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# ARO-C3, an investigational RNAi Therapeutic Targeting Complement C3, Reduces Proteinuria, Hematuria, and Complement Activity in IgAN Patients

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# Disclosures

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# Background

- Dysregulated activation of the complement cascade mediates tissue injury in complement-mediated kidney diseases such as IgA Nephropathy
- The central role of complement component 3 (C3) in the cascade makes it a unique therapeutic target for complement inhibition
- ARO-C3 is an siRNA designed to achieve potent and durable complement inhibition by targeting hepatic synthesis of C3

# ARO-C3 is Designed to Target and Silence C3 mRNA Expression in the Liver, Reducing Serum C3 Protein Levels

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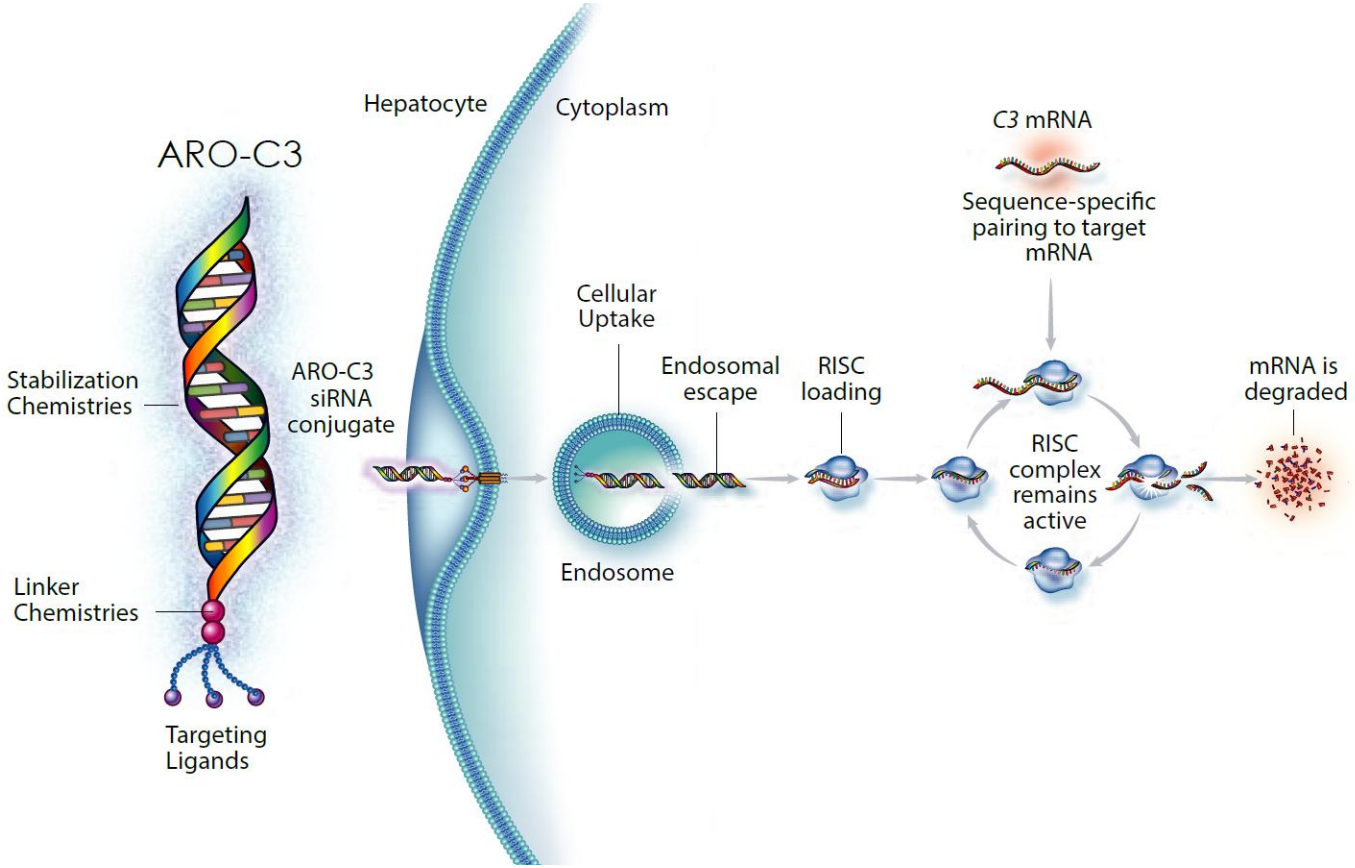
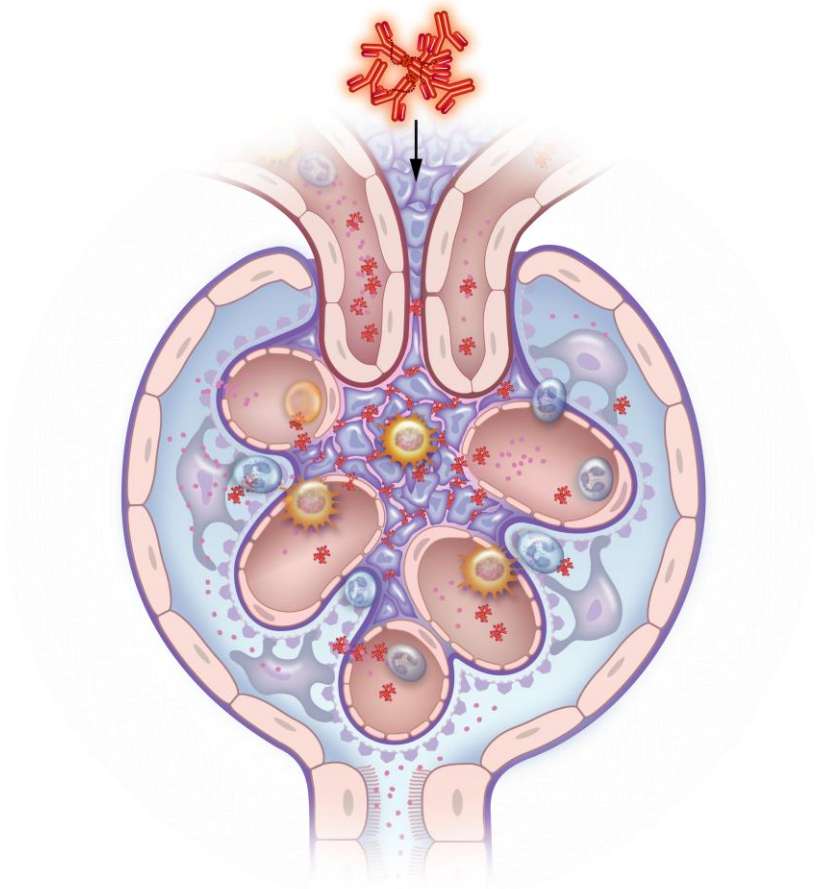
- ARO-C3 is a synthetic, double-stranded oligonucleotide
- Chemical modifications enhance pharmacokinetics (PK) and pharmacodynamics (PD)
- The GalNAc (N-Acetylgalactosamine) ligand facilitates uptake into hepatocytes via asialoglycoprotein receptor



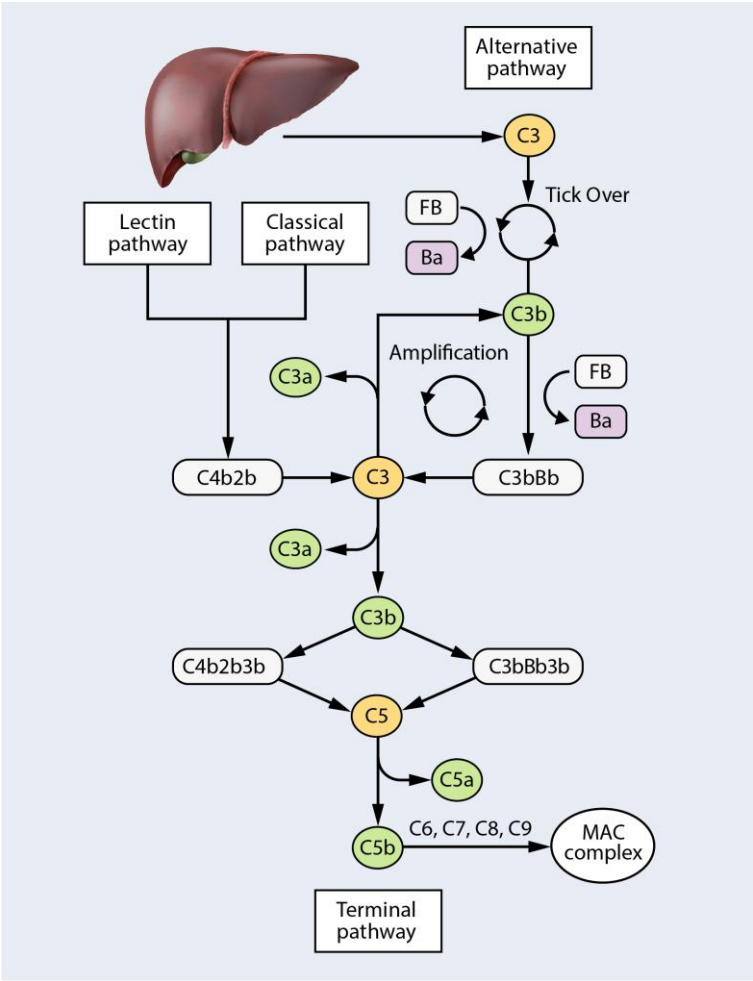
# Complement Mediates Glomerular Injury in IgAN

