Safety, Tolerability, and Pharmacodynamics of ARO-C3, a Subcutaneously Administered Investigational RNA-interference Therapeutic Targeting Complement C3 in Adult Healthy Volunteers

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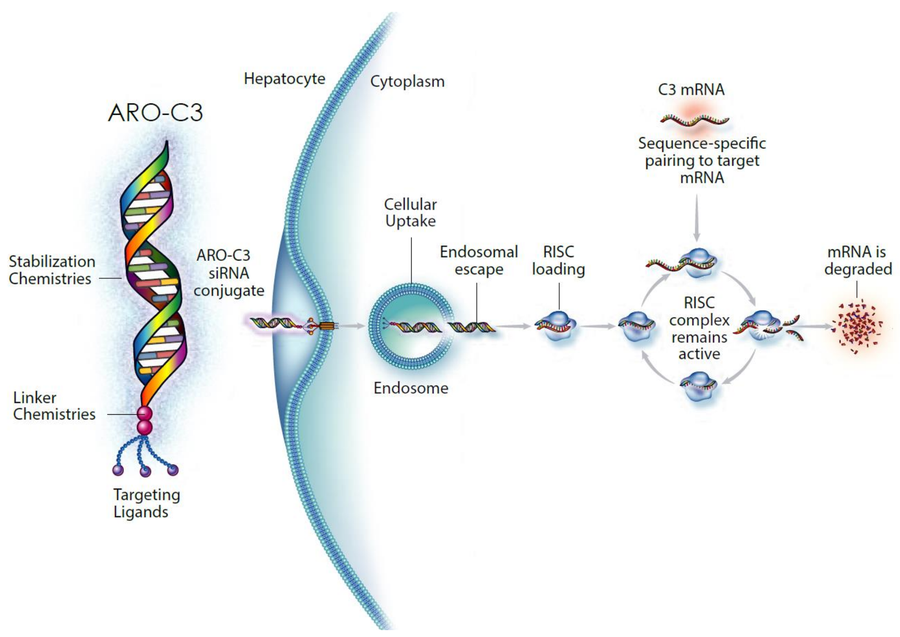
INTRODUCTION

- Complement dysregulation has been implicated in the pathogenesis of various glomerular diseases, including C3 Glomerulopathy (C3G) and IgA Nephropathy (IgAN).
- Despite increasing recognition of the role of complement in mediating renal injury and disease progression in these conditions, no therapies targeting complement have been approved to treat renal diseases.
- ARO-C3 is an RNA-interference therapeutic that reduces hepatic expression of complement component 3 (C3).

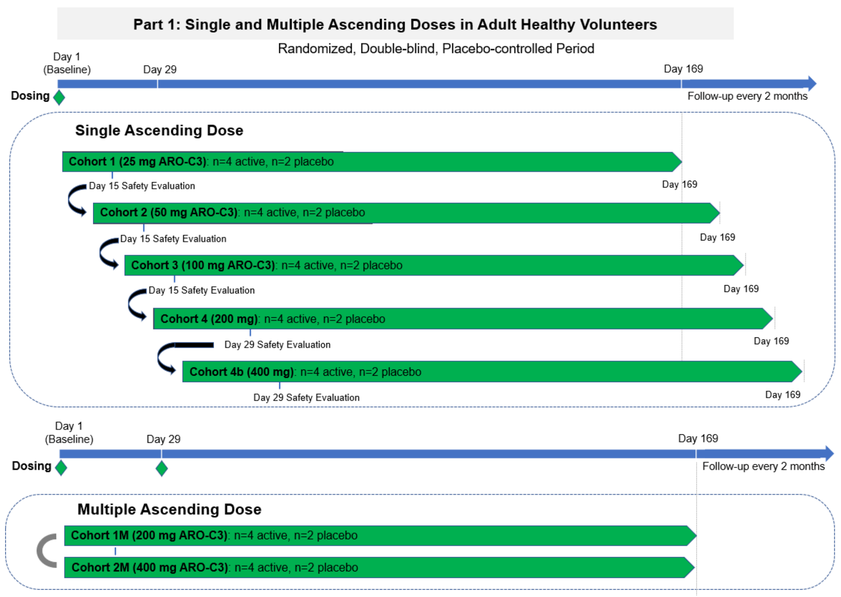


AIM

- The aim of the ongoing AROC3-1001 Phase 1/2a dose-escalating study (NCT05083364) is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ARO-C3, in healthy volunteers (HV) and patients with C3G or IgAN.

