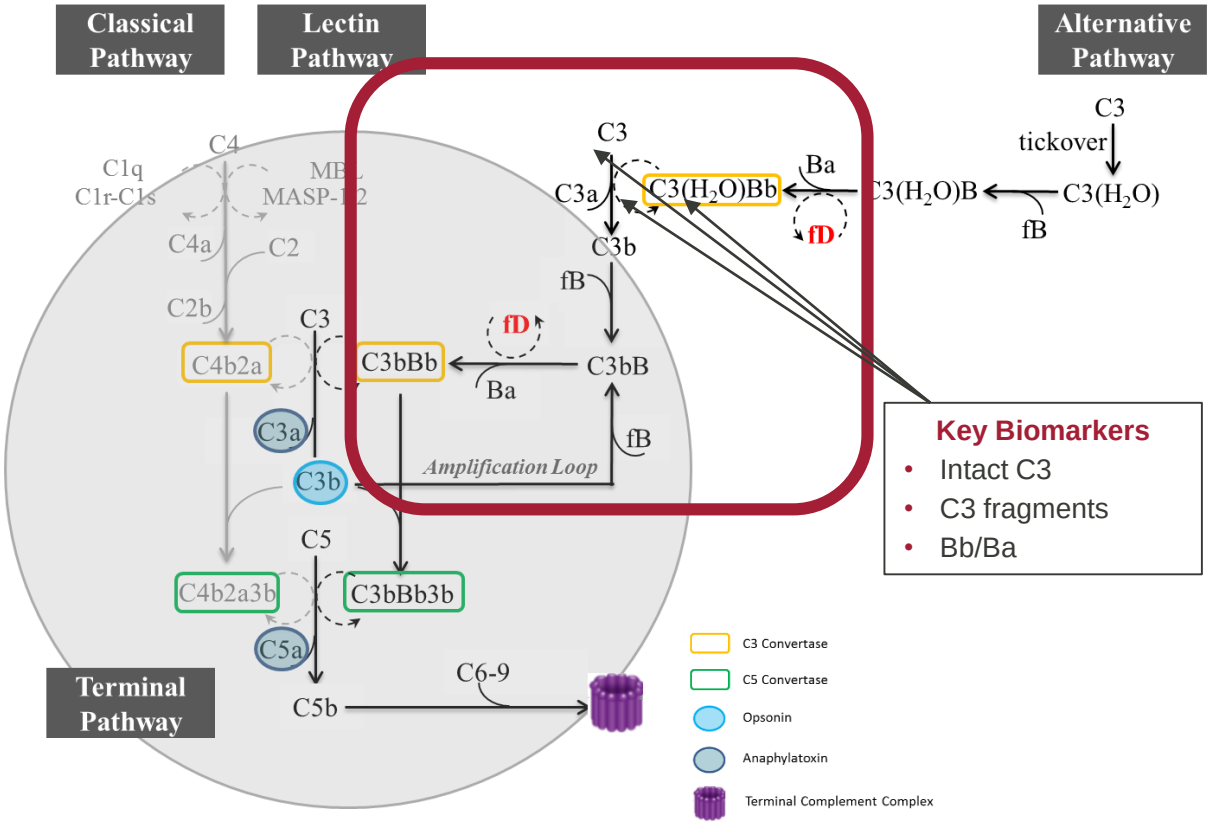


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# ACH-4471: First-in-Class Oral Factor D Inhibitor

## ACH-4471

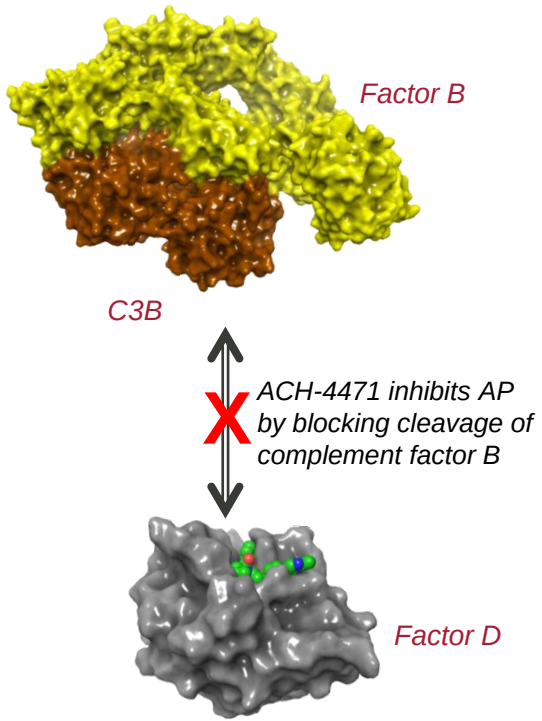
- Potent and specific modulator of AP
- More than 150 healthy volunteers exposed with acceptable safety profile at target exposures