Gd-IgA-containing Immune Complexes



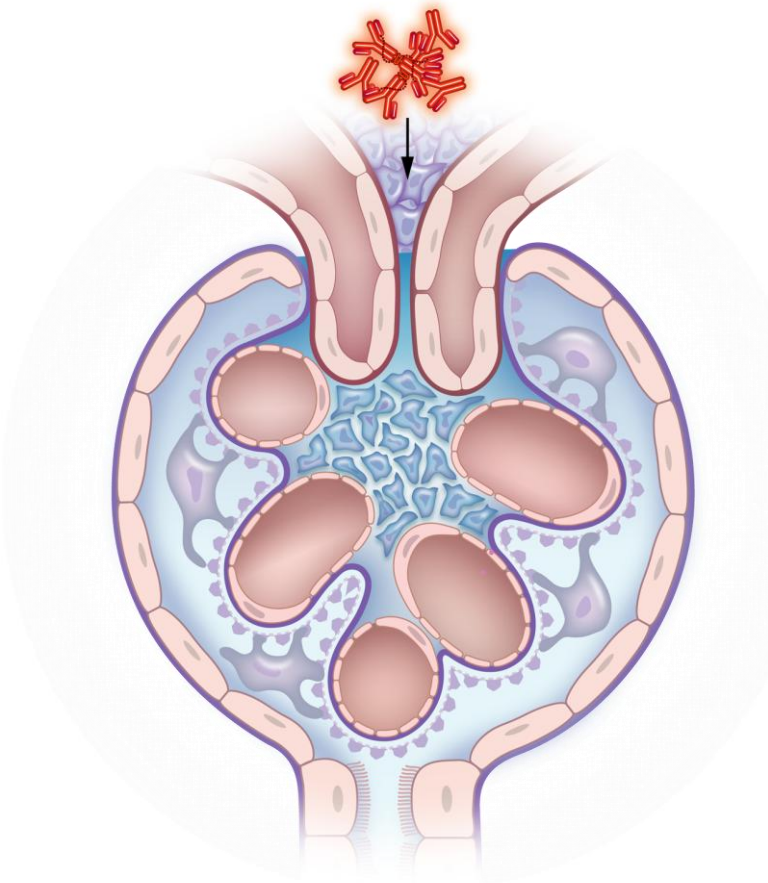
Inflammation and Tissue Injury

Complement Cascade



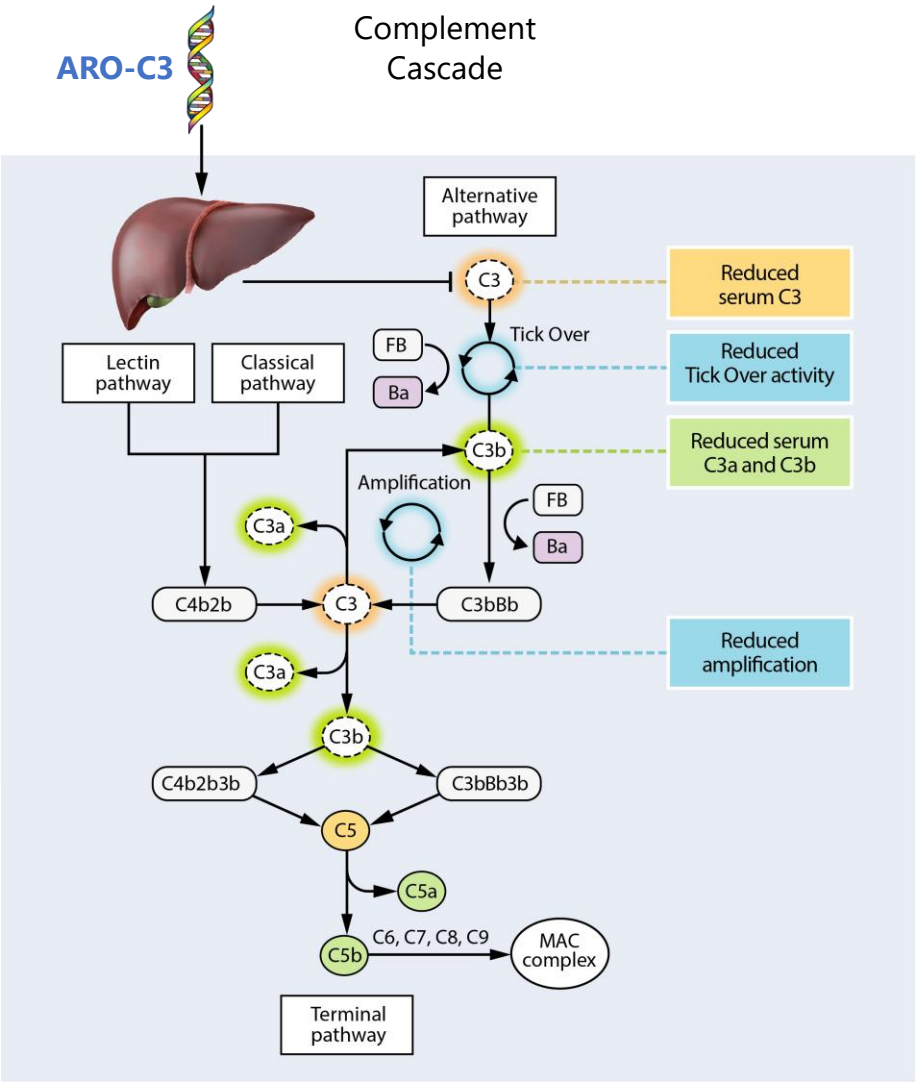
# ARO-C3 Reduces Serum C3 and Inhibits Complement Activation

Gd-IgA-containing Immune Complexes



ARO-C3

Complement Cascade




Reduced Inflammation and Tissue Injury

# AROC3-1001 Study Design, Part 1: Phase 1 Randomized, Placebo-Controlled SAD/MAD Study in Healthy Volunteers

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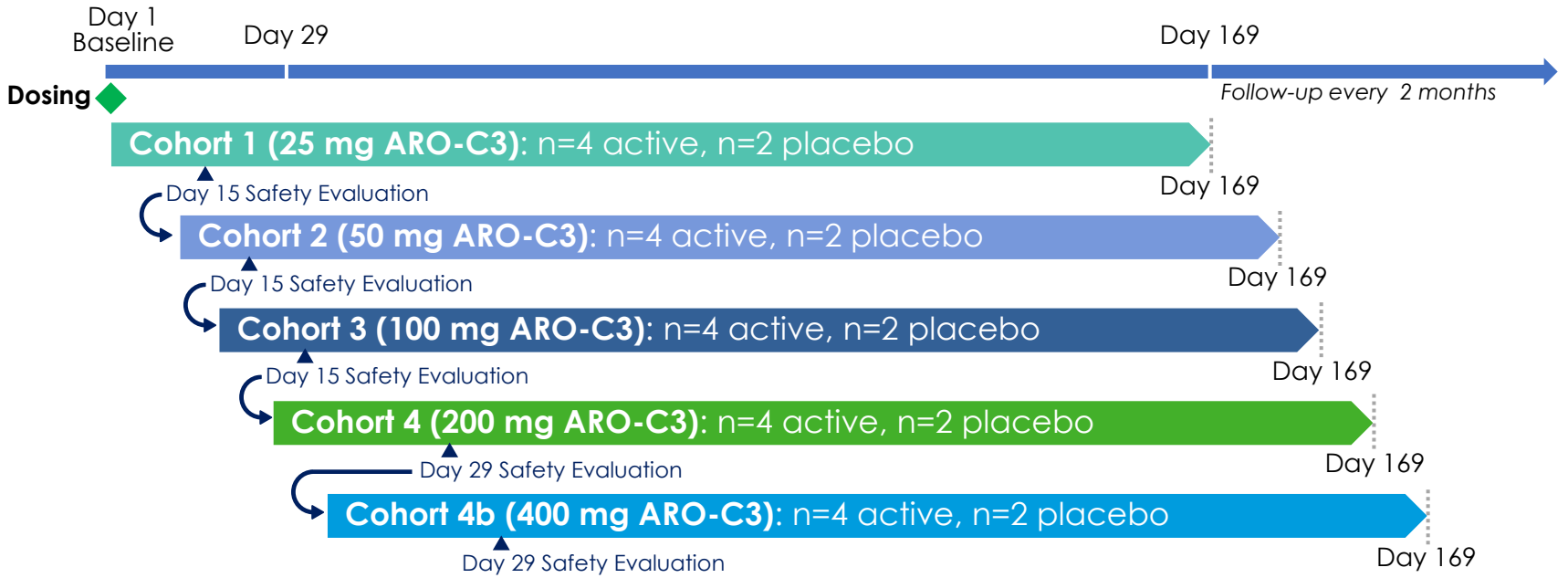
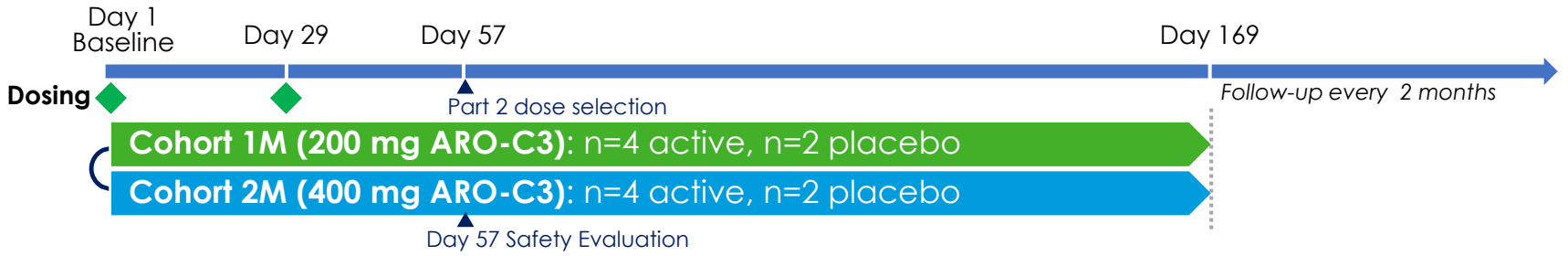
## Single Ascending Dose