METHODS

Figure 1. AROC3-1001 Phase 1 Study Design - Adult Healthy Volunteer Cohorts



- 42 adult HVs were randomized to receive ARO-C3 (n=28) or placebo (n=14).
- **Assessments:** Safety – [adverse events (AEs) and lab results] and PD parameters, including changes in serum C3, alternative and total hemolytic activity (AH50 & CH50), Wieslab® alternative pathway assay
- **Data cut:** 06 March 2024

RESULTS

Table 1. Baseline HV Characteristics

	Pooled Placebo (N=14)	Pooled Active (N=28)
Age (years)	33.4 (10.4)	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 (18.9)
Wieslab AP (%)[1]	61.6 (19.1)	71.7 (19.6)

[1] Wieslab AP results calculated per the assay manufacturer's recommended PC/NC (Positive Control/Negative Control) ratio from a cumulative rerun of all subject samples performed at the end of Phase 1.

RESULTS

Pharmacodynamics

- ARO-C3 doses between 25-400mg, administered as one or two subcutaneous injections, resulted in durable, dose-dependent decreases in serum complement C3 levels **[Fig 2]**, total complement activity (CH50), and alternative pathway (AP) activity (AH50 and Wieslab AP) **[Fig 3]**.
- Following a single 400mg dose of ARO-C3, mean(±SD) C3 reduction of 81±10% from baseline was observed at week 4, with sustained reduction of 79±11% at week 16 **[Fig 2a]**. Repeat 400mg doses (on Days 1 and 29) led to mean C3 reductions of 88±6% by week 8 and 85±7% at week 16 **[Fig2b]**.
- Decreases of 63±8%, 91±15%, and 98±2% from baseline in CH50, AH50, and Wieslab AP, respectively, were seen 4 weeks after the second dose of ARO-C3 **[Fig 3]**. Decreases in complement activity were sustained through week 16.

Figure 2. Measured serum complement C3 levels in **(a)** single ascending dose (SAD) healthy volunteer cohorts and **(b)** multiple ascending dose (MAD) healthy volunteer cohorts.

