Targeting Complement Factor B with siRNA: Concept to Clinic

Complement Based Drug Development Summit

Boston, MA

December 11, 2024

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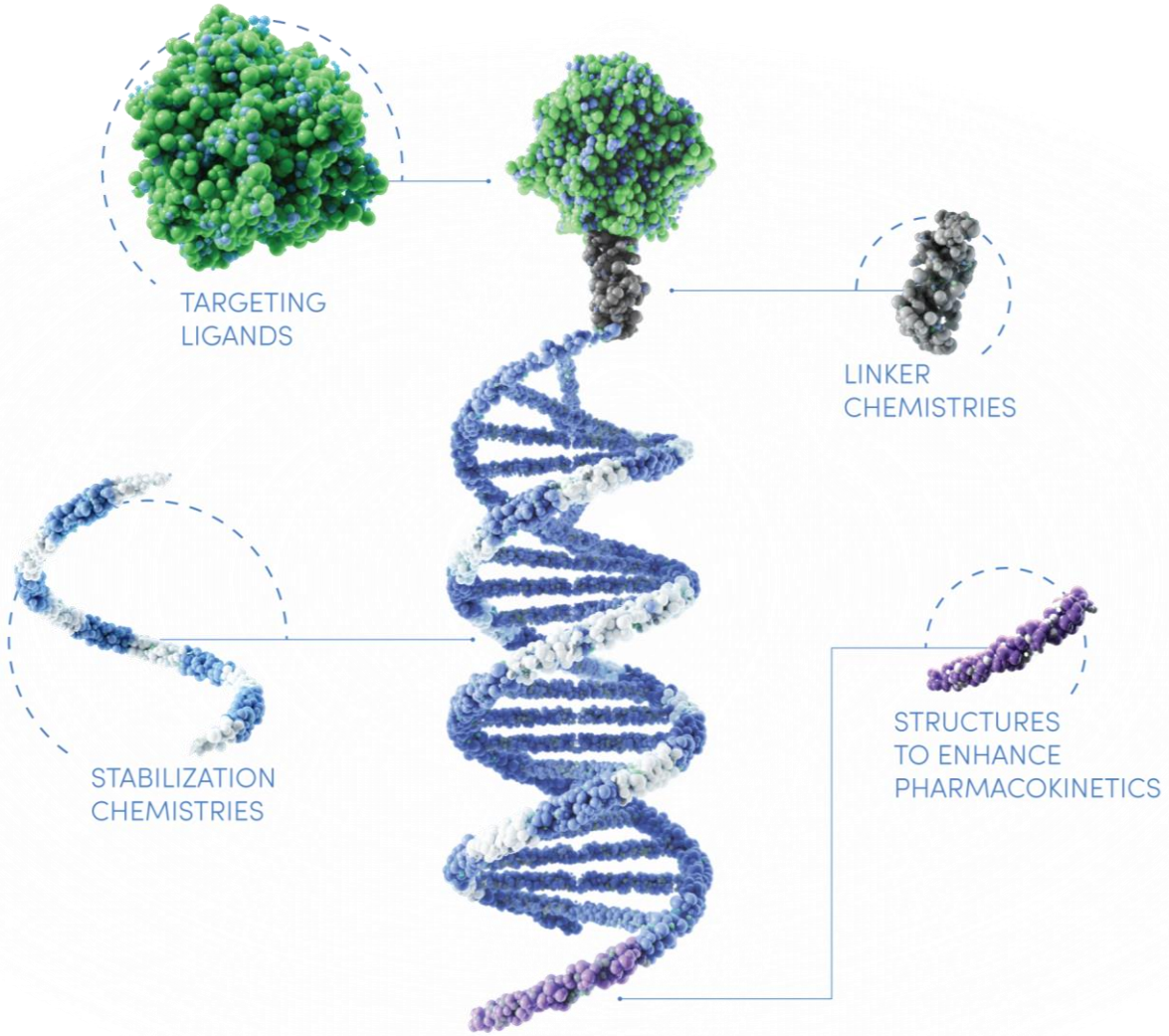
Conflicts

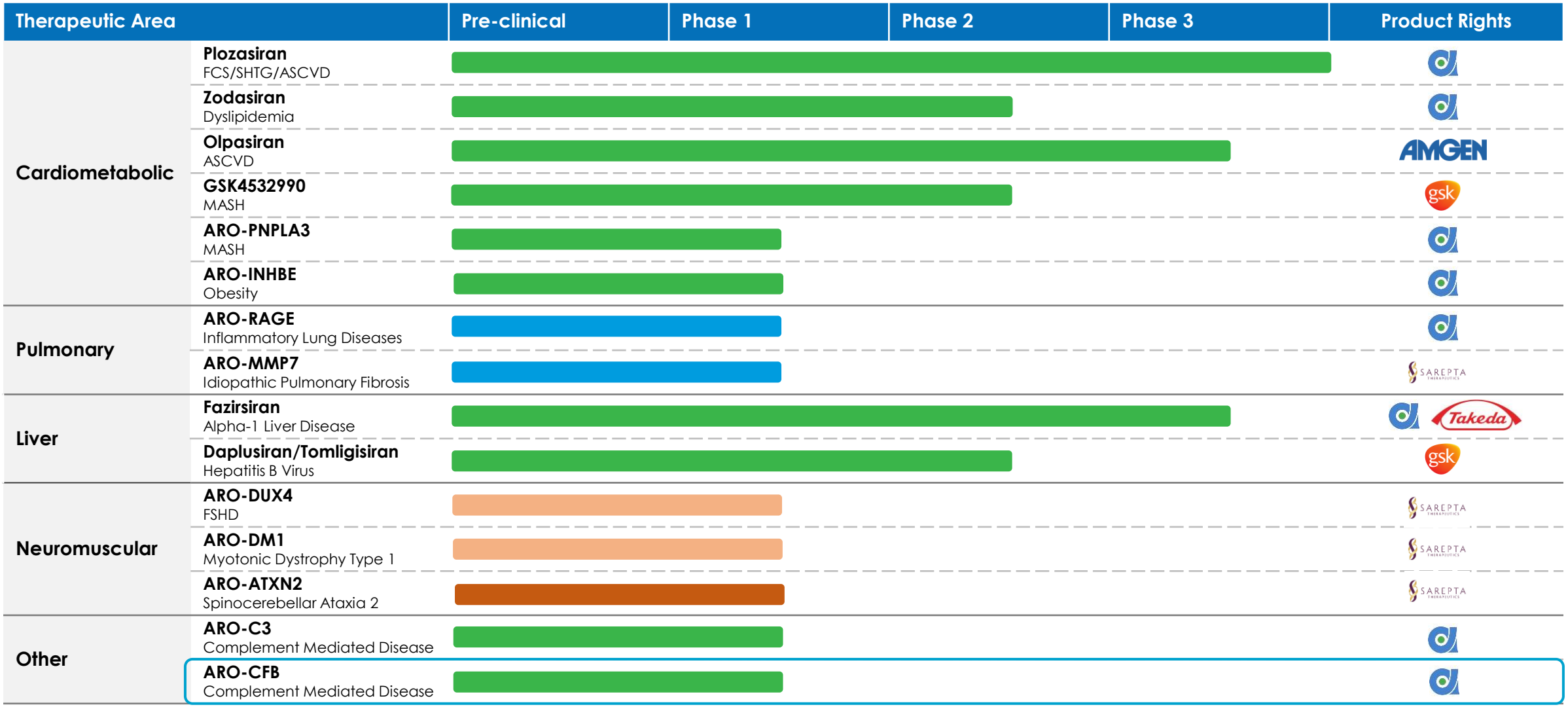
- Arrowhead employee and shareholder

TRiM™ Platform: Targeted RNAi Molecule



- Rules and algorithms to inform siRNA sequence selection and trigger design
- Library of linkers and targeting ligands facilitate delivery to new cell types
- CMC, Tox well characterized, enabling rapid progression to Phase 1

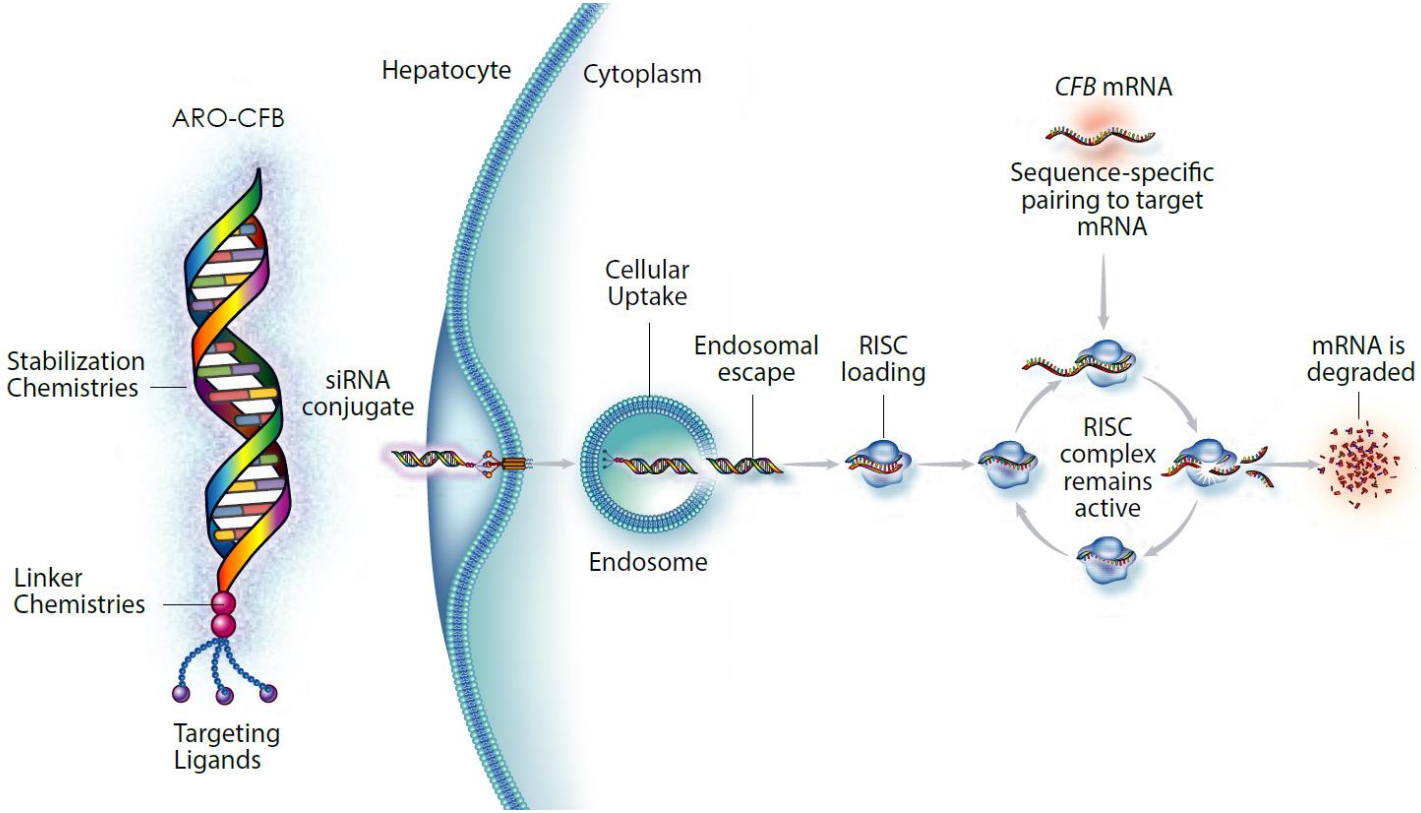
Arrowhead Clinical Pipeline



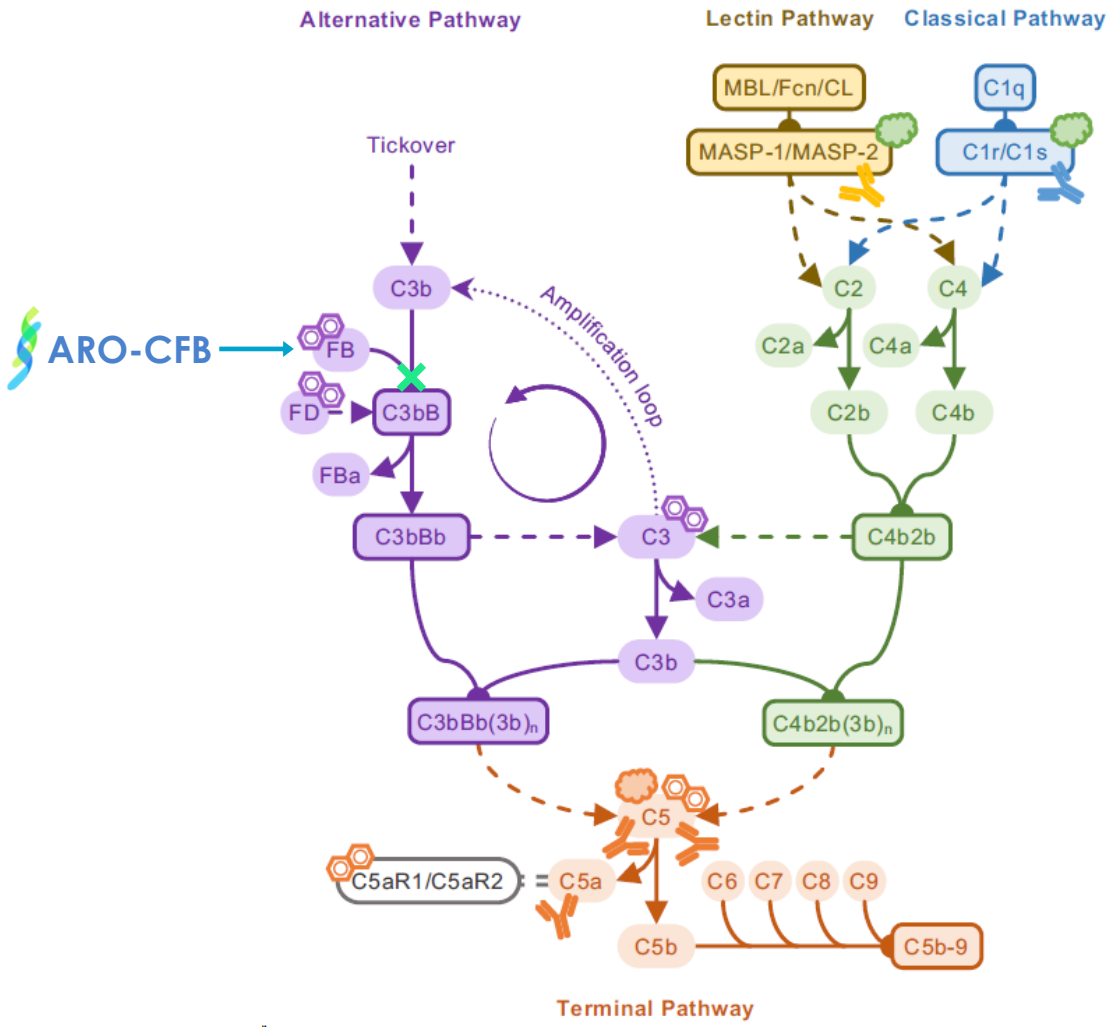
ARO-CFB specifically designed target and silence *CFB* mRNA expression by the liver, reducing plasma complement levels

ARO-CFB

- RNAi GalNAc conjugates designed to target and silence hepatic *CFB* mRNA which inhibit production of complement factor B
- Conjugates are composed of synthetic, double-stranded oligonucleotides



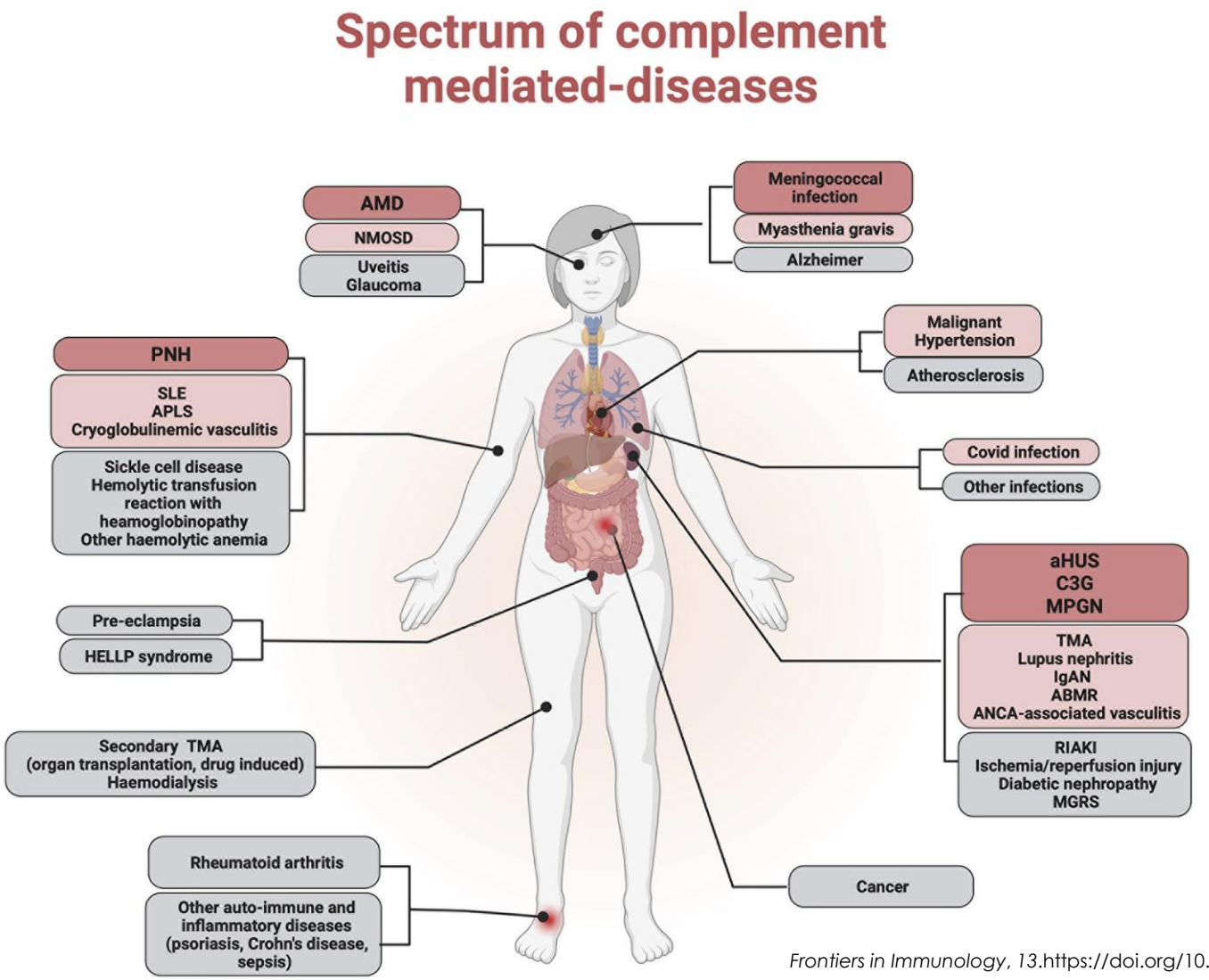
Targeting the alternative pathway and Complement Factor B



- CFB primarily expressed by hepatocyte
- Depletion of FB reduces tick over, amplification, and activity of the AP without directly inhibiting the classical or lectin pathways.
- Pharmacodynamics can be readily measured via blood biomarkers including CFB, Bb, alternative pathway complement activity (AH50 and Wieslab AP).

Semin Immunopathol. 2021;43(6):757-71. doi: 10.1007/s00281-021-00892-7.

Therapeutic Landscape for Complement-targeted siRNA



Frontiers in Immunology, 13.https://doi.org/10.3389/fimmu.2022.860689

Preclinical Development of ARO-CFB

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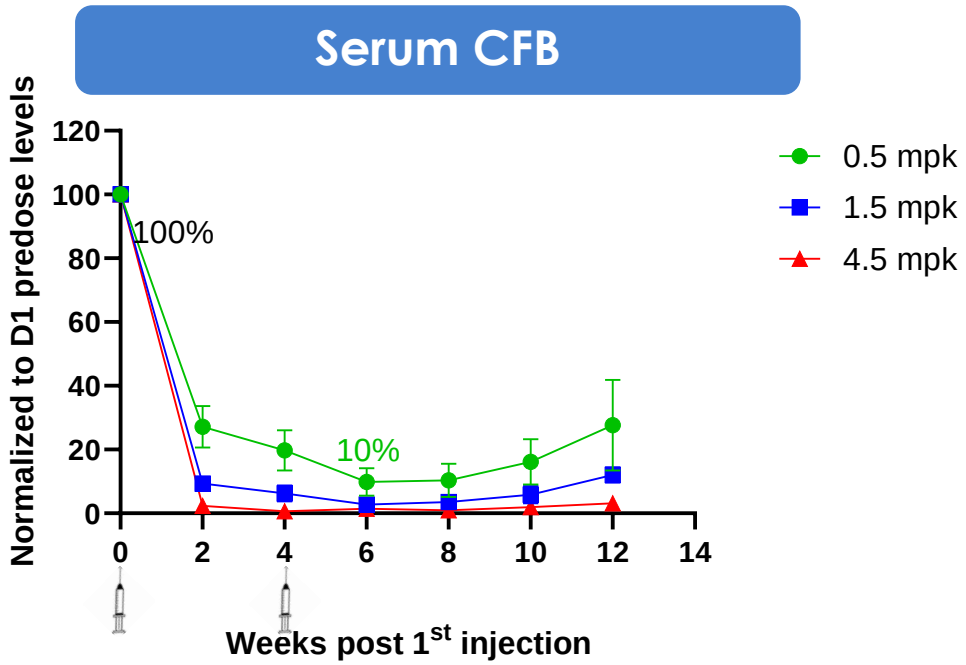
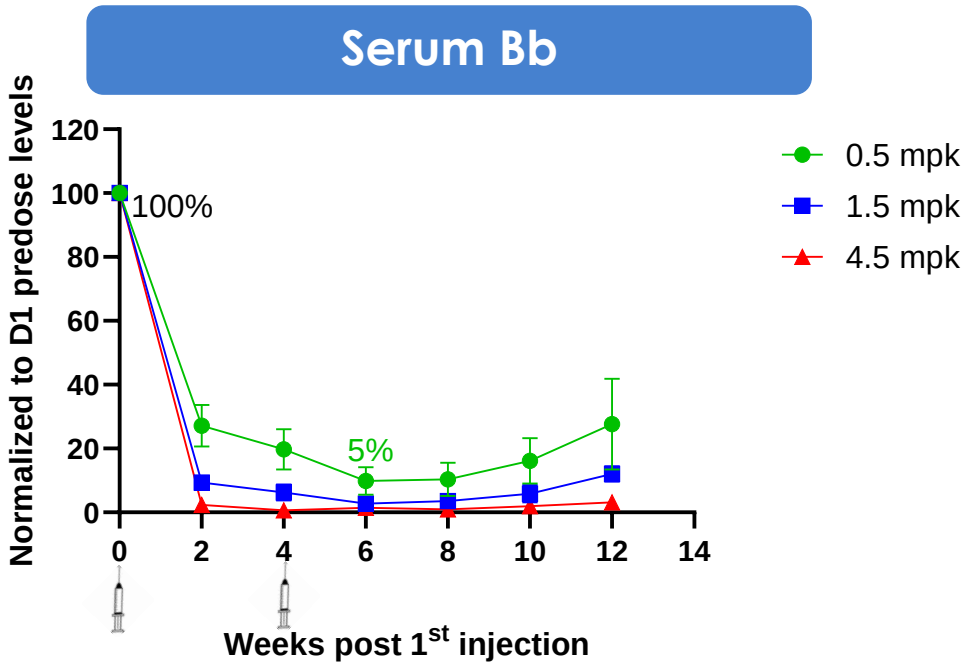
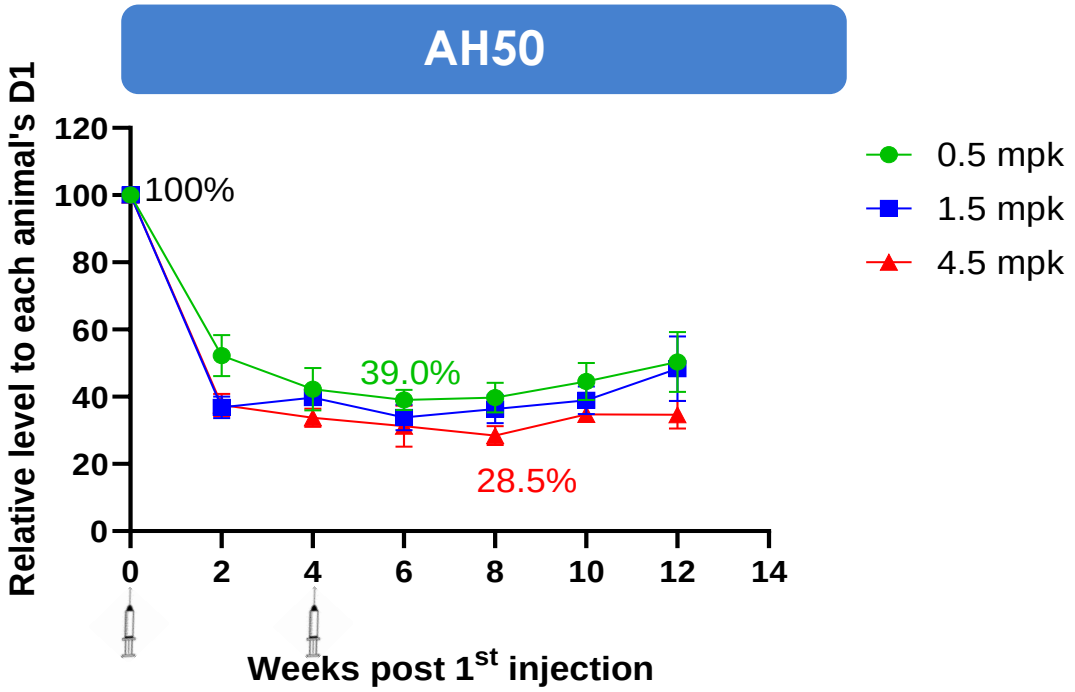
ARO-CFB reduces CFB and Bb protein by >98% in cynomolgus monkeys



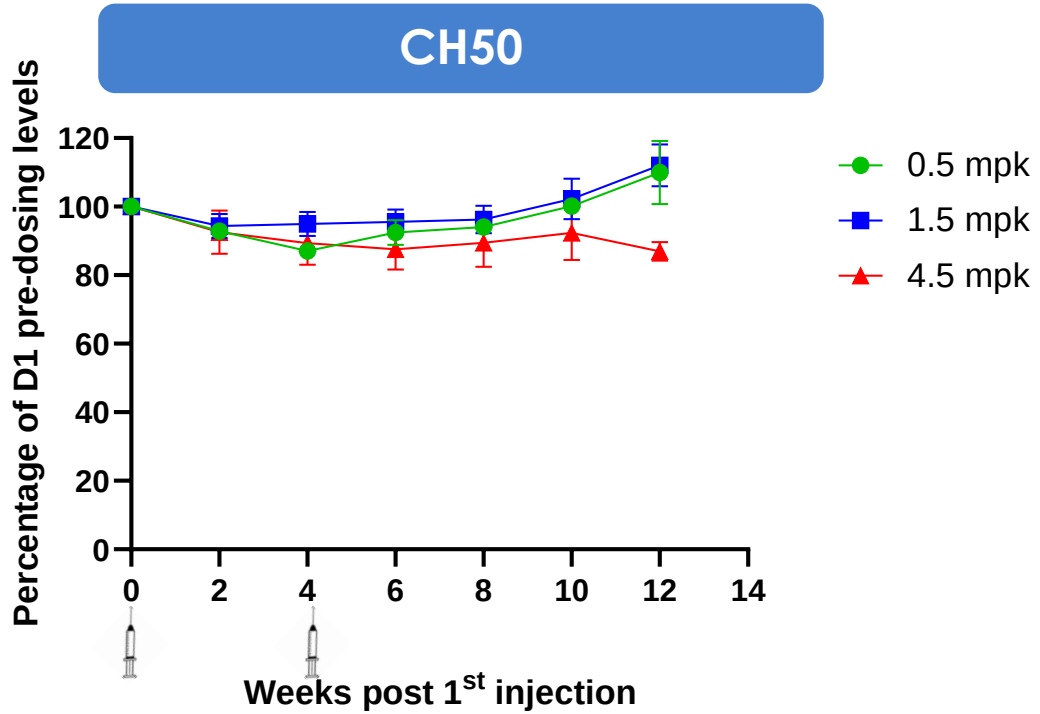


Greater than **98%** reduction in serum CFB and Bb
after multiple doses at 1.5 and 4.5 mpk (mg/kg) (n=3 per dose level)

Silencing CFB selectively decreases alternative pathway activity while leaving total complement activity intact in monkeys

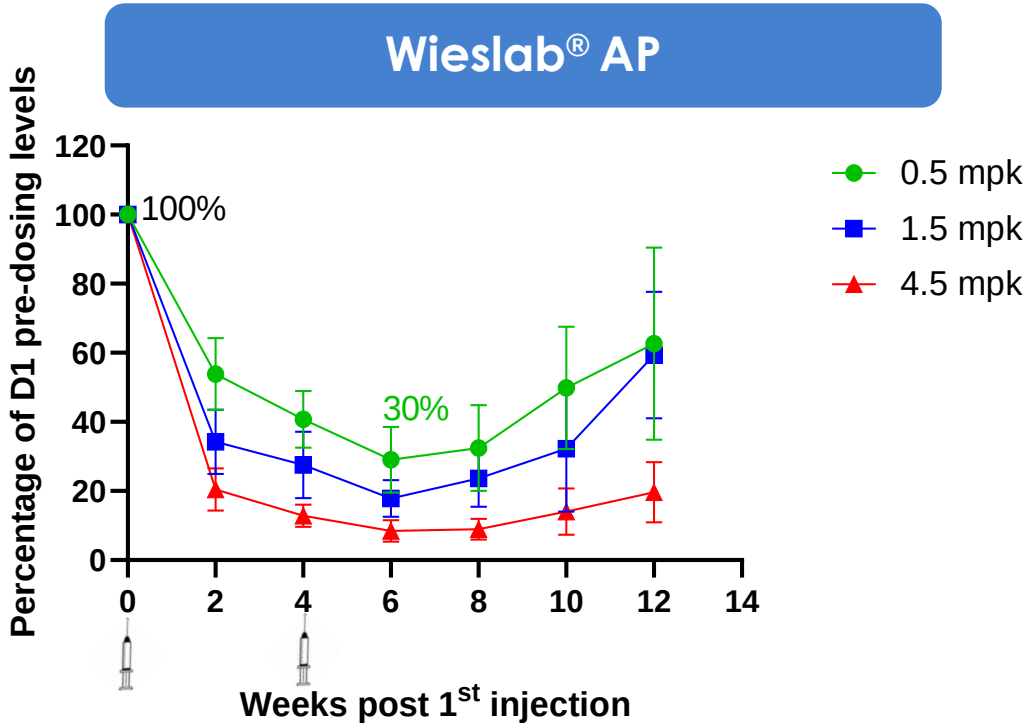


Up to **71%** reduction in AH50
after multiple doses at 4.5 mpk (mg/kg) (n=3)

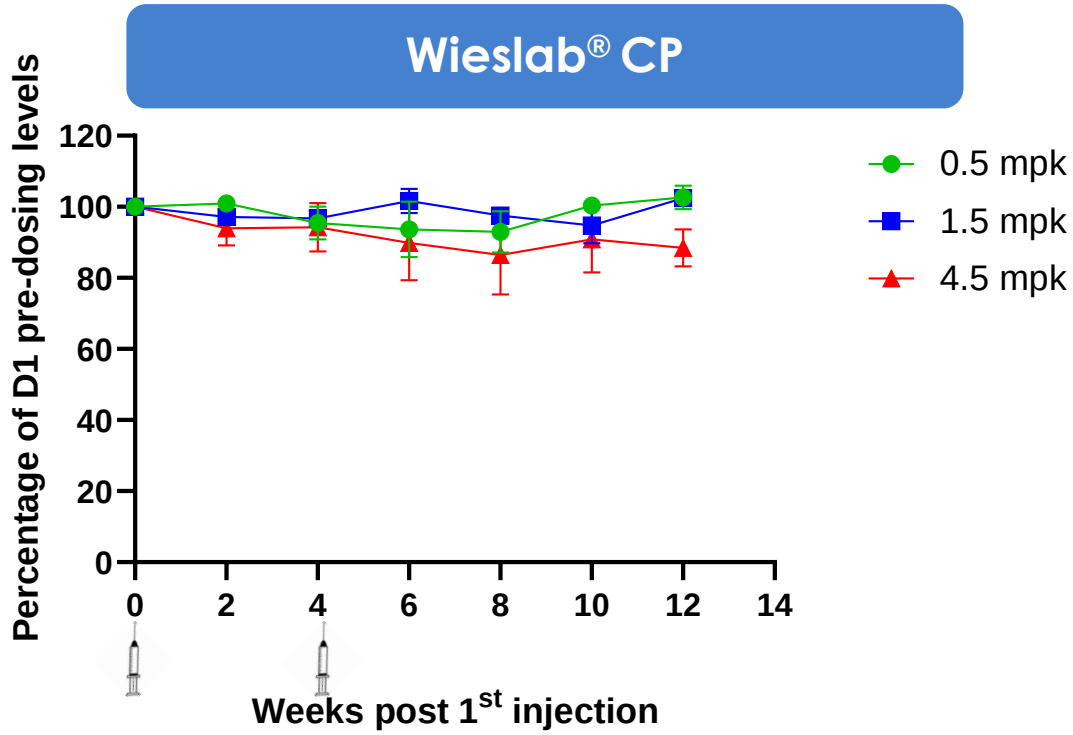


No significant effect on total complement activity at any dose level (n=3 per dose level)

Silencing CFB selectively decreases the formation of membrane attach complex (MAC) mediated via alternative pathway



82% and **92%** mean reduction in Wieslab® AP by week 4 at 1.5 and 4.5 mpk (n=3 per dose level), respectively



No effect on total complement activity at any dose level (n=3 per dose level)

Early Clinical Development of ARO-CFB

AROCFB-1001 Study

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Phase 1/2a Study to Evaluate the Safety, Tolerability and Pharmacokinetics and Pharmacodynamics of ARO-CFB in Adult Healthy Volunteers and Patients with Complement-Mediated Kidney Disease

Part 1: Randomized, double-blind, placebo-controlled cohorts to evaluate single- and multiple-ascending doses of ARO-CFB in adult healthy volunteers.

Single Ascending Dose

Day 1 (Baseline) — Day 225

Dosing — Follow-up every 2 months

Dosing and enrollment completed

Cohort 1 (25 mg ARO-CFB): n=4 active, n=2 placebo

Day 15 Safety Evaluation

Cohort 2 (50 mg ARO-CFB): n=4 active, n=2 placebo

Day 15 Safety Evaluation

Cohort 3 (100 mg ARO-CFB): n=4 active, n=2 placebo

Day 15 Safety Evaluation

Cohort 4 (200 mg ARO-CFB): n=4 active, n=2 placebo

Day 15 Safety Evaluation

Cohort 5 (400 mg ARO-CFB): n=4 active, n=2 placebo

Day 15 Safety Evaluation

Multiple Ascending Dose

Day 1 (Baseline) — Day 29 — Day 57 — Day 225

Part 2 dose selection

Follow-up every 2 months

Cohort 3b (100 mg ARO-CFB): n=4 active, n=2 placebo

Cohort 4b (200 mg ARO-CFB): n=4 active, n=2 placebo

Cohort 5b (400 mg ARO-CFB): n=4 active, n=2 placebo

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 factor B(CFB) and breakdown products Ba and Bb, alternative complement pathway activity (AH50 + Wieslab® AP Assay)

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Demographics and Baseline Complement Parameters