**400mg Dose Selected for Part 2 based on Part 1 Pharmacodynamic and Safety Data**

## Multiple Ascending Dose




**MAD** = multiple ascending dose; **SAD** = single ascending dose.

# AROC3-1001 Study Design, Part 2: Open-Label Phase 2a in Patients with IgA Nephropathy

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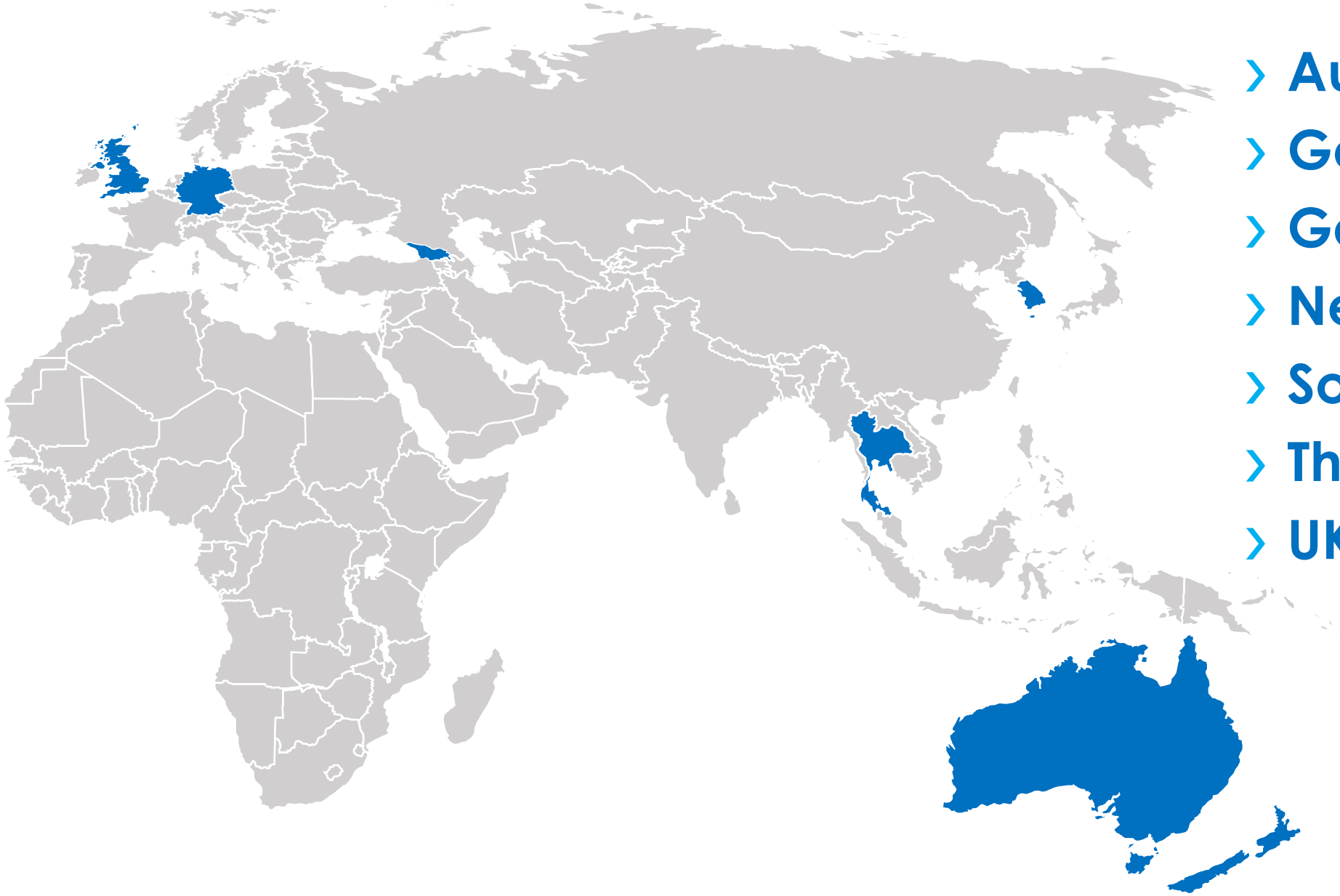
**400mg Dose Selected for Part 2 based on Part 1 Pharmacodynamic and Safety Data**

# Study Endpoints

- **Primary:** Incidence, frequency, and severity of treatment-emergent adverse events (TEAEs)
- **Secondary:** Plasma Pharmacokinetics (PK) of ARO-C3
- **Exploratory:**
  - Serum Complement Levels
  - Complement Function:
    - Total complement activity, hemolytic (CH50)
    - Alternative pathway activity, hemolytic (AH50)
    - Wieslab Alternative Pathway (AP) Immunoassay
  - Efficacy (IgAN Patients only)
    - Renal Function (eGFR)
    - Spot and 24hr Urine Parameters
    - Hematuria

**AH50** = alternative pathway activity (hemolytic); **AP** = alternative pathway; **CH50** = total complement activity (hemolytic); **eGFR** = estimated glomerular filtration rate; **IgAN** = IgA Nephropathy.

# Recruitment at 26 sites in 7 Countries



- Australia
- Georgia
- Germany
- New Zealand
- South Korea
- Thailand
- UK

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# Part 1: Phase 1 Randomized, Placebo-Controlled SAD/MAD Study in Healthy Volunteers

## Baseline Characteristics and Demographics

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**Healthy volunteers received vaccination against:**

- *N. meningitidis* (two weeks prior to dosing with booster at Day 57)
- *S. pneumoniae* (PCV13 two weeks prior to dosing, PPSV23 at Day 57)
- *H. influenzae* (two weeks prior to dosing)

**Antibiotic prophylaxis required by protocol:**

- Ciprofloxacin 500mg BID x 14 days
- Penicillin 500mg daily until AH50 & CH50 were ≥ LLN or ≥ approximate Day 1 baseline (if <LLN)

| Baseline Characteristics | | |
|---|---|---|
| **Parameter** | **Pooled Placebo (N=14)** | **Pooled Active (N=28†)** |
| **Age (years)** | 33.0 (10.7) | 30.8 (11.8) |
| **Sex (%M)** | 5 (35.7%) | 10 (35.7%) |
| **BMI (kg/m²)** | 25.4 (4.5) | 25.7 (4.3) |
| **C3 (mg/dL)** | 94.8 (15.8) | 96.7 (12.7) |
| **AH50 (U/mL)** | 112.6 (13.8) | 115.7 (19.0) |
| **Wieslab AP (%)** | 118.5 (99.8) | 129.4 (100.7) |

† One subject in MAD 400mg group withdrew at Week 12 for non-safety related reasons.
**AH50** = alternative pathway activity (hemolytic); **BID** ≈ twice daily; **BMI** = body mass index; **LLN**: lower limit of normal; **PCV13** = 13-valent pneumococcal conjugate vaccine; **PPSV23** = 23-valent pneumococcal polysaccharide vaccine.