## 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

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# Phase 2 14-day Trial in Patients with C3G or IC-MPGN


## CRITERIA

Must have diagnosis of C3G or IC-MPGN based on central review of historical biopsy

Low C3 with normal/ near-normal C4

## CLINICAL TRIAL DESIGN

**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

**Status:** Data available for 4 patients; recruitment ongoing

## 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

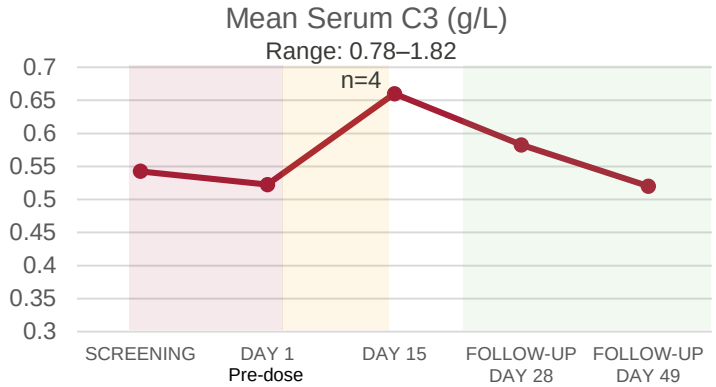
# Key Baseline Patient Characteristics

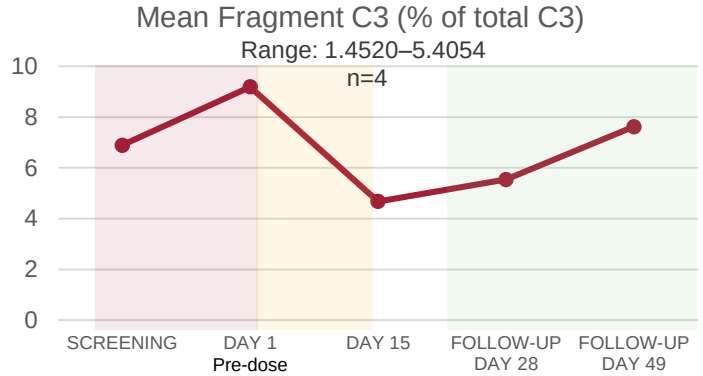
| Group | Patient | Age (Y) | Sex | Weight (kg) | Urine dipstick for protein | ACR (0-2.5 mg/mmol) Day 1 Pre-dose | BP (mmHg) | Renal Biopsy Diagnosis |
|---|---|---|---|---|---|---|---|---|
| 1 | A | 30 | M | 67 | 3+ | 259.3 | 126/72 | C3GN |
| | B | 19 | M | 68 | 3+ | 580.3 | 123/80 | IC-MPGN* |
| | | | | | | | | |
| 2 | C | 27 | M | 90 | Trace | 57.7 | 129/83 | C3GN |
| | D | 22 | M | 39 | 3+ | 276.3 | 119/74 | C3GN |

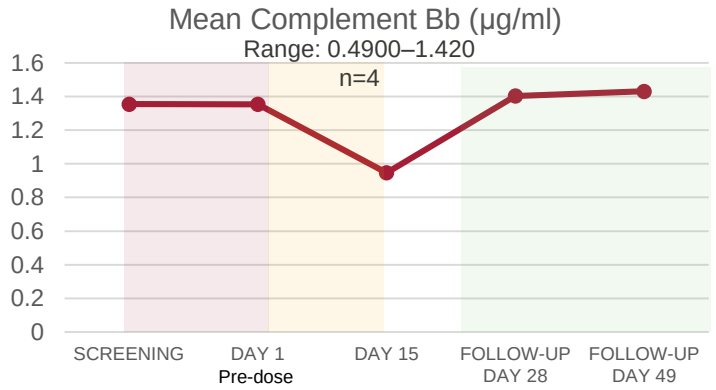
- Concomitant medication doses were stable for at least one month prior to the first dose of study drug, and included mycophenolate mofetil (n=2), prednisone (n=2), ACE/ARB (n=4), atorvastatin (n=2), and spironolactone (n = 3)
- eGFR > 60 ml/min/1.73m$^2$ in all patients