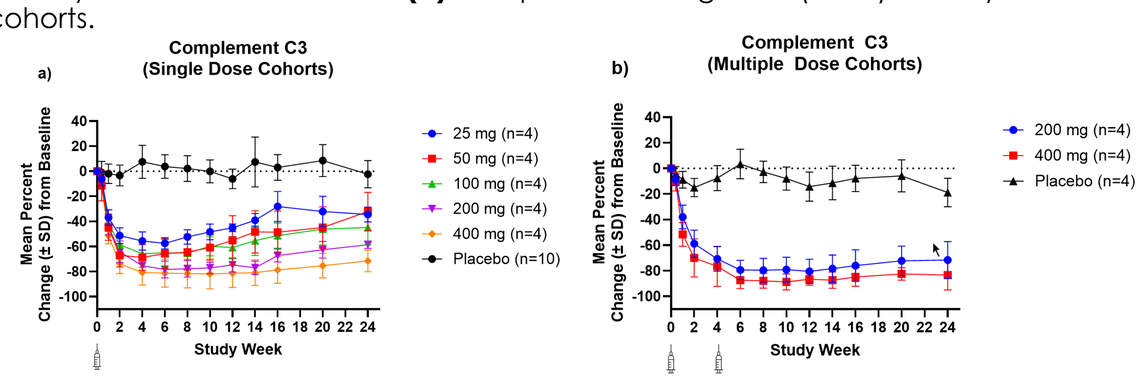
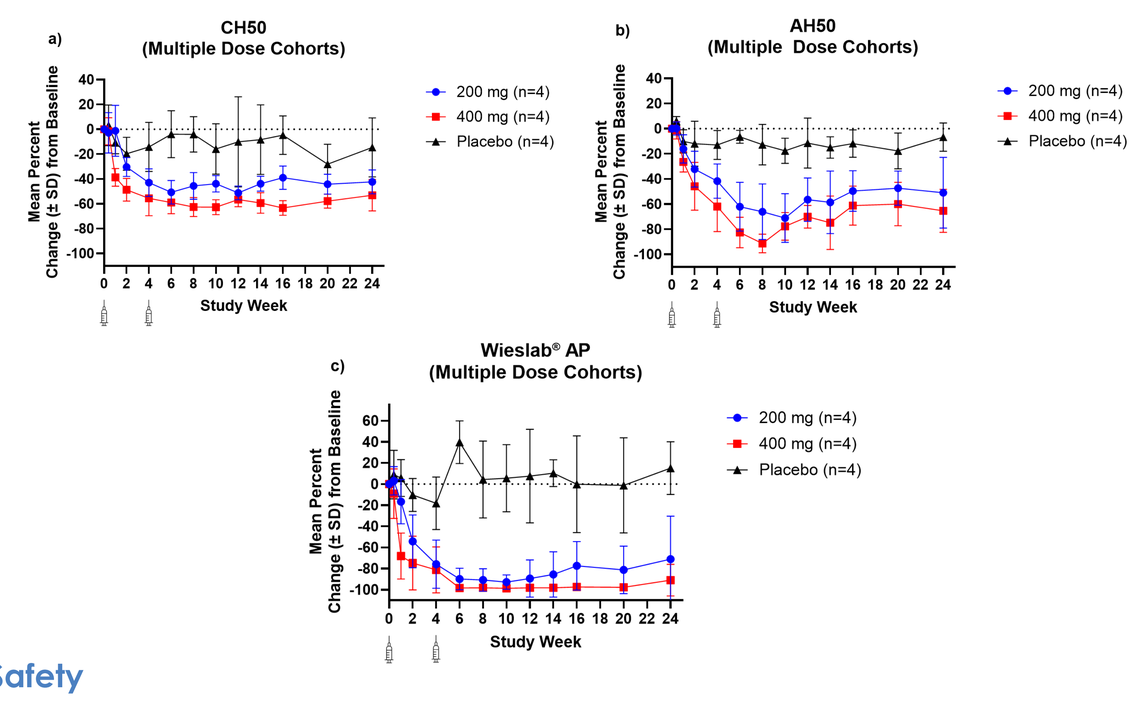


Figure 3. Measures of Complement Activity in multiple ascending dose (MAD) healthy volunteer cohorts: **(a)** Total Complement Activity (CH50), **(b)** Alternative Pathway Activity (AH50), and **(c)** Wieslab® Alternative Pathway (AP) Activity (PC/NC).



Safety

- ARO-C3 was well-tolerated, with no drug-related serious adverse events (SAEs), dose-limiting adverse events (AEs), or AEs resulting in study drug discontinuation. Most AEs were mild in severity.

Table 2. TEAEs Reported in ≥15% of Subjects

	Total (%) (N=42)	Pooled Active (N=28)	Pooled Placebo (N=14)
Headache	17 (40)	12 (43)	5 (36)
COVID-19	13 (31)	8 (29)	5 (36)
Upper Respiratory Infection	12 (29)	7 (25)	5 (36)
Vaccination-related	9 (21)	5 (18)	4 (29)
Nausea	7 (17)	3 (11)	4 (29)

CONCLUSIONS

ARO-C3 is well tolerated and achieves sustained reductions in complement C3 and suppression of total and alternative pathway activity after single and repeat subcutaneous doses, supporting a quarterly dosing regimen. The Phase 2a portion of the study, enrolling patients with C3G and IgAN, is ongoing.

ACKNOWLEDGEMENTS

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REFERENCES

Clinicaltrials.gov identifier: NCT05083364