# ARO-C3 Reduces Serum C3 in Healthy Volunteers Up to 88% from Baseline after Two Doses

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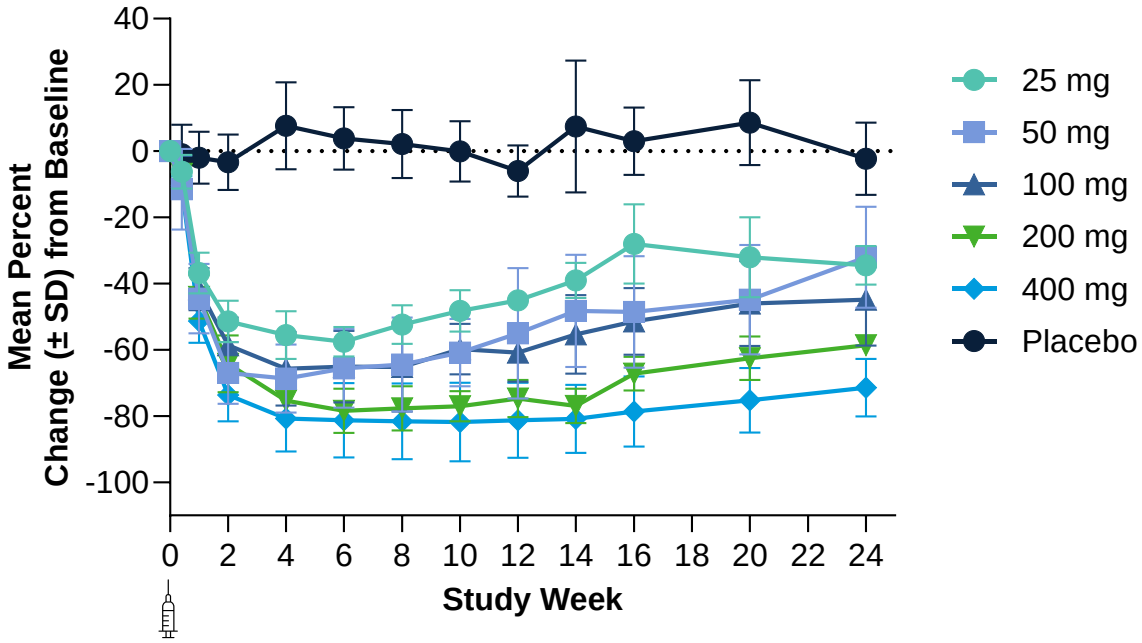
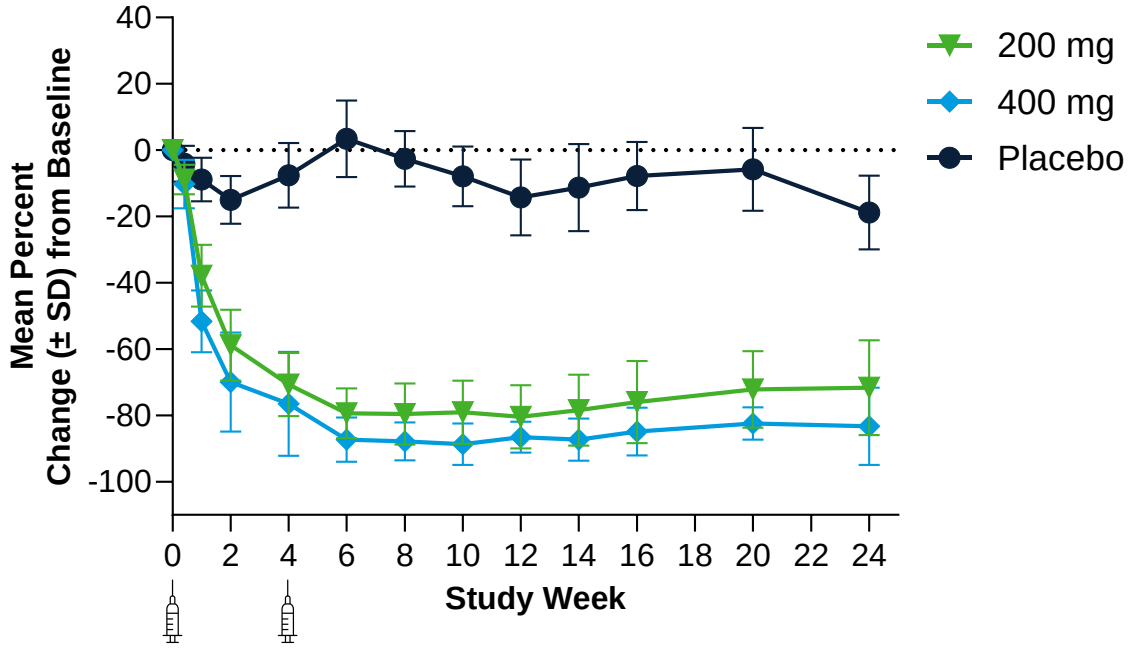
## Single Dose Cohorts




Up to **82%** mean reduction in C3 sustained through week 16 after a single 400mg dose

## Multiple Dose Cohorts




Up to **88%** mean reduction in C3 sustained through week 16 after two 400mg doses

Baseline defined as the last pre-dose measurement. N = 4 for each dose level, N = 14 for placebo (pooled); one subject in MAD 400mg group withdrew at Week 12 for non-safety related reasons.

# Individual Reductions in Serum C3 of up to 93% After Two Doses of ARO-C3

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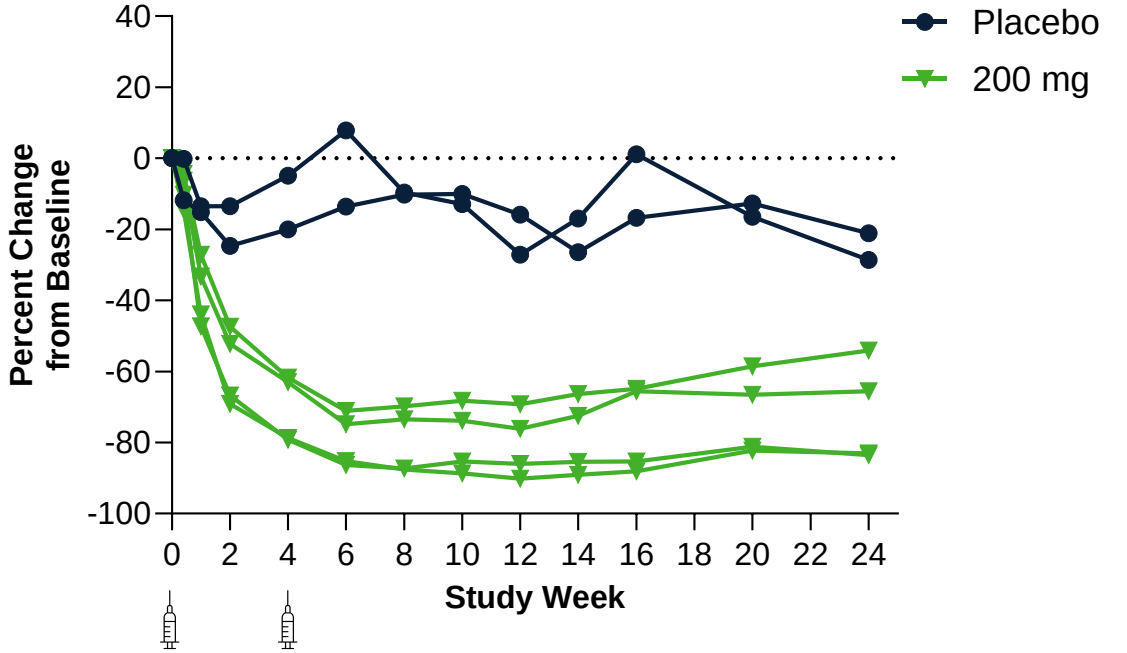
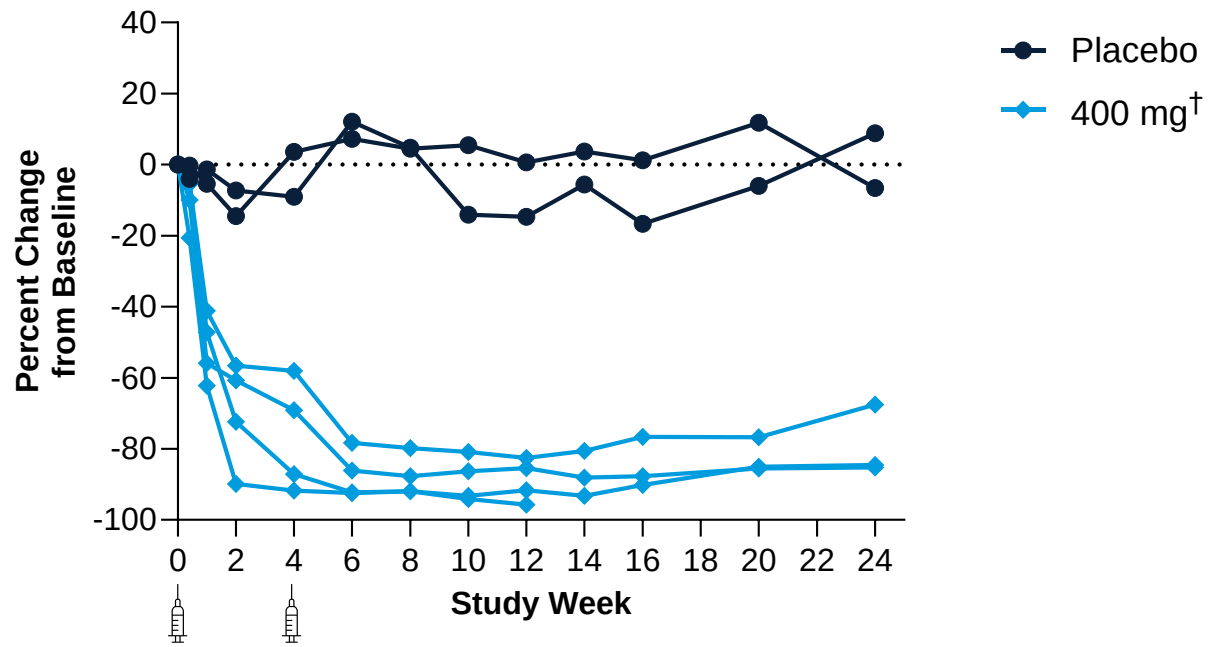
## Multiple Dose Cohorts - Individuals




## Multiple Dose Cohorts - Individuals




Maximum individual C3 reductions of **90%** and **93%** after two doses of 200 mg and 400mg, respectively

*One subject in MAD 400mg group withdrew at Week 12 for non-safety related reasons. Baseline defined as the last pre-dose measurement.