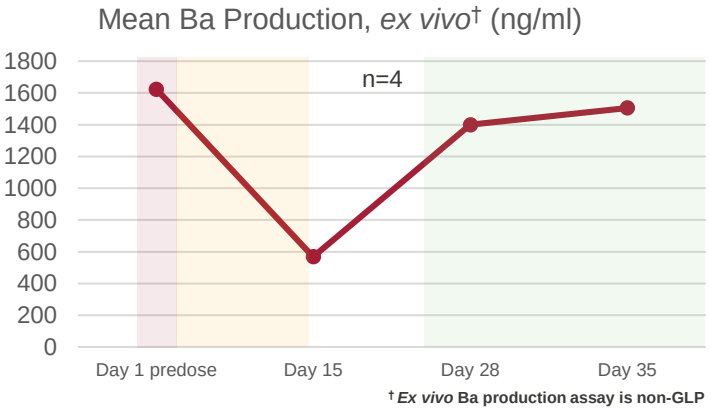
* Final review by central pathologist confirmed that the historical biopsy met criteria for IC-MPGN

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




† *Ex vivo* Ba production assay is non-GLP

- 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

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# Evidence of fD Inhibition and the AP Response

| PATIENT | BIOMARKER | BASELINE |
|---|---|---|
| A | Serum C3 | Low |
| | Fragment C3* (% of total) | High |
| | Bb | Normal |
| B | Serum C3 | Low |
| | Fragment C3* (% of total) | High |
| | Bb | High |
| C | Serum C3 | Low |
| | Fragment C3* (% of total) | Normal |
| | Bb | Normal |
| D | Serum C3 | Near lower limit of normal |
| | Fragment C3* (% of total) | Fragment undetectable |
| | Bb | Normal |

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

| PATIENT | BIOMARKER | BASELINE | ON-TREATMENT |
|---|---|---|---|
| A | Serum C3 | Low | Increased |
| | Fragment C3* (% of total) | High | Decreased |
| | Bb | Normal | Slightly decreased |
| B | Serum C3 | Low | Slightly increased |
| | Fragment C3* (% of total) | High | Decreased |
| | Bb | High | Decreased |
| C | Serum C3 | Low | Increased |
| | Fragment C3* (% of total) | Normal | Normal |
| | Bb | Normal | Decreased |
| D | Serum C3 | Near lower limit of normal | Increased |
| | Fragment C3* (% of total) | Fragment undetectable | Fragment undetectable |
| | Bb | Normal | Decreased |

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# Evidence of fD Inhibition and the AP Response

