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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Financial Disclosures

Presenter:

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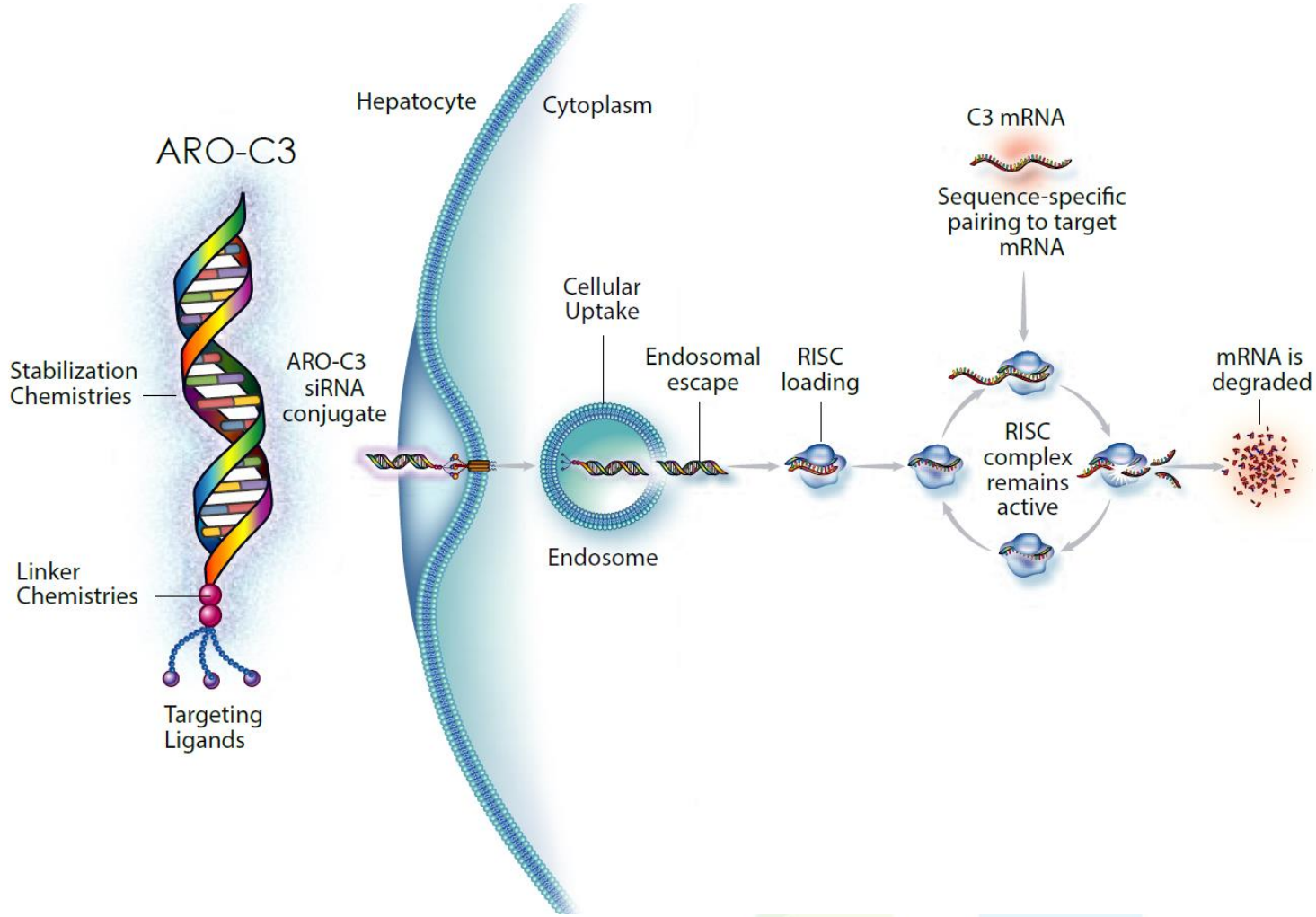
M. Marshall is a current employee of New Zealand Clinical Research, University of Auckland, and Health New Zealand.