# Reductions of >90% in Alternative Pathway and >60% in Classical Pathway Activity after Two Doses of ARO-C3 in Healthy Volunteers

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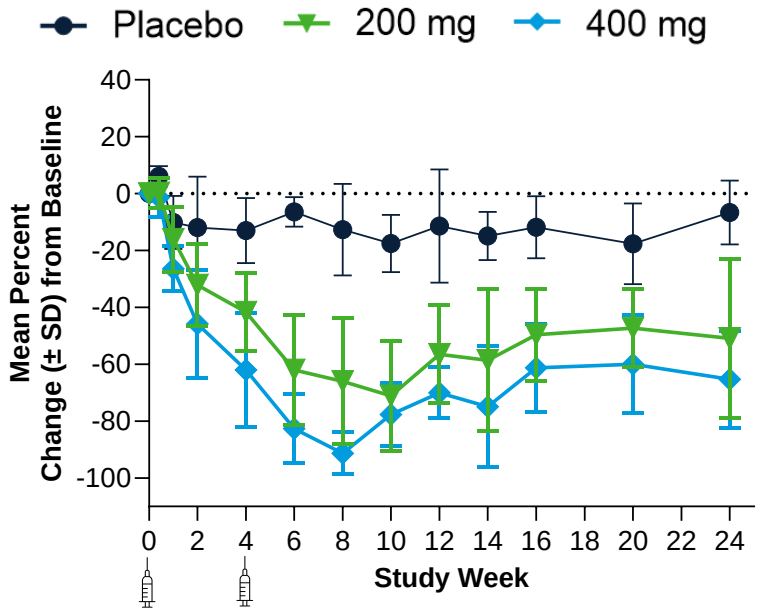
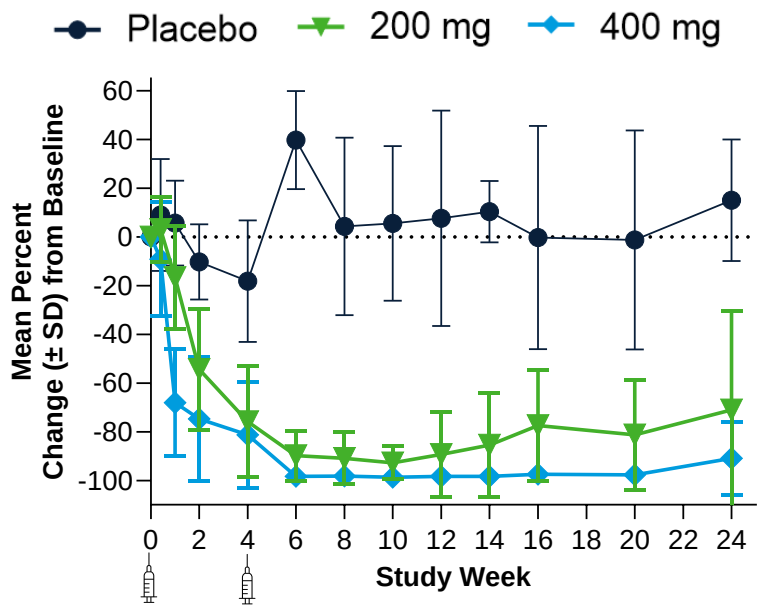
## AH50



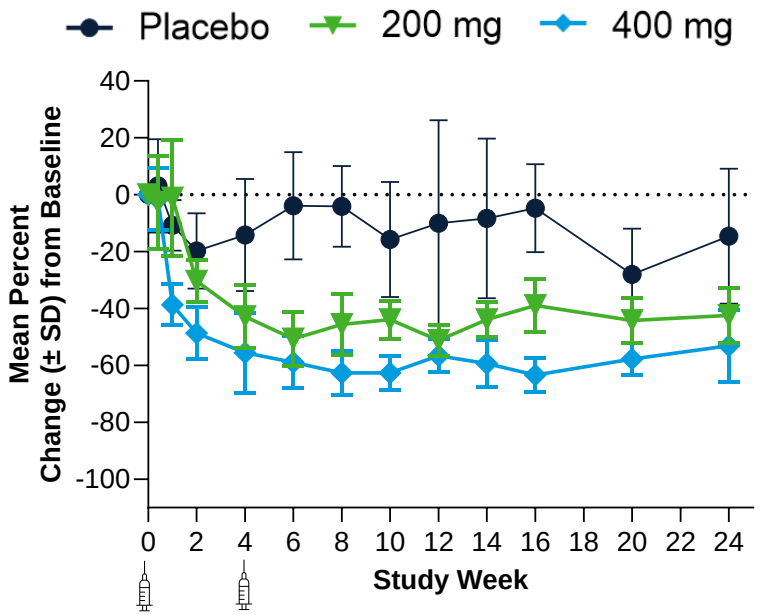

**91%** mean reduction in AH50 at week 8 after two 400 mg doses

## Wieslab® AP




**99%** mean reduction in Wieslab® AP at week 8 after two 400mg doses

## CH50




**63%** mean reduction in CH50 at week 8 after two 400 mg doses

Baseline defined as the last pre-dose measurement. One subject in MAD 400mg group withdrew at Week 12 for non-safety related reasons. Wieslab AP results were calculated per the assay manufacturer's recommended NC/PC (Negative Control/Positive Control) semiquantitative method. **AH50** = alternative pathway activity (hemolytic); **AP =** alternative pathway; **CH50** = total complement activity (hemolytic).

# ARO-C3 Demonstrates a Favorable Safety Profile in Healthy Volunteers

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- ARO-C3 was well-tolerated overall.
  - Most TEAEs were mild in severity.
  - No TEAEs led to study or study drug discontinuation.
- No infections with encapsulated organisms.
- Injection site reactions were all mild in severity & all resolved without sequelae.
- 1 SAE of "*Abdominal pain*" reported, attributed to pre-existing ovarian cysts and assessed as unrelated to study drug by both Sponsor and site investigator.
- Vaginal candidiasis likely related to use of prophylactic antibiotics.

| Adverse Event | Pooled Active N=28 n (%) | Pooled Placebo N=14† n (%) |
|---|---|---|
| **Headache** | 12 (43) | 5 (36) |
| **COVID-19** | 8 (29) | 5 (36) |
| **Upper Respiratory Infection** | 7 (25) | 5 (36) |
| **Vaccination-related** | 5 (18) | 4 (29) |
| **Nausea** | 3 (11) | 4 (29) |
| **Abdominal Pain** | 4 (14) | 3 (21) |
| **Fatigue** | 2 (7) | 3 (21) |
| **Injection Site Reactions** | 5 (18) | 0 (0) |
| **Vulvovaginal Candidiasis** | 2 (7) | 3 (21) |

†One subject in MAD 400mg group withdrew at Week 12 for non-safety related reasons.
**TEAE** = treatment-emergent adverse event; **SAE** = serious adverse event.

# IgAN Study Population

## Key Inclusion Criteria

- Adults, 18 – 70 years old
- Renal biopsy demonstrating IgAN with positive C3 deposition within 5 years
- Proteinuria >750mg/day on a 24hr urine collection during Screening
- eGFR ≥30 mL/min/1.73m$^2$
- Maximum recommended/tolerated dose of ACEi or ARB, with stable dose for at least 90 days
- Stable dose of any other anti-proteinuric, anti-hypertensive, or immunosuppressive therapies
- Vaccinated or willing to receive vaccination against *N. meningitidis, S. pneumoniae, and H. influenzae*

## Key Exclusion Criteria

- History of chronic or recurrent infection, including HIV, HBV, HCV
- Uncontrolled hypertension (BP ≥160 / 100 at Screening)
- Decline in eGFR ≥ 50% within 90 days of Screening
- Interstitial fibrosis / Tubular atrophy >50% on eligibility-defining biopsy.

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**ACEi =** angiotensin converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **BMI =** body mass index; **BP** = blood pressure; **eGFR** = estimated glomerular filtration rate; **MAD** = multiple ascending dose; **SAD** = single ascending dose.

# Part 2: Open-Label Phase 2a in Patients with IgA Nephropathy
## Baseline Characteristics and Demographics

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- All patients:
  - Received protocol-required vaccinations within 2 years, or
  - Were vaccinated per-protocol on the same schedule as healthy volunteers, or
  - Were vaccinated in accordance with local standards of care for patients starting complement inhibitors
- Antibiotic prophylaxis was permitted at the discretion of the investigator.
  - 2/14 (14%) patients received prophylactic antibiotics

| Characteristic | Cohort 8 (IgAN, n = 14†) |
|---|---|
| **Age, mean (SD)** | 40 (11) |
| **Sex, male, n (%)** | 5 (36) |
| **Race** | |
| **Asian, n (%)** | 12 (86) |
| **White, n (%)** | 2 (14) |
| **Serum C3, mean (SD)** | 102.1 (18.5) mg/dL |
| **CH50, mean (SD)** | 61.2 (18.7) U/mL |
| **Wieslab AP, mean (SD)‡** | 84.0 (13.3) % |
| **AH50, mean (SEM)** | 131.6 (18.2) |
| **Serum creatinine, mean (SD)** | 1.05 (0.35) mg/dL |
| **eGFR, mean (SD)** | 80.6 (26.52) mL/min/1.73m$^2$ |
| **Spot UPCR, mean (SD)** | 2051.1 (1431.4) mg/g |
| **Hematuria present, n (%)††** | 10 (71) |
| **Serum albumin, mean (SD)** | 3.9 (0.66) g/dL |
| **SBP, mean (SD)** | 128 (15) mmHg |
| **DBP, mean (SD)** | 80 (11) mmHg |
| **ACEi/ARB use, n (%)** | 13 (93) |
| **SGLT2 Inhibitor use, n (%)** | 3 (21) |

Baseline defined as the last pre-dose measurement. †One subject withdrew at Week 4 for non-safety related reasons. ‡Wieslab AP results were calculated per the assay manufacturer's recommended NC/PC (Negative Control/Positive Control) semiquantitative method. †† Hematuria defined as dipstick measurement ≥1+ at baseline. **AH50** = alternative pathway activity (hemolytic); **CH50** = total complement activity (hemolytic); **AP =** alternative pathway; **eGFR** = estimated glomerular filtration rate; **UPCR** = urine protein to creatinine ratio; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **ACEi =** angiotensin converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **SGLT2** = sodium-glucose cotransporter 2.