| PATIENT | BIOMARKER | BASELINE | ON-TREATMENT | POST-TREATMENT |
|---|---|---|---|---|
| A | Serum C3 | Low | Increased | Decreased to baseline |
| | Fragment C3* (% of total) | High | Decreased | Increased to baseline |
| | Bb | Normal | Slightly decreased | Normal |
| B | Serum C3 | Low | Slightly increased | Decreased to baseline |
| | Fragment C3* (% of total) | High | Decreased | Remains decreased |
| | Bb | High | Decreased | Increased to baseline |
| C | Serum C3 | Low | Increased | Decreased to baseline |
| | Fragment C3* (% of total) | Normal | Normal | Normal |
| | Bb | Normal | Decreased | Normal |
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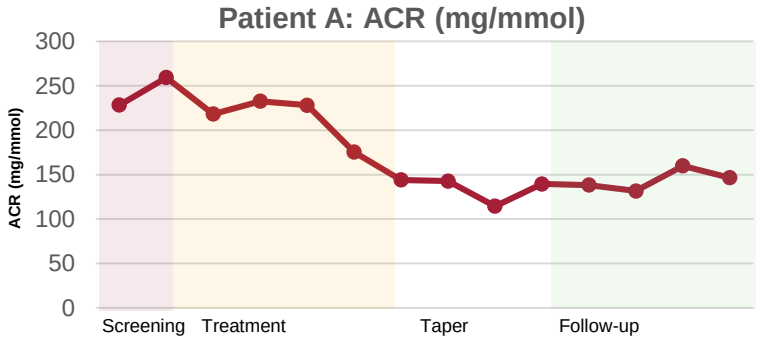
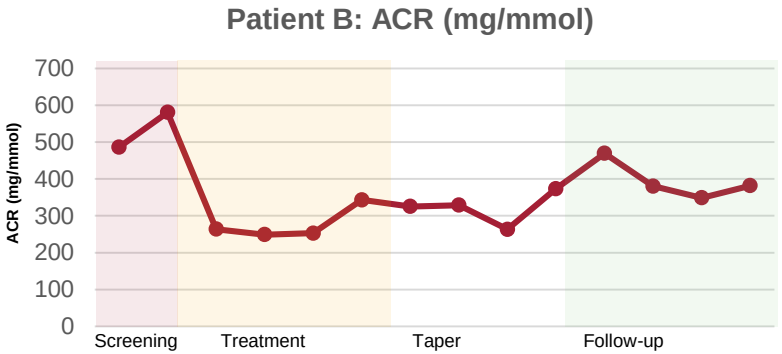
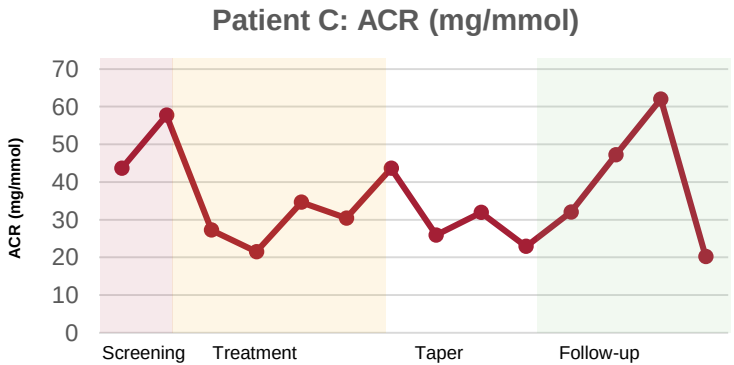
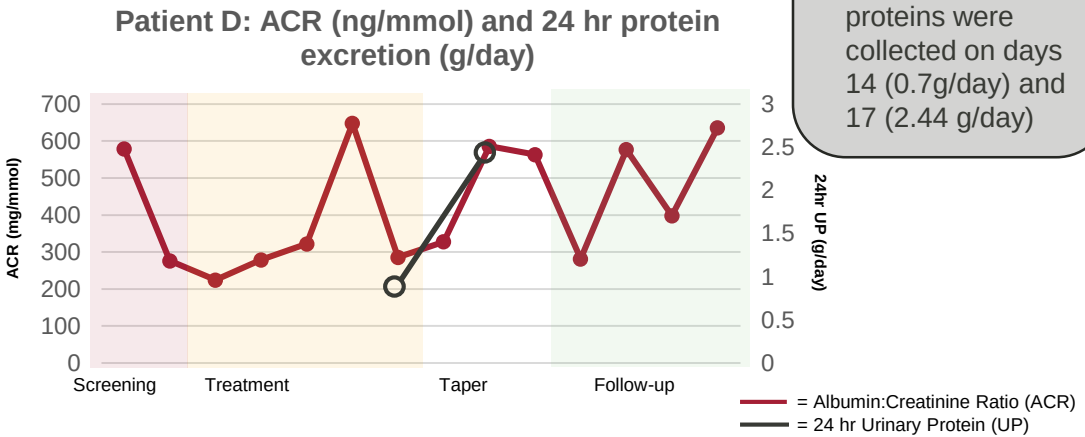
ON-TARGET EFFECT WITH REDUCED AP HYPERACTIVITY

# 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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# Acknowledgements


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**ACHILLION TEAM MEMBERS**

- Clinical, Regulatory, CMC, Project Management
- Chemistry, DMPK, Toxicology, and Complement biology

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