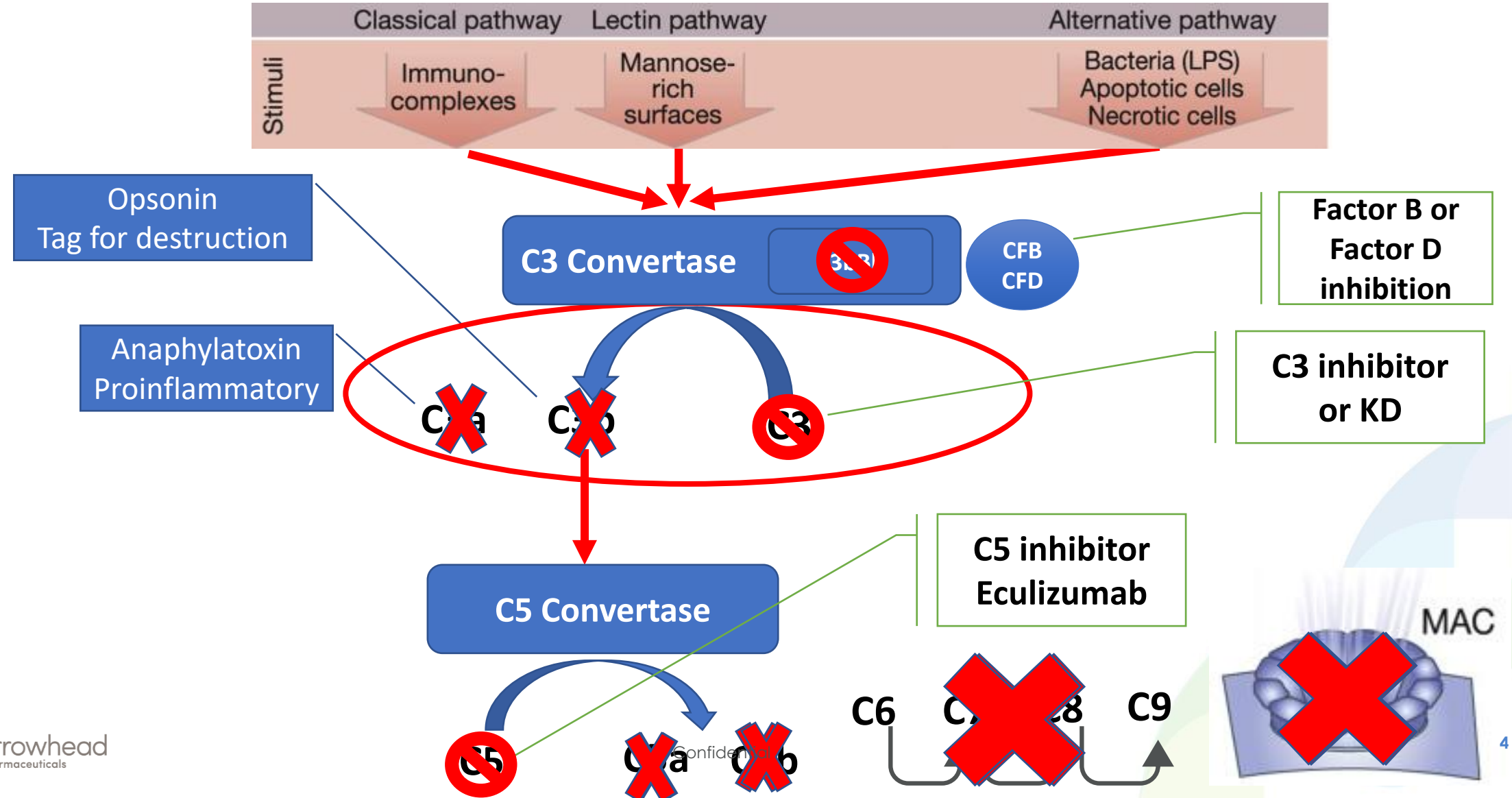
ARO-C3 specifically targets and silences C3 mRNA expression, reducing plasma complement component 3 levels