# Biopsy Characteristics

| Characteristic | Cohort 8 (IgAN, n = 14†) |
|---|---|
| **Time Since Biopsy, mean (SD)** | 613 (543) days |
| **C3 Intensity, n (%)** | |
| 1+ \| 2+ \| 3+ | 6 (43) \| 6 (43) \| 2 (14) |
| **M (mesangial hypercellularity), n (%)** | |
| M0 (<50%) \| M1 (>50%) | 9 (64) \| 5 (36) |
| **E (endocapillary hypercellularity):** | |
| E0 (none) | 10 (71) |
| E1 (present in any glomeruli) | 4 (29) |
| **S (segmental glomerulosclerosis):** | |
| S0 (absent) | 0 |
| S1 (present in any glomeruli) | 14 (100) |
| **T (tubular atrophy / interstitial fibrosis):** | |
| T0 (0-25%) \| T1 (26-50%) | 9 (64) \| 5 (36) |
| **C (cellular or fibrocellular crescents)‡:** | |
| C0 (absent) | 12 (86) |
| C1 (0-25% of glomeruli) | 1 (7) |

†One subject withdrew at Week 4 for non-safety related reasons. ‡ C score available for 13/14 patients.

# ARO-C3 Reduces Serum C3 in IgAN Patients up to 94% After Multiple 400mg Doses

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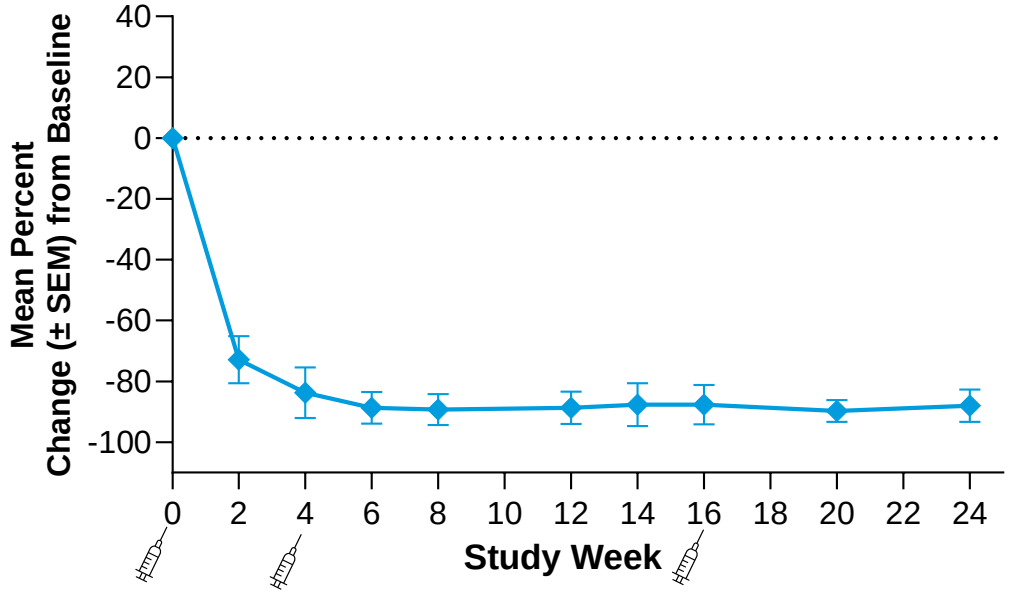
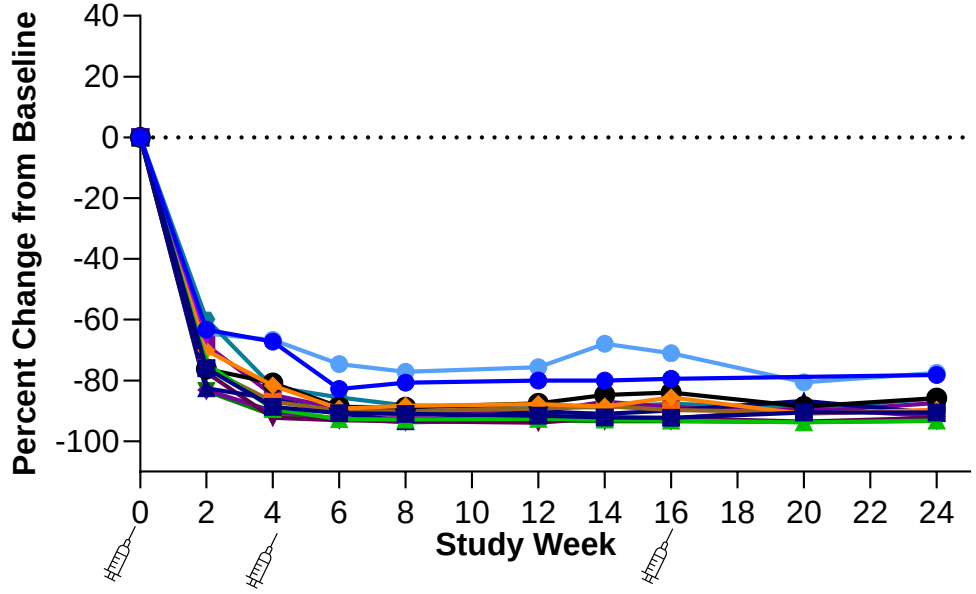
## Mean Percent Change in Serum C3




Maximum mean reduction of **90%**

Sustained reduction of **>87%** from baseline through Week 24†

## Percent Change in Serum C3




Maximum individual reduction of **94%** from baseline

† Sustained (mean) reduction measured after second dose on Day 29 and through Week 24 (three doses total). Baseline defined as the last pre-dose measurement.
One subject withdrew at Week 4 for non-safety related reasons.

# Maximum Reductions of >85% in Alternative Pathway and >60% in Classical Pathway Activity after Multiple Doses of ARO-C3 in IgAN Patients

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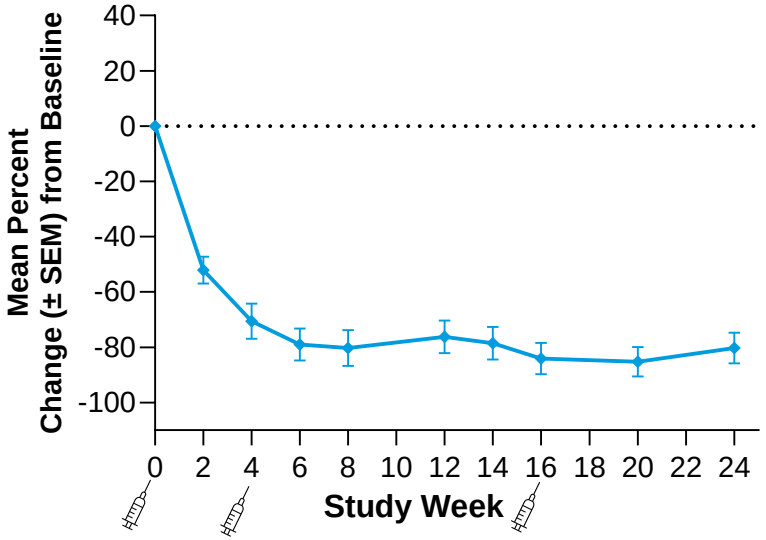
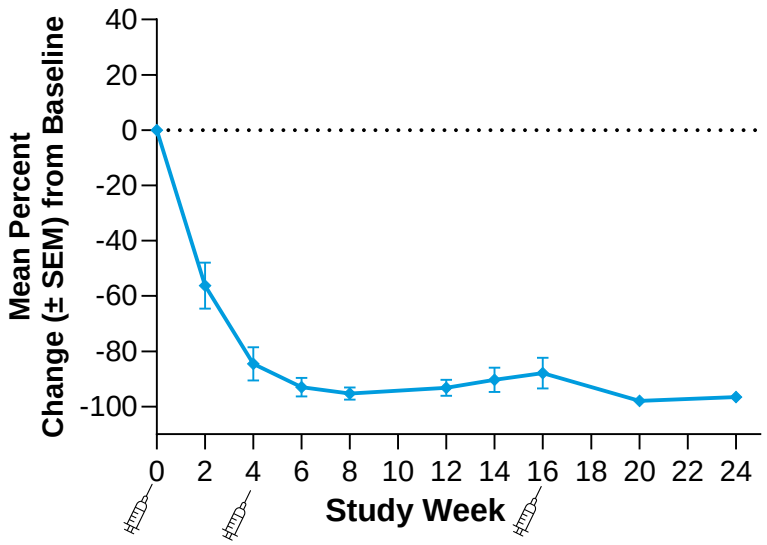
## AH50




