Safety, Tolerability and Pharmacodynamic Effects of ARO-C3, a Subcutaneously Administered Investigational RNAi Therapeutic Targeting Complement C3, in Adult Healthy Volunteers

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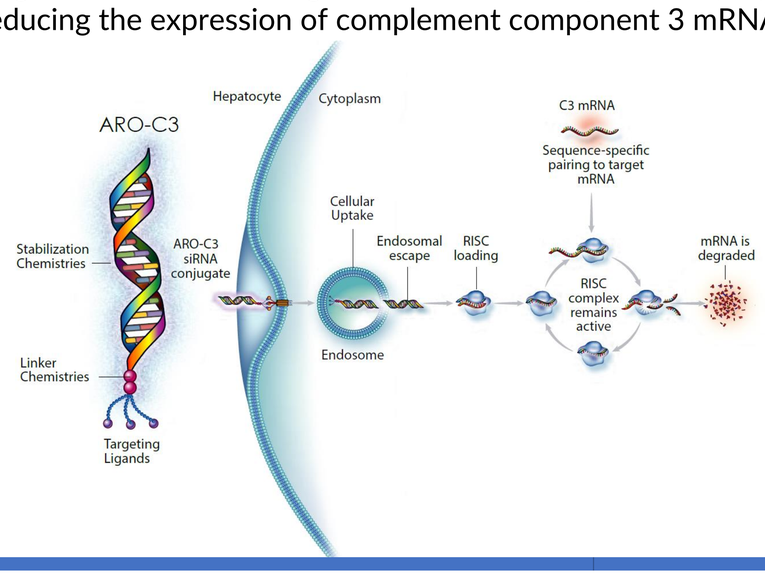
INTRODUCTION

The complement system is an important part of innate immunity. However, dysregulated complement activity plays a pathogenic role in many diseases. Several therapies targeting the complement cascade are effective in treating these conditions.

ARO-C3 is an RNAi based therapeutic composed of synthetic double-stranded RNAi trigger designed to selectively target complement component 3 (C3) in hepatocytes thereby reducing the expression of complement component 3 mRNA and protein.

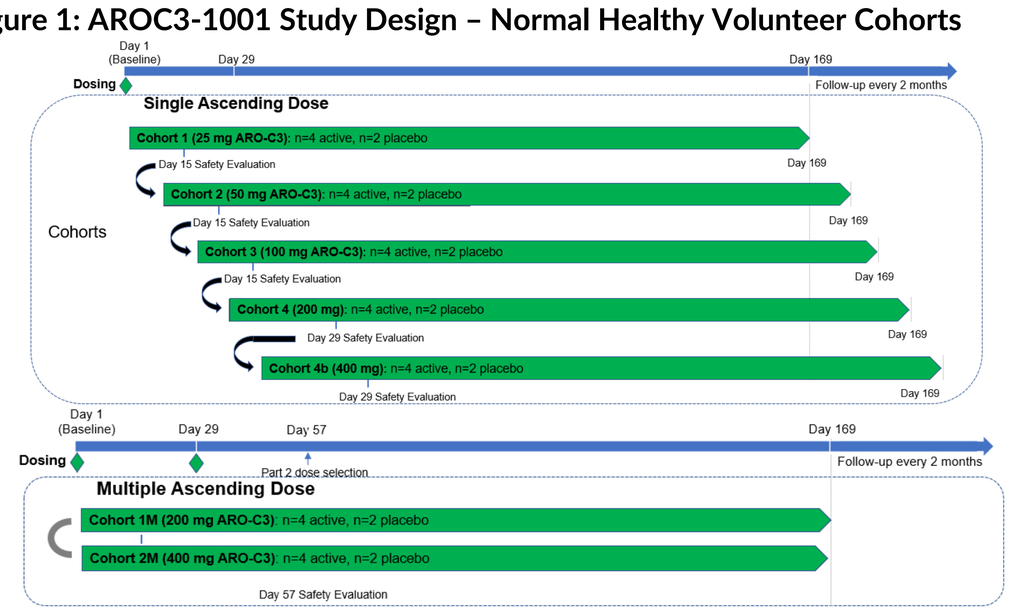


AIM

The aim of the ongoing AROC3-1001 study (NCT05083364) is to evaluate the safety and pharmacodynamic effects of ARO-C3 in adult normal healthy volunteers (NHVs) as well as in patients with complement mediated renal disease.