ARO-C3

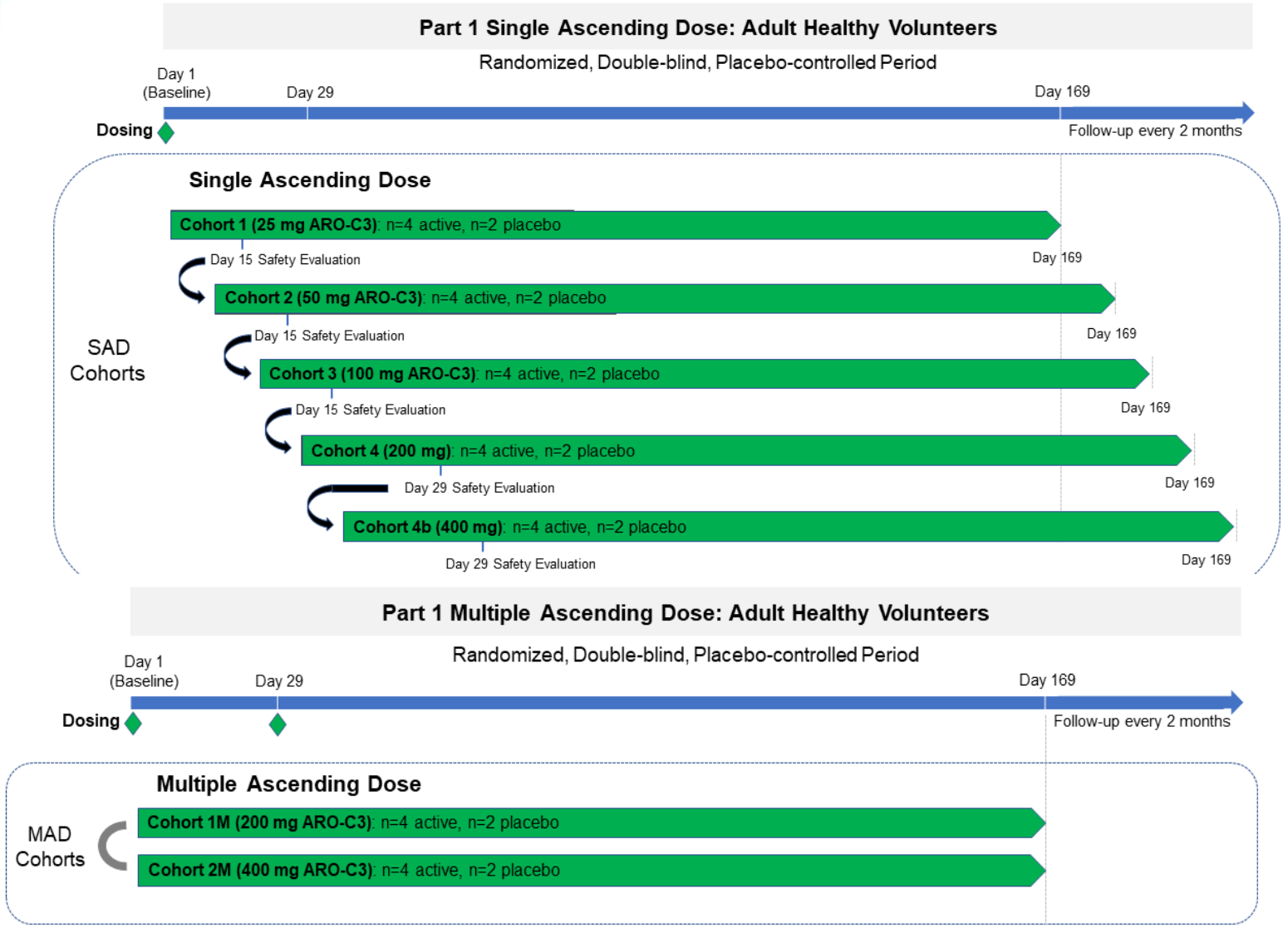
- RNAi conjugate designed to target and silence hepatic C3 mRNA which inhibits production of complement component 3
- Conjugate is composed of synthetic, double-stranded oligonucleotide
- Linked to a ligand containing N-acetyl-galactosamine (NAG) targeting moieties with high affinity to asialoglycoprotein receptor (ASGPR) present on hepatocyte surfaces



ARO-C3 targets proximal/alternative pathway of complement



Phase 1 study to evaluate effect of ARO-C3 in healthy volunteers



Study Endpoints

- Safety (Primary):
  - Incidence, frequency, and severity of treatment-emergent adverse events (TEAEs)
- Key Pharmacodynamics Parameters:
  - Change and percent change from baseline over time in serum complement component 3 (C3), alternative complement pathway hemolytic activity (AH50), and Wieslab® alternative pathway assay

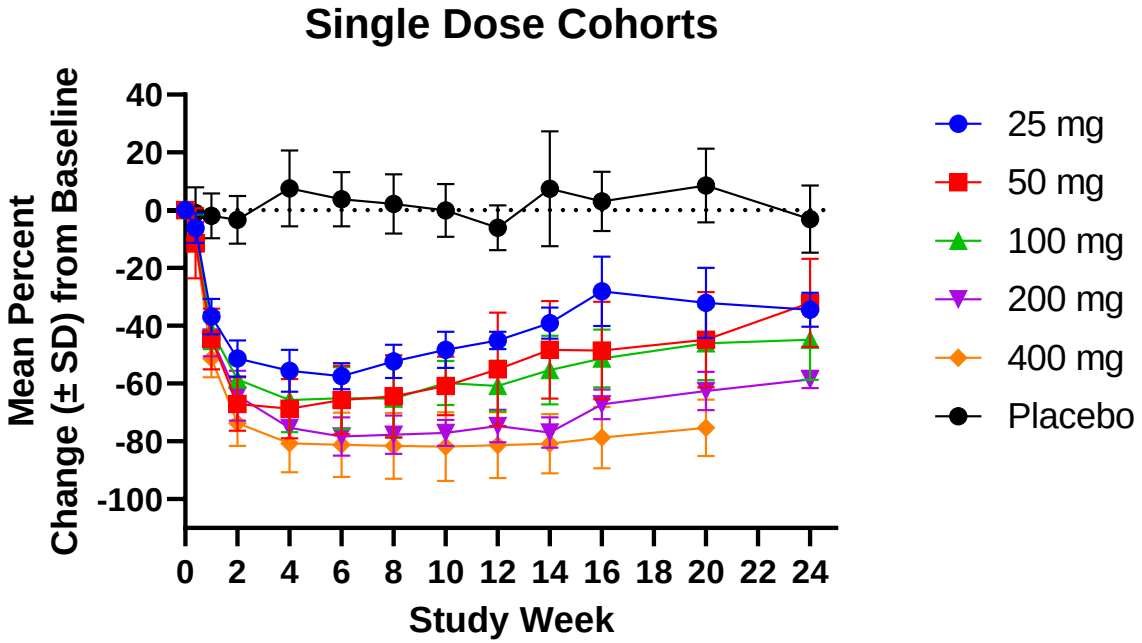
Baseline characteristics of healthy volunteers

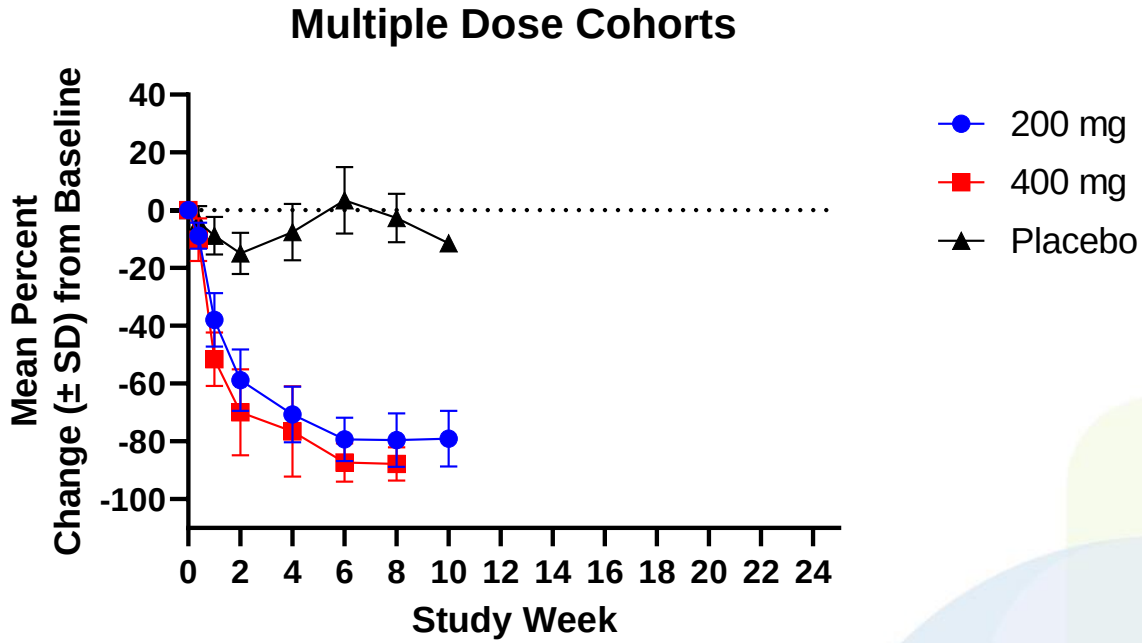
Parameter	Pooled Placebo (N=14)	Pooled Active (N=28)
Age (years)	33.0 (10.7)	30.8 (11.8)
Sex (%M)	5 (35.7%)	10 (35.7%)
BMI (kg/m2)	25.4 (4.5)	25.7 (4.3)
C3 (mg/dL)	94.8 (15.8)	96.7 (12.7)
AH50 (U/mL)	112.6 (13.8)	115.7 (19.0)
Wieslab (%)	118.5 (99.8)	129.4 (100.7)

Healthy volunteer cohorts fully enrolled. Study is ongoing and is still blinded.

Interim data cutoff: 15 February 2023

Reduction in serum complement component 3 after single and repeat doses of ARO-C3





Up to 82**%** mean reduction was sustained through week 16 at 400mg

Up to **79%** and **88%** mean reductions in C3 by week 8 at 200 mg and 400 mg, respectively

Giving a second dose at week 4 results in ~2% more reduction at 200mg, and ~6% more reduction in C3 at 400mg

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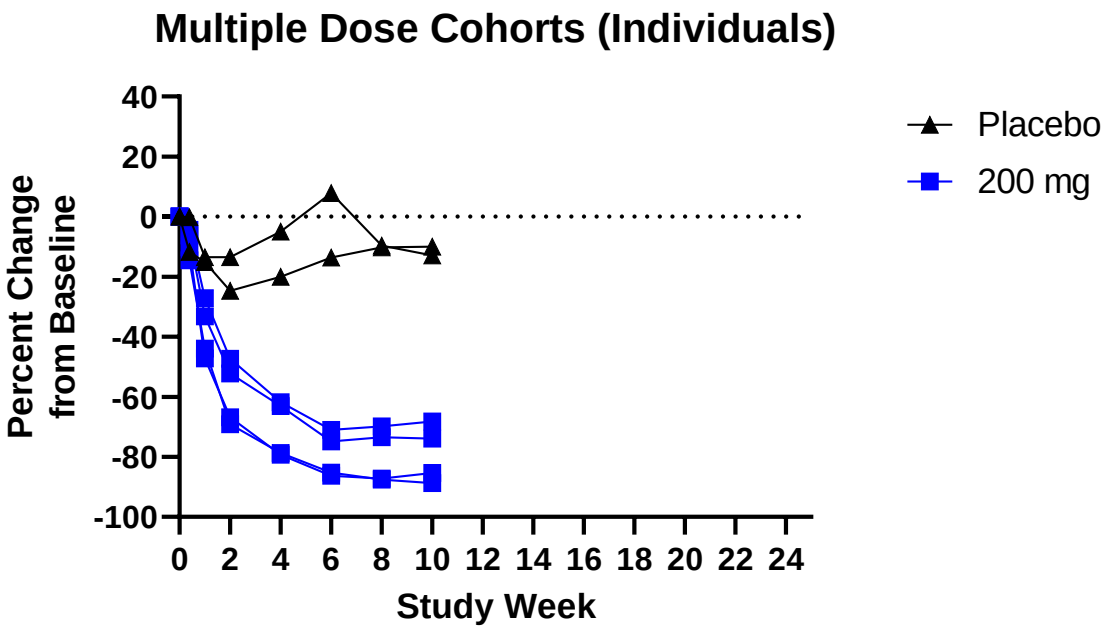
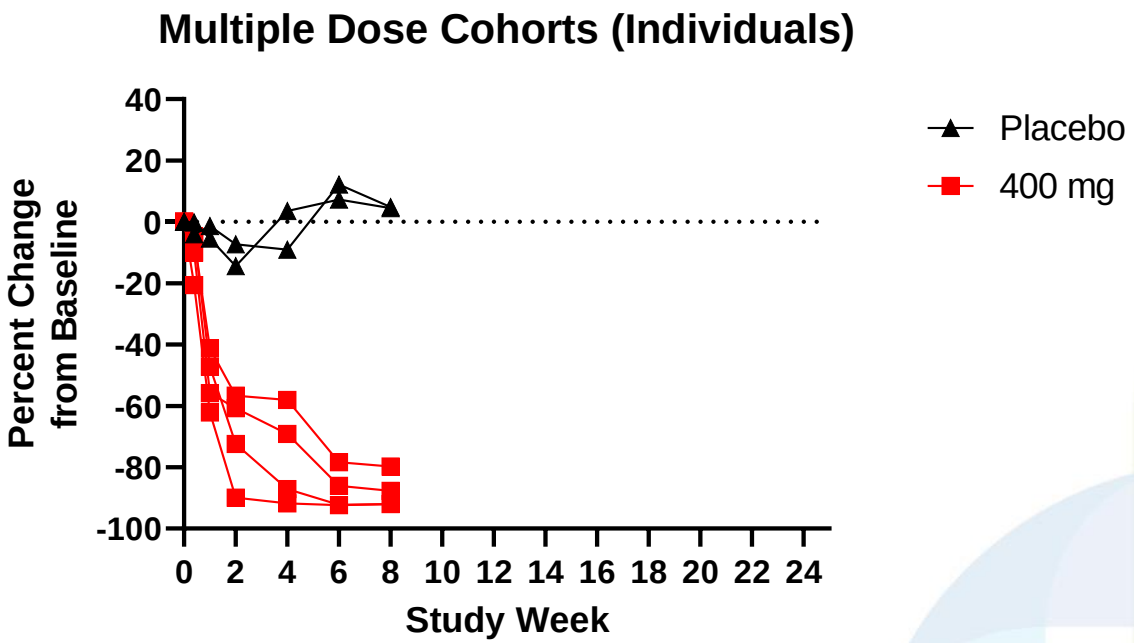
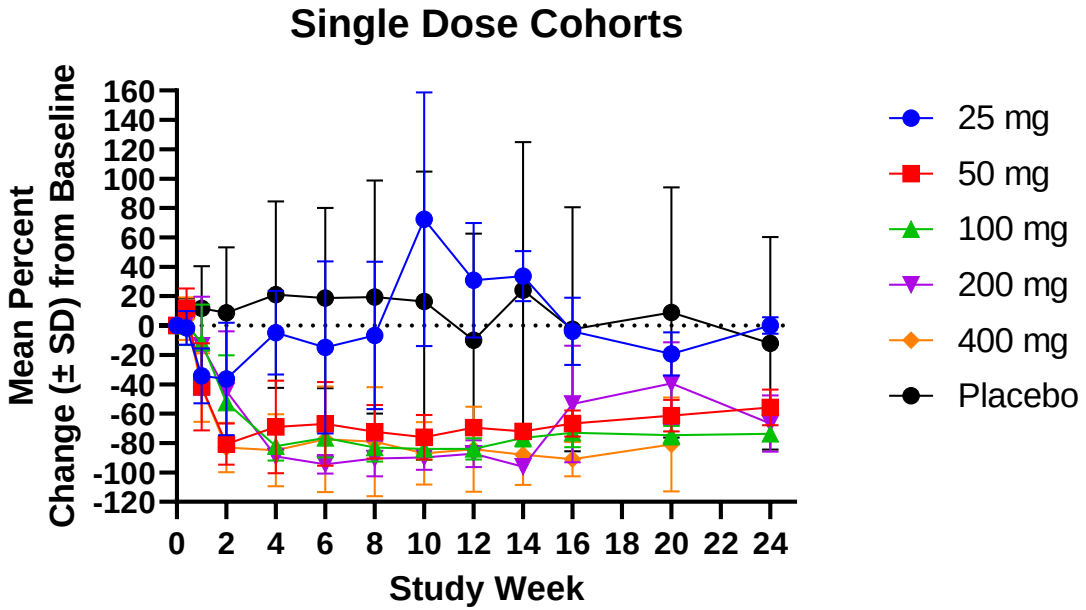
Individual subject response after multiple doses of ARO-C3 - % reduction in serum C3

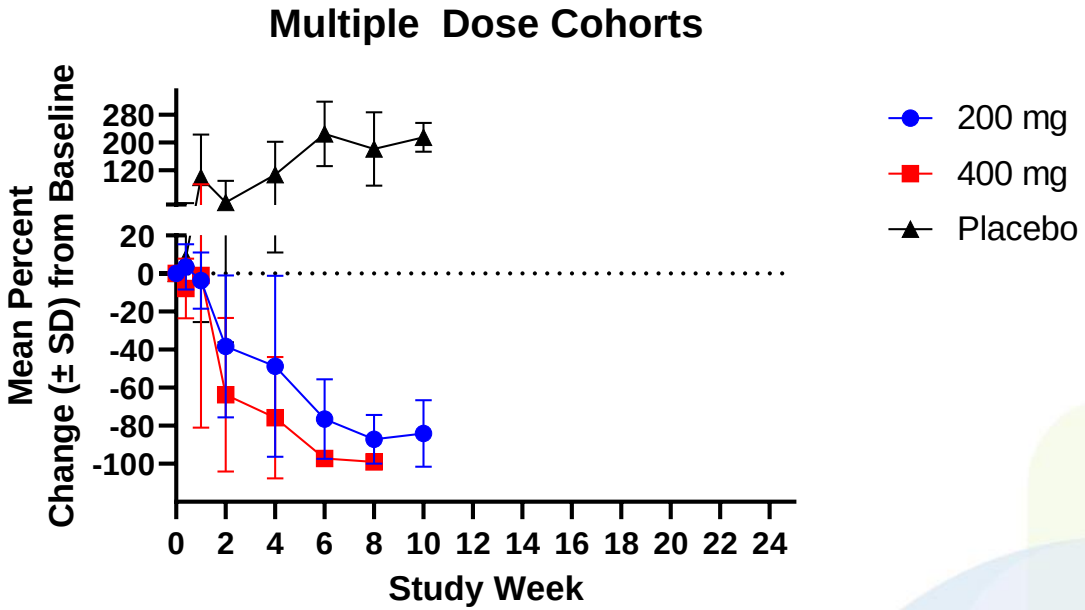




Maximum C3 reduction of 86% and 92% after multiple doses of 200 mg and 400mg, respectively

Reduction in functional activity of alternative pathway as measured by Wieslab ® AP



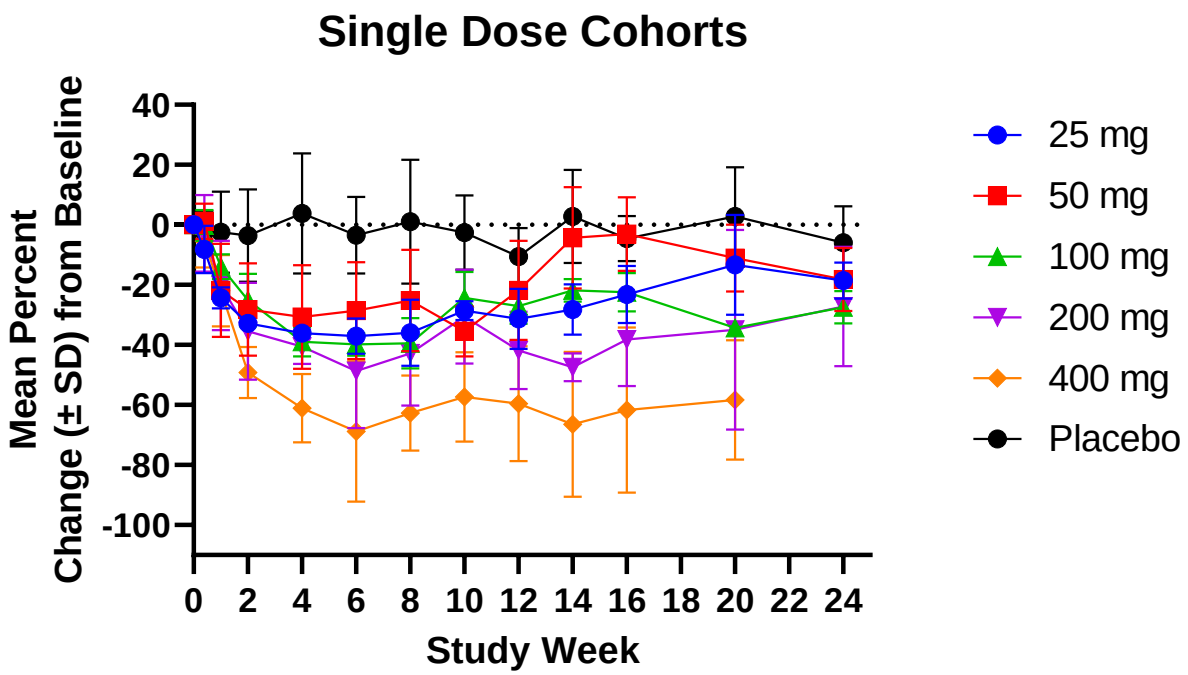


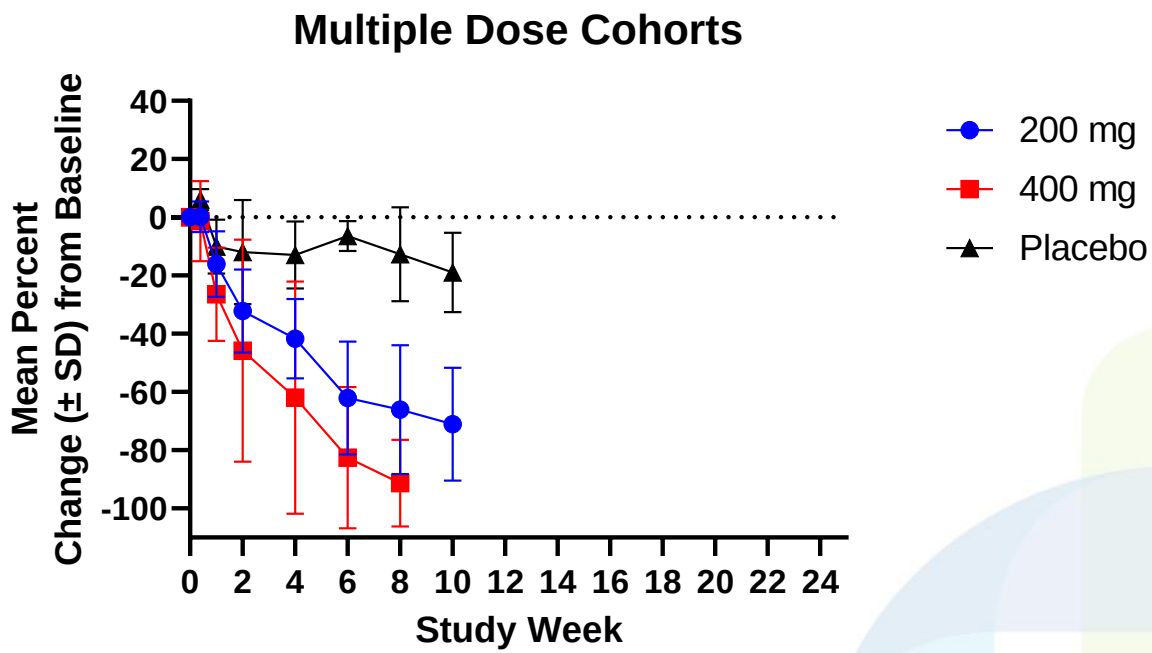
85-91% mean reduction in Wieslab ® AP sustained through week 16 at 400 mg

87% and **99%** mean reduction in Wieslab ® AP at week 8 at 200 and 400mg, respectively

Results were calculated per the assay manufacturer's recommended NC/PC (Negative Control/Positive Control) Ratio

Reduction in hemolytic activity as measured by AH50





Up to **69%** mean reduction in AH50 by Week 6 at 400mg

Up to **66%** and **91%** mean reduction in AH50 by Week 8 at 200 mg and 400 mg, respectively

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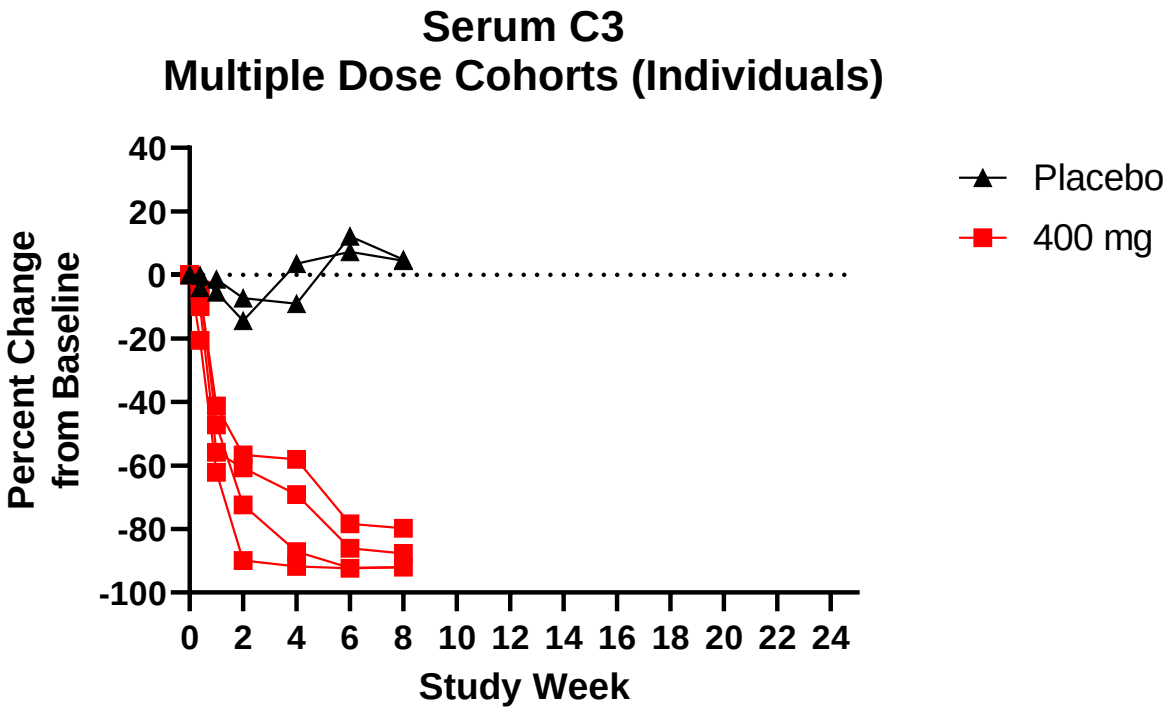
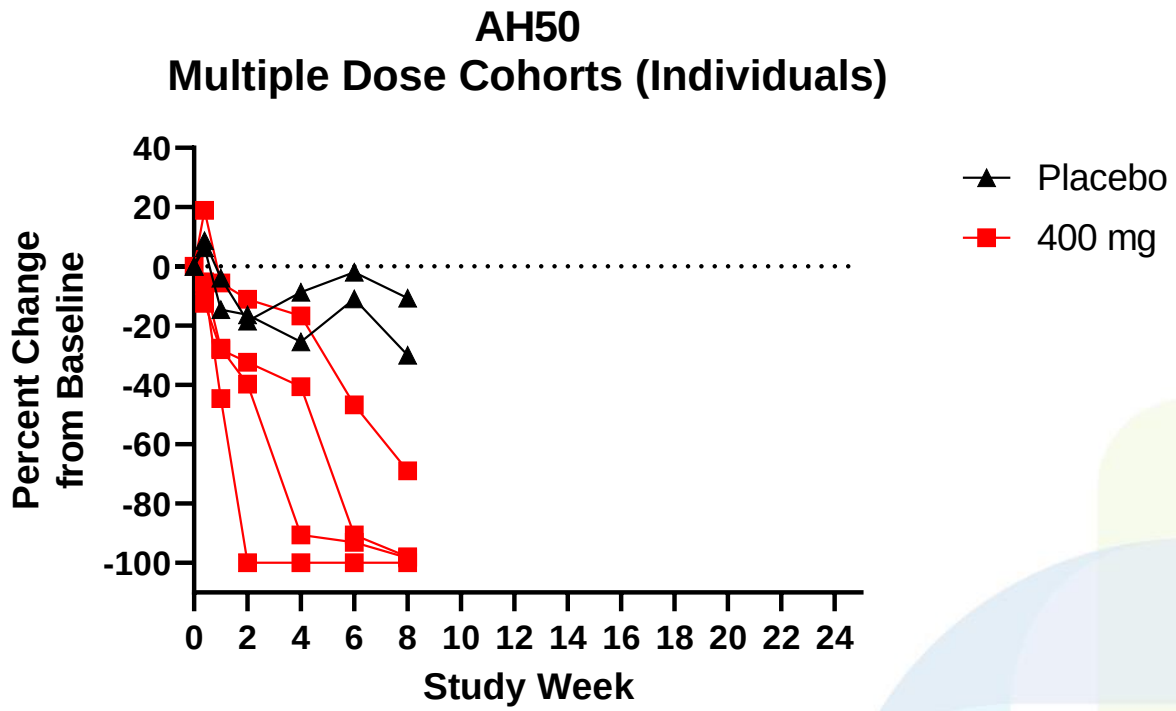
Individual subject responses in hemolytic activity





In 3 out of 4 subjects, more than 95% reduction in hemolytic activity (AH50) at highest dose level at Week 8.

Summary of Treatment-emergent Adverse Events in Healthy Volunteers

Preferred Term # (%)	Pooled Placebo (n=14)	Pooled Active (n=28)
Headache	5 (36%)	13 (46%)
Upper Resp Infection	4 (29%)	5 (18%)
Injection site AEs	0	5 (18%)
Seasonal Allergy	0	4 (14%)

- No SAEs or dropouts due to AEs.
- No dose limiting toxicity
- Most common AEs include headache > Upper Respiratory Infection > Injection site AEs > Seasonal Allergy
- 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
- Safety findings not a factor in selecting dose for patient cohorts

Summary

- ARO-C3 achieved mean C3 knockdown of 88% at the highest dose level, with enough duration to justify quarterly or less frequent dosing.
- ARO-C3 achieved corresponding reductions in hemolytic activity and functional activity of alternative pathway that should be competitive with other AP-targeted therapeutics.
- No TEAEs secondary to adverse changes in electrolytes, renal function, liver function/injury, or platelet count.
- Overall, no clinically significant laboratory findings or patterns of adverse changes in any clinical laboratory parameters.
- ARO-C3 may represent a promising RNAi therapeutic for the treatment of complement-mediated diseases with infrequent dosing

Thank you

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