Maximum mean reduction of **85%**

Sustained reduction of **>76%** from baseline through Week 24†

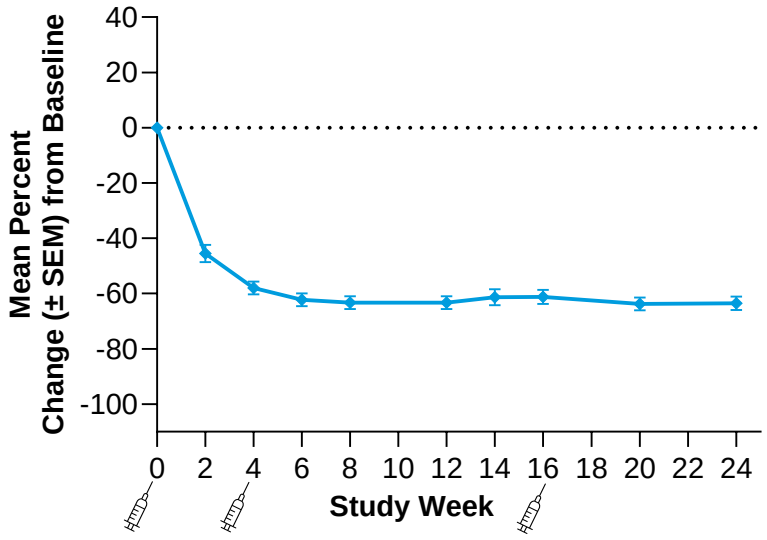
## Wieslab® AP




Maximum mean reduction of **98%**

Sustained reduction of **>87%** from baseline through Week 24†

## CH50




Maximum mean reduction of **64%**

Sustained reduction of **>61%** from baseline through Week 24†

† Sustained (mean) reduction measured after second dose on Day 29 and through Week 24 (three doses total). Baseline defined as the last pre-dose measurement. One subject withdrew at Week 4 for non-safety related reasons. **AH50** = alternative pathway activity (hemolytic); **CH50** = total complement activity (hemolytic); **AP =** alternative pathway.

# ARO-C3 Decreases Markers of AP Activation

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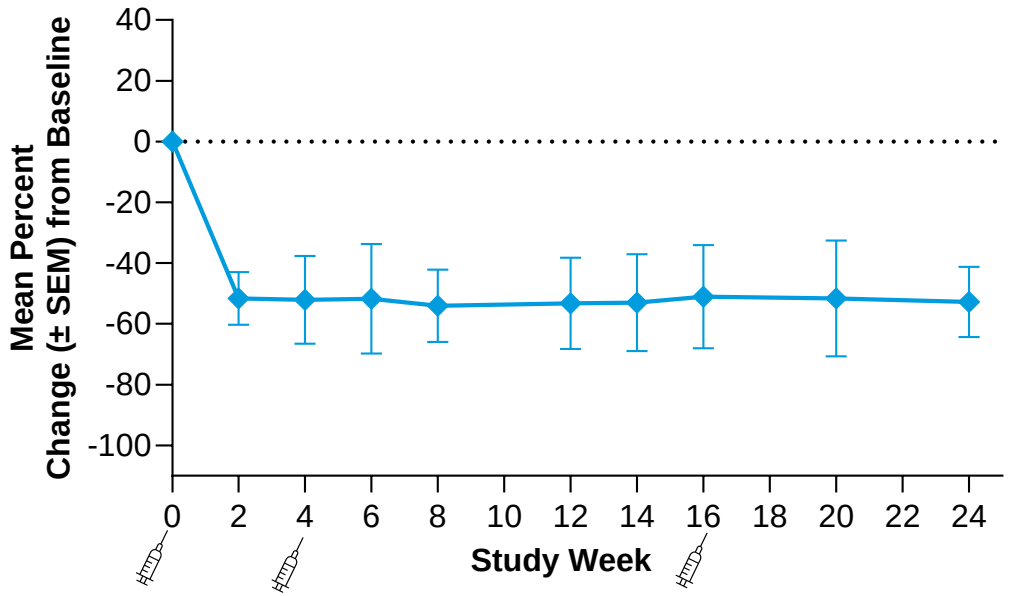
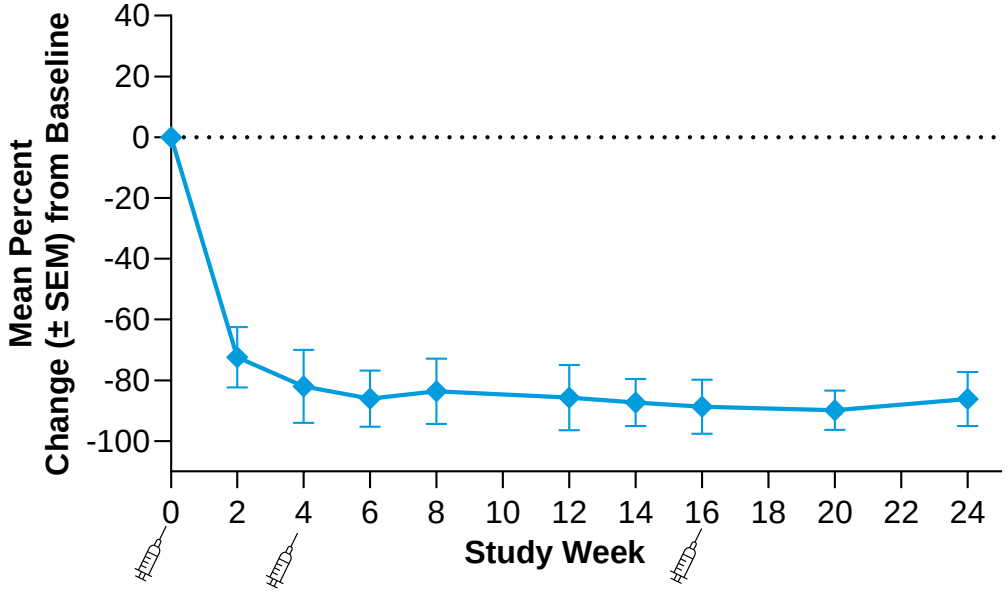
## Mean Percent Change in Serum Bb




Maximum mean reduction of **54%**

Sustained reduction of **>50%** from baseline through Week 24†

## Mean Percent Change in Serum C3b




Maximum mean reduction of **90%**

Sustained reduction of **>83%** from baseline through Week 24†

† Sustained (mean) reduction measured after second dose on Day 29 and through Week 24 (three doses total). Baseline defined as the last pre-dose measurement. One subject withdrew at Week 4 for non-safety related reasons.

# Mean Proteinuria Reduction of 41.1% in Spot UPCR at Week 24

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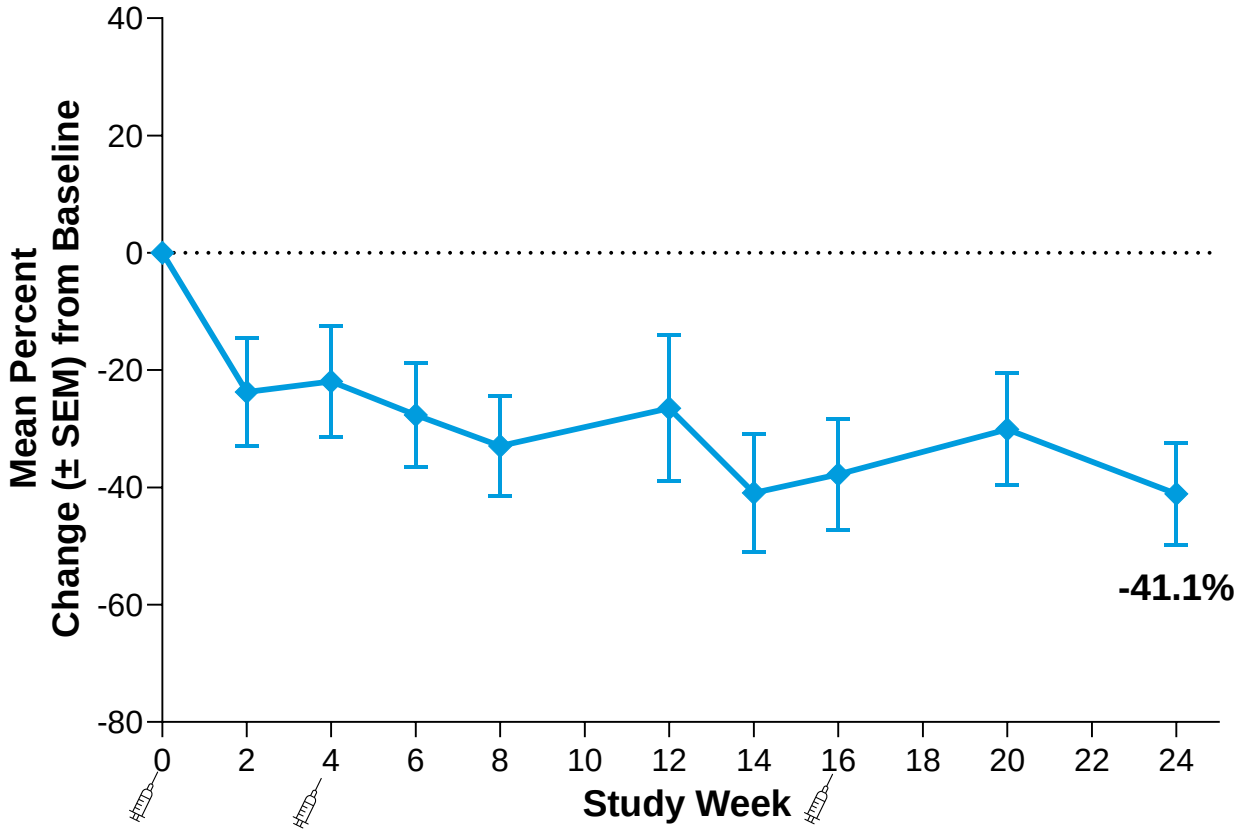
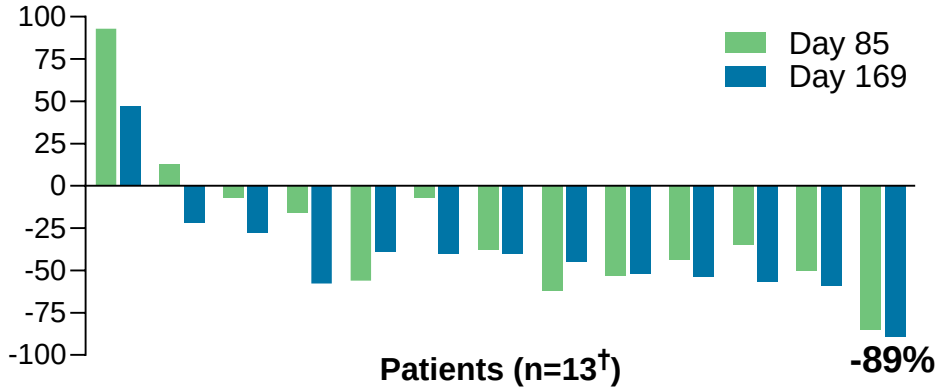
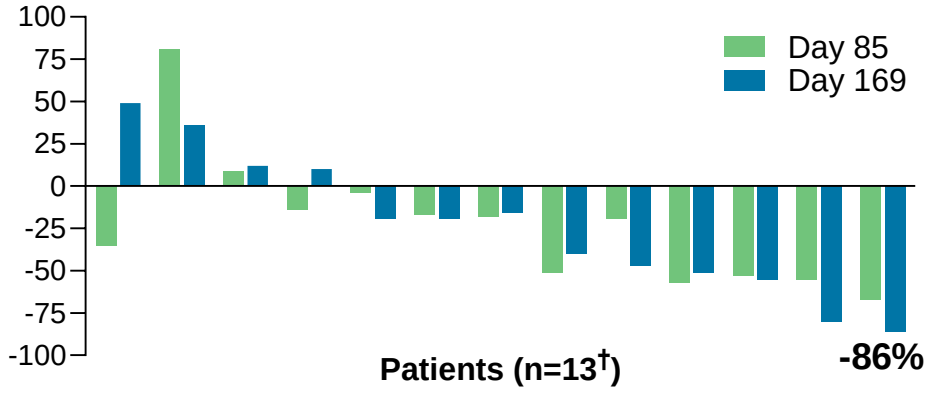
## Percent Change in Spot UPCR




## Individual Percent Change in Spot UPCR




## Individual Percent Change in 24hr UPCR




† One subject withdrew at Week 4 for non-safety related reasons. Baseline for spot samples defined as the last pre-dose measurement; for 24hr samples, all values (incl. baseline) represent an average from valid samples obtained at relevant timepoints (Screening, D85, and D169).

# Improvement in Hematuria and Stable eGFR through Week 24

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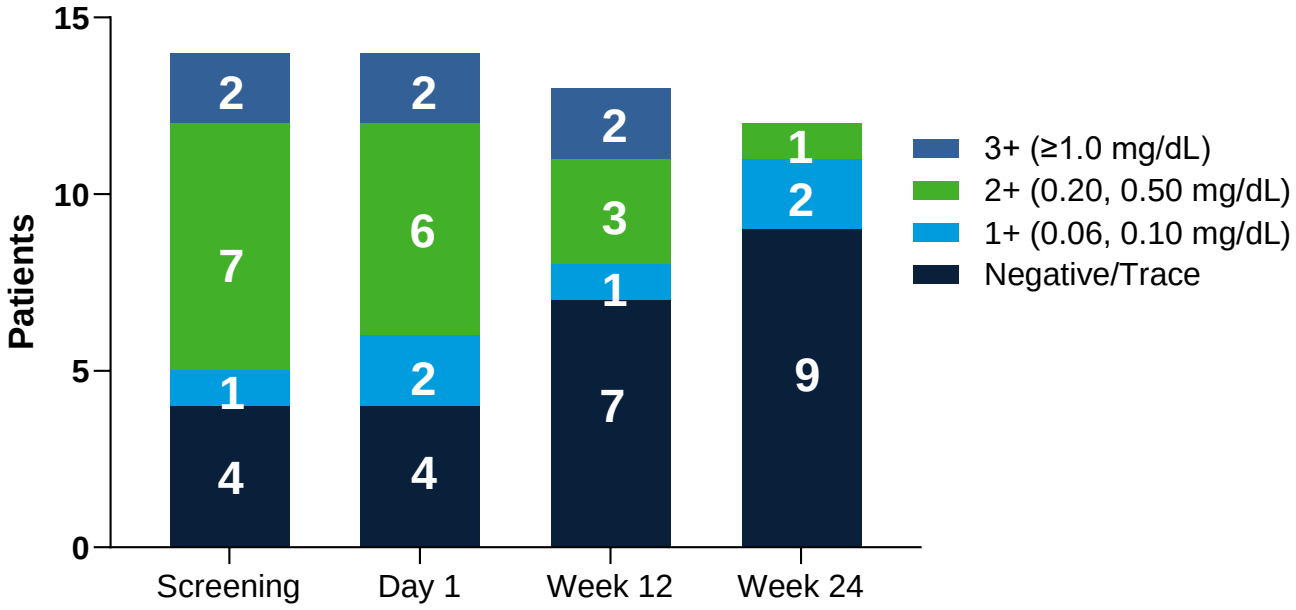
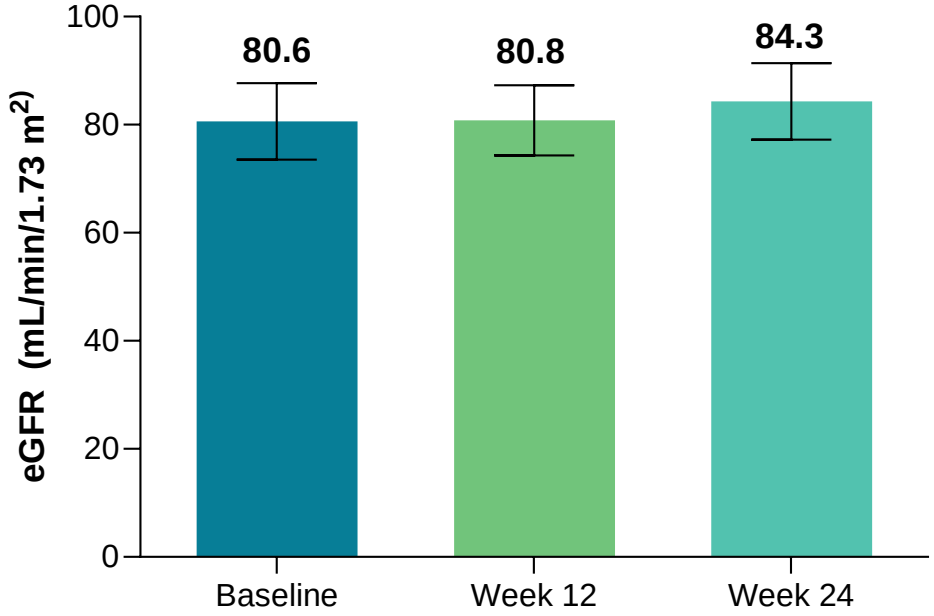
## Hematuria Over Time




By week 24, only **3 of 12 (25%)** had 1+ or greater hematuria by dipstick, compared to **10 of14 (71.4%)** pre-dose.

## eGFR Over Time




Estimated GFR stable over the treatment period.

One subject withdrew at Week 4 for non-safety related reasons. Baseline defined as the last pre-dose measurement.

# ARO-C3 Demonstrates Favorable Safety Profile in Patients with IgAN

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- ARO-C3 was well-tolerated overall.
  - All TEAEs were mild or moderate in severity.
  - No TEAEs led to study or study drug discontinuation.
- No infections with encapsulated organisms.
- Only one subject with injection site reactions, both mild and resolved without sequelae.

| | IgAN, N=14† n (%) |
|---|---|
| **Any TEAE** | 11 (78.6) |
| **Serious TEAEs** | 0 |
| **Severe TEAEs** | 0 |
| **TEAEs leading to study or study drug discontinuation** | 0 |
| **Infections with Encapsulated Organisms** | 0 |
| **Most common TEAEs (>1 patient), n (%)** | |
| Headache | 2 (14.3) |
| Cough | 2 (14.3) |
| Nasopharyngitis | 2 (14.3) |

†One subject withdrew at Week 4 for non-safety related reasons.
**TEAE** = treatment-emergent adverse event; **SAE** = serious adverse event.

# Conclusions

- ARO-C3 was well-tolerated and had a **favorable safety profile at all dose levels** evaluated across SAD, MAD, and CMRD cohorts.
- In patients with IgAN, administration of ARO-C3 400mg led to **robust reductions in serum C3** and measures of **alternative and classical complement activity**.
- **Improvements in proteinuria and hematuria** at 24 weeks suggest potent disease-modifying activity.
- The observed **duration of effect supports quarterly dosing** in later phase studies.
- AROC3-1001 is the **first clinical study** demonstrating proteinuria reduction in patients with IgAN using an siRNA targeting complement C3 – our findings support the continued development of ARO-C3 as a treatment for IgA Nephropathy.

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*Our heartfelt gratitude to the investigators, coordinators, staff, patients, and their families.*