METHODS

Figure 1: AROC3-1001 Study Design – Normal Healthy Volunteer Cohorts



- NHVs eligible to receive ARO-C3 by subcutaneous injection in a double blind, placebo-controlled fashion were enrolled in the study.
- All subjects were vaccinated against *S. pneumoniae, N. meningiditis*, and *H. influenzae* at baseline and used antibiotic prophylaxis until the end of study.
- Safety assessments included AEs, laboratory evaluations (chemistry, hematology, coagulation) , pharmacodynamic assessments included serum C3, alternative complement pathway hemolytic activity (AH50), and Wieslab® alternative pathway (AP) assay.
- All NHV cohorts have fully enrolled.
- **Data Cut: 15 February 2023**

RESULTS

BASELINE CHARACTERISTICS & SAFETY

- Overall, ARO-C3 as a subcutaneous injection has been well tolerated in NHVs
- No SAEs or dropouts due to AEs
- No dose limiting toxicities
- No infections with encapsulated organisms
- Injection site AEs showed a dose response with more ISRs (Injection site reactions) at higher doses, although all were mild

Table 1: 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)

Table 2:Summary of Safety and Adverse Events (incidents >3)

Subject Incidence, n (%)	Pooled Placebo (N=14)	Pooled Active (n=28)
Headache	5 (36%)	13 (46%)
Upper Respiratory Infection	4 (29%)	5 (18%)
Injection Site AE's	0	5 (18%)
Seasonal Allergy	0	4 (14%)

RESULTS

PHARMACODYNAMICS

Figure 1: Percent change from baseline in serum Complement C3

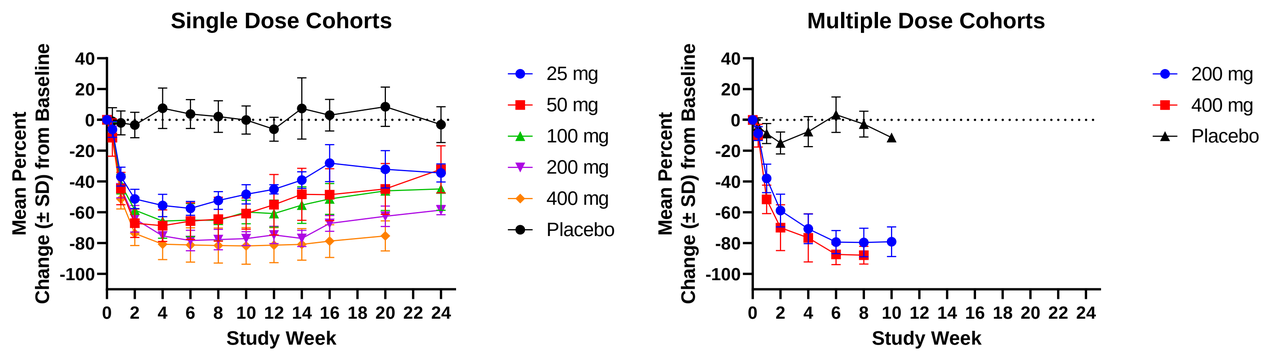


Figure 2: Percent change from baseline in alternative pathway complement activity (Wieslab ® AP)

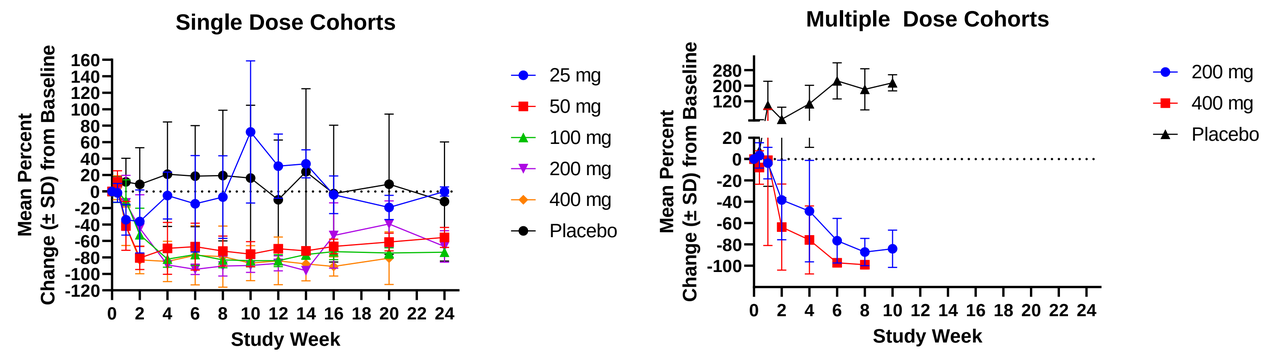


Figure 3: Percent change from baseline in alternative pathway complement activity (AH50)

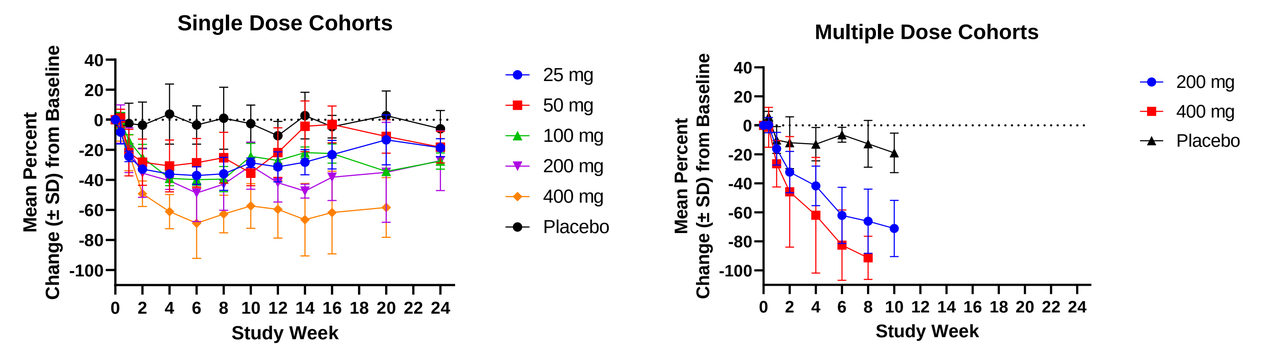
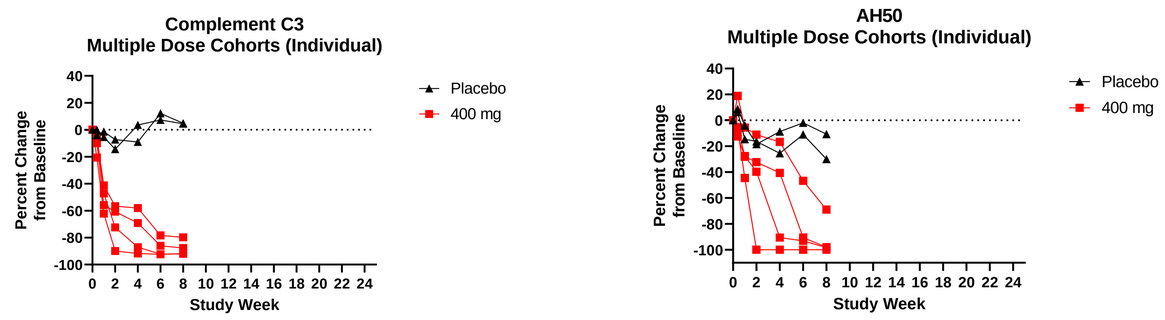


Figure 4: Percent change from baseline in serum Complement C3 and AH50 in individuals



After single dose of ARO-C3:

- Up to **82% mean** reduction in C3 sustained through week 16 at 400mg
- Up to **91% mean** reduction in Wieslab ® AP sustained through week 16 at 400mg
- Up to **69% mean** reduction in AH50 by week 6 at 400mg

After multiple doses of ARO-C3:

- Up to **79%** and **88% mean** reductions in serum C3 by week 8 at 200 mg and 400 mg , respectively
- Overall, maximum reduction of **92%** serum C3 achieved at 400 mg
- **87%** and **99% mean** reductions in Wieslab ® AP at week 8 at 200 and 400mg, respectively
- **3 of 4** subjects on active treatment achieved **>95%** reduction in AH50 at 400mg

CONCLUSIONS

ARO-C3 has been well tolerated at single and multiple doses up to 400 mg. Dose dependent reductions in serum C3 were observed and corresponded with reductions in alternative pathway hemolytic activity. Duration of pharmacological effect is supportive of quarterly or less frequent subcutaneous dose administration.

ACKNOWLEDGEMENTS

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REFERENCES

Clinicaltrials.gov identifier: NCT05083364