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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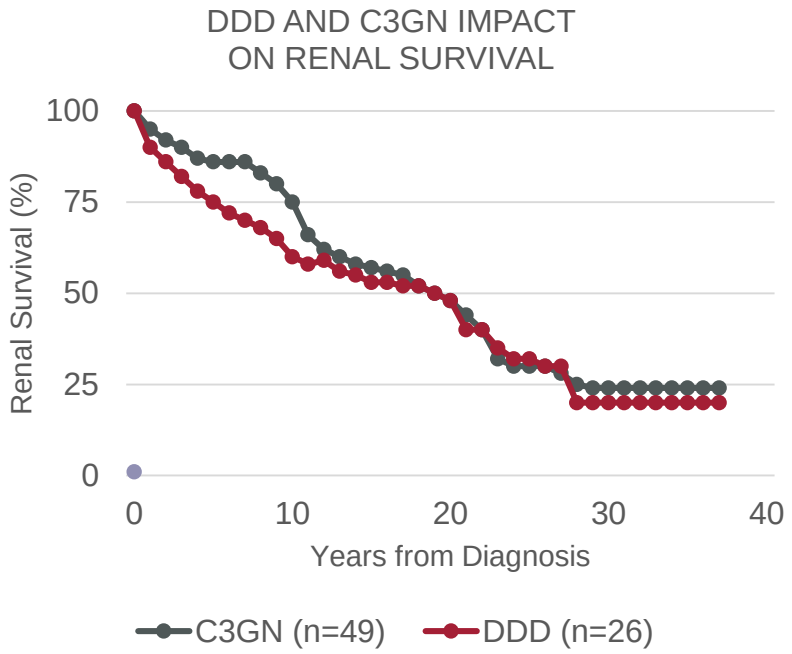
C3 Glomerulopathy (C3G)

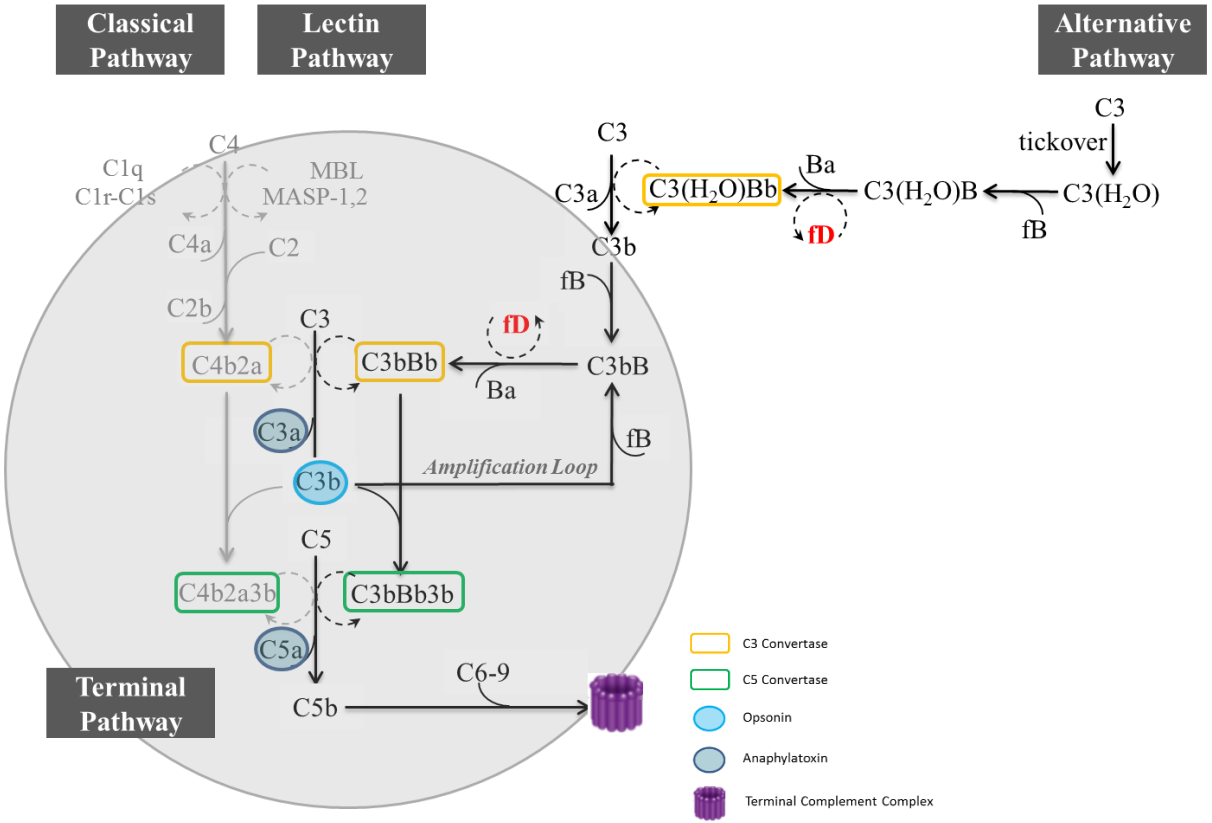
- C3G
  - Dense deposit disease (DDD)
  - C3 glomerulonephritis (C3GN)
- Estimated prevalence of 8–12 people affected per million in major markets
  - Incidence rate of 1–2 per million patients diagnosed with C3G on an annual basis
- There are no approved treatments indicated for patients with C3G
 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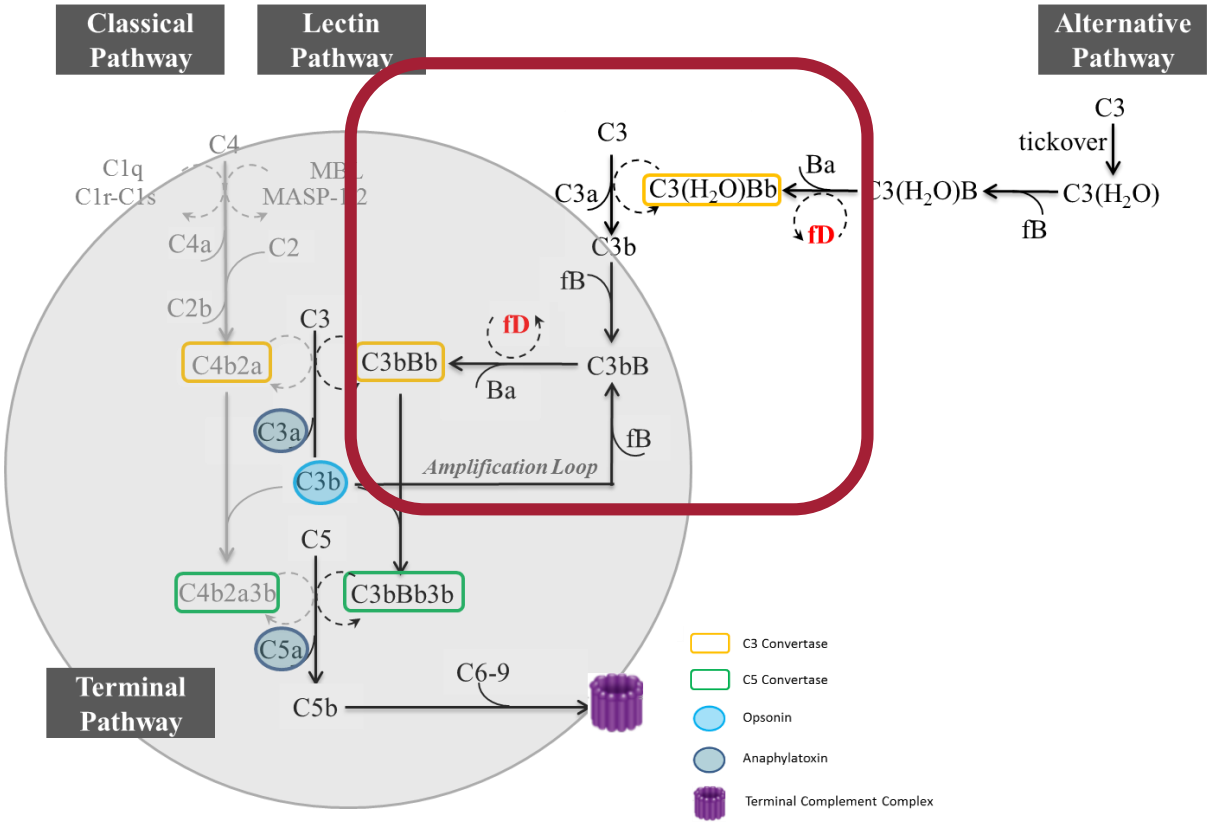
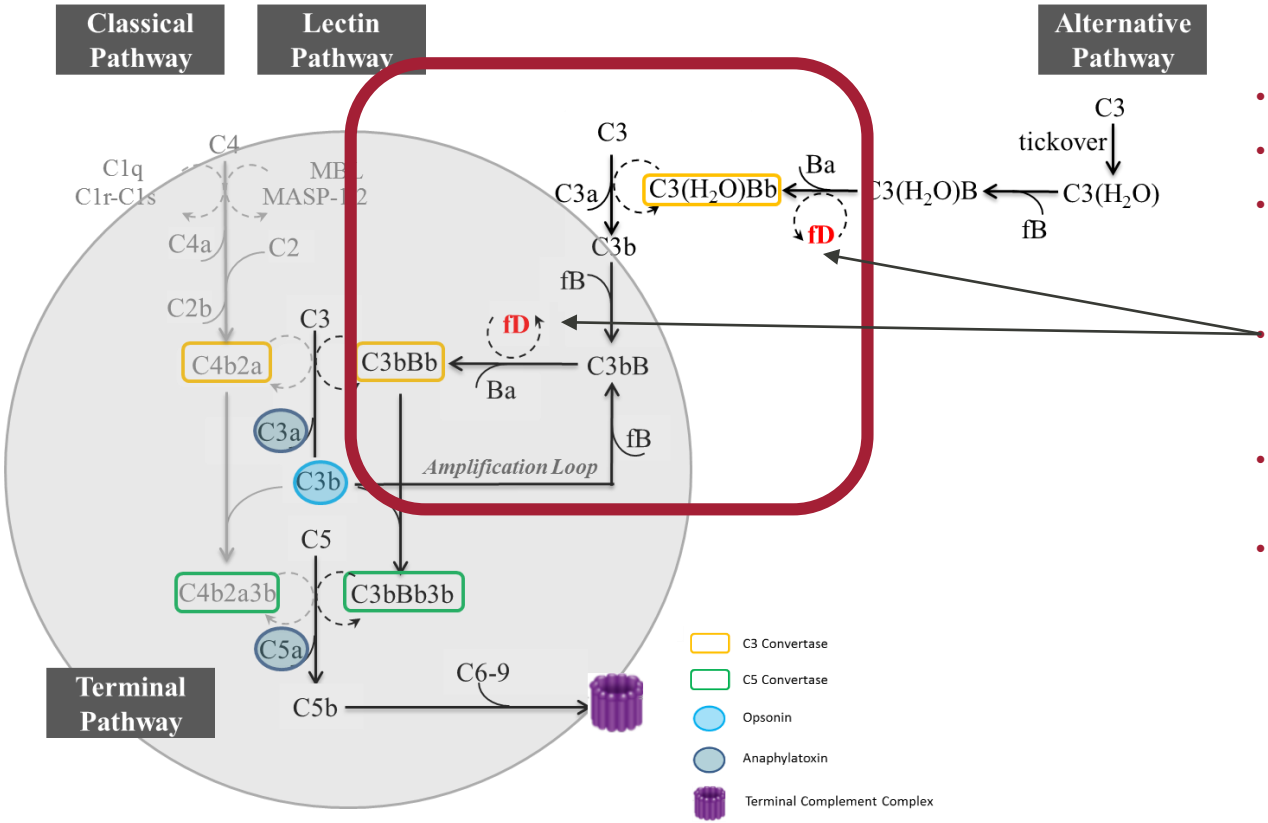


C3G: A Disease of Alternative Pathway (AP) Hyperactivity

- 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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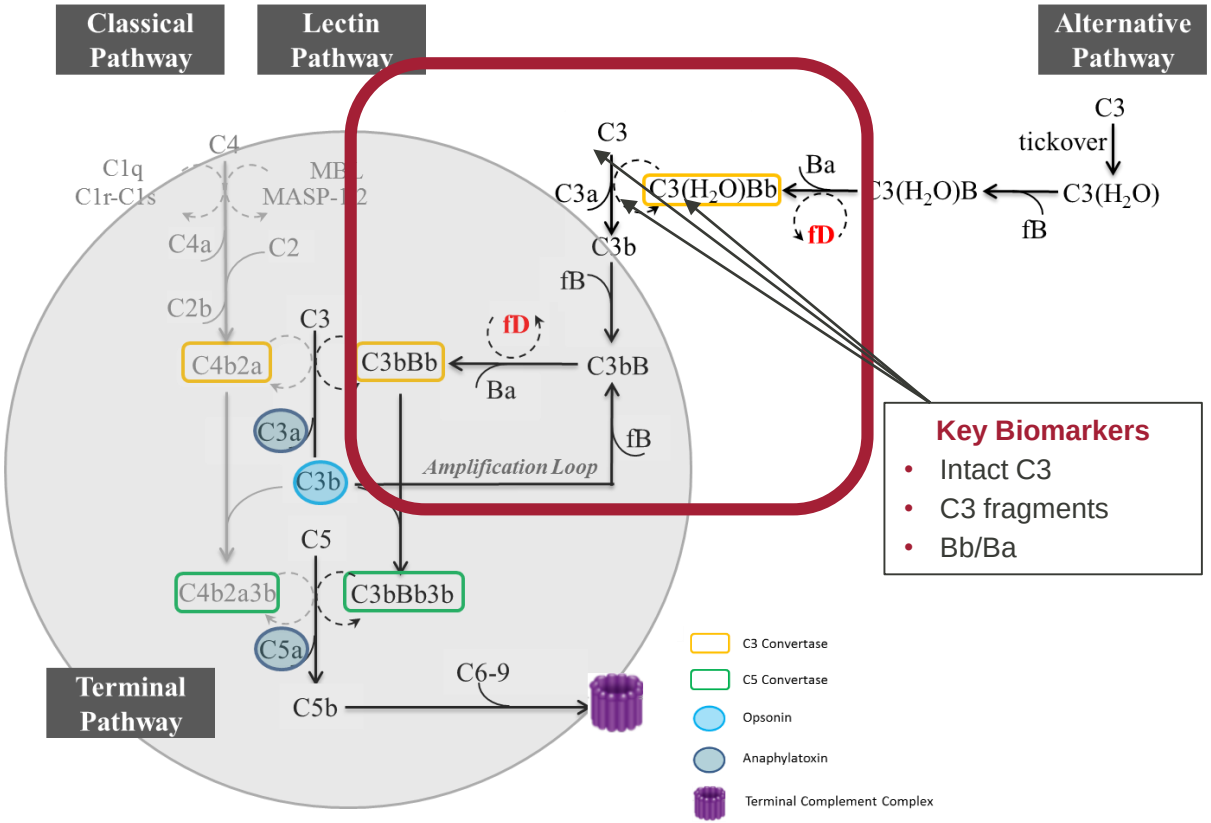
Factor D Inhibitor for the Treatment of C3G



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

ACH-4471

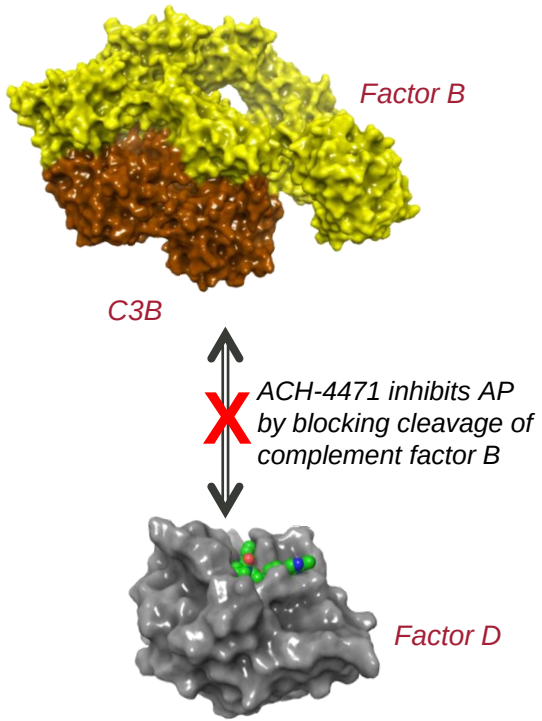
- Potent and specific modulator of AP
- More than 150 healthy volunteers exposed with acceptable safety profile at target exposures

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

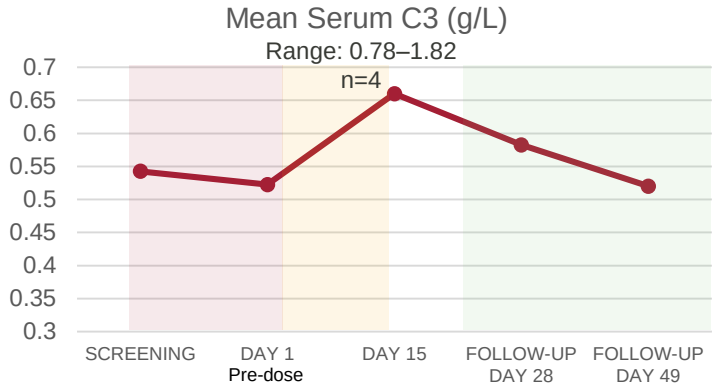
Key Baseline Patient Characteristics

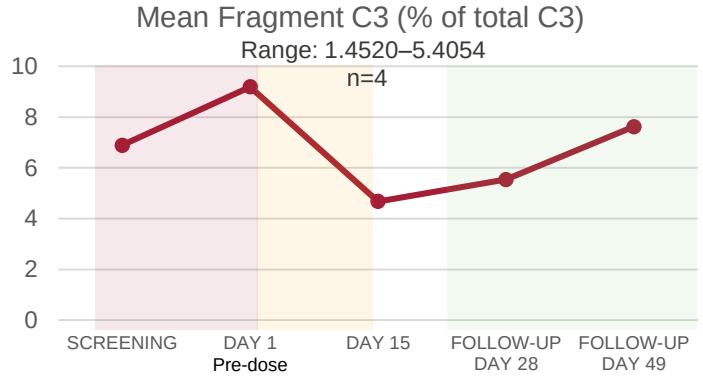
Group	Patient	Age (Y)	Sex	Weight (kg)	Urine dipstick for protein	ACR (0-2.5 mg/mmol) Day 1 Pre-dose	BP (mmHg)	Renal Biopsy Diagnosis
1	A	30	M	67	3+	259.3	126/72	C3GN
	B	19	M	68	3+	580.3	123/80	IC-MPGN*
2	C	27	M	90	Trace	57.7	129/83	C3GN
	D	22	M	39	3+	276.3	119/74	C3GN

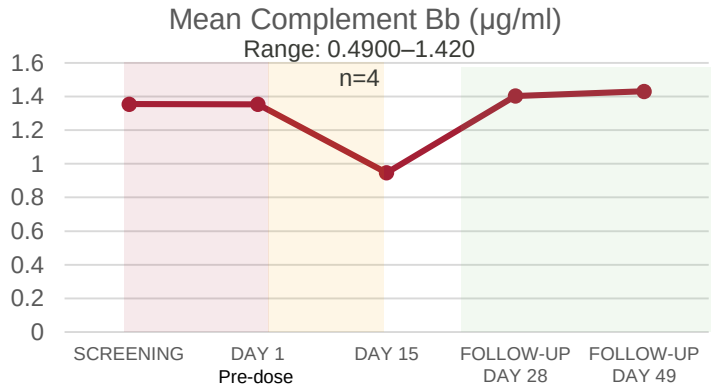
- Concomitant medication doses were stable for at least one month prior to the first dose of study drug, and included mycophenolate mofetil (n=2), prednisone (n=2), ACE/ARB (n=4), atorvastatin (n=2), and spironolactone (n = 3)
- eGFR > 60 ml/min/1.73m^2 in all patients

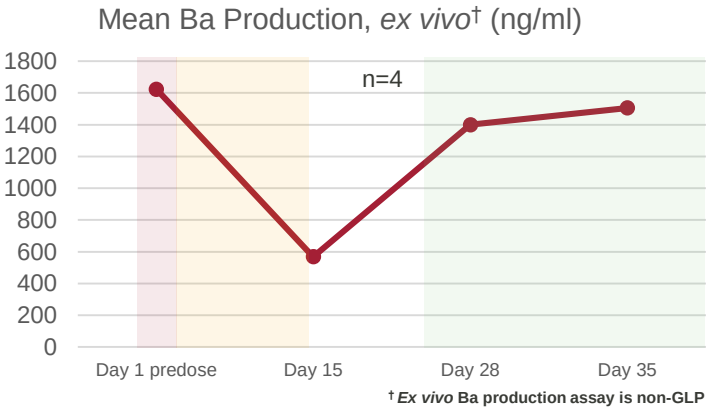
* Final review by central pathologist confirmed that the historical biopsy met criteria for IC-MPGN

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
D	Serum C3	Near lower limit of normal	Increased	Decreased to baseline
	Fragment C3* (% of total)	Fragment undetectable	Fragment undetectable	Fragment undetectable
	Bb	Normal	Decreased	Normal

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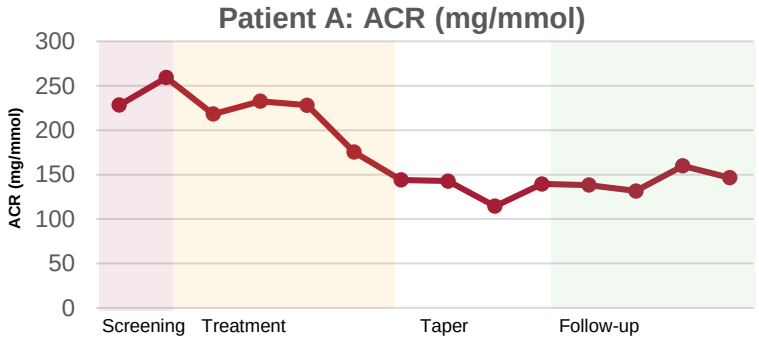
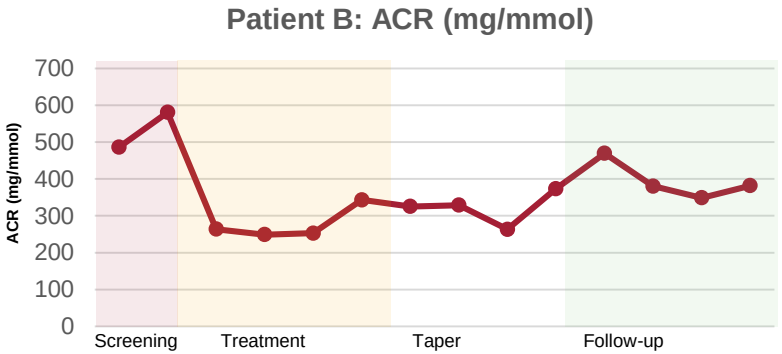
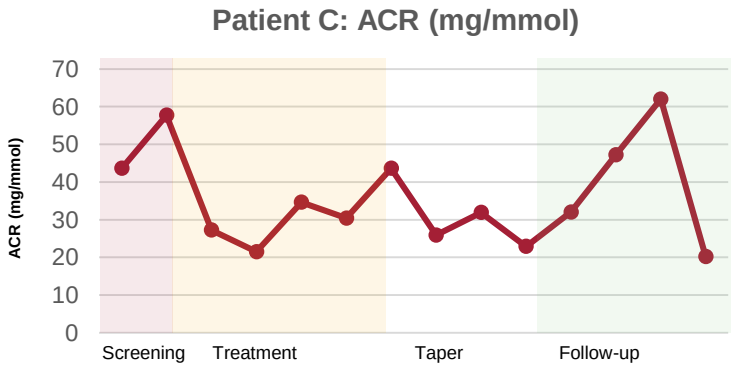
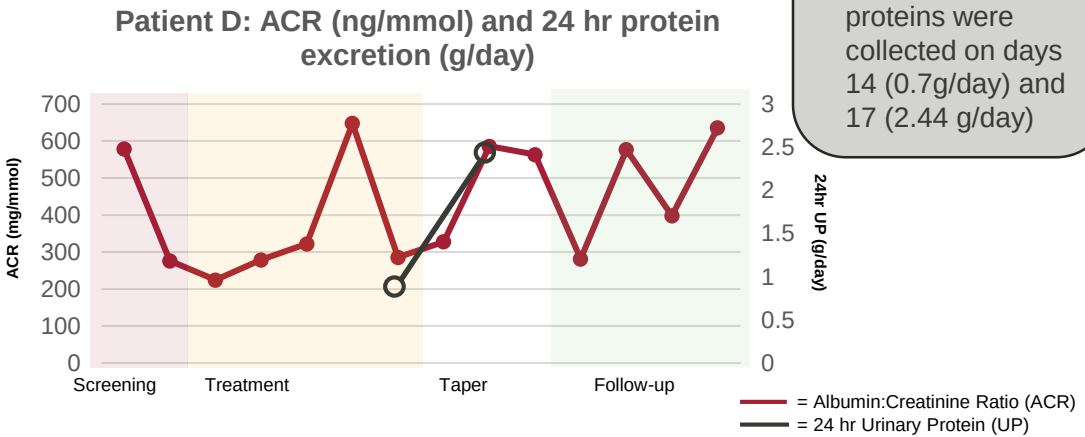
ON-TARGET EFFECT WITH REDUCED AP HYPERACTIVITY

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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ACHILLION TEAM MEMBERS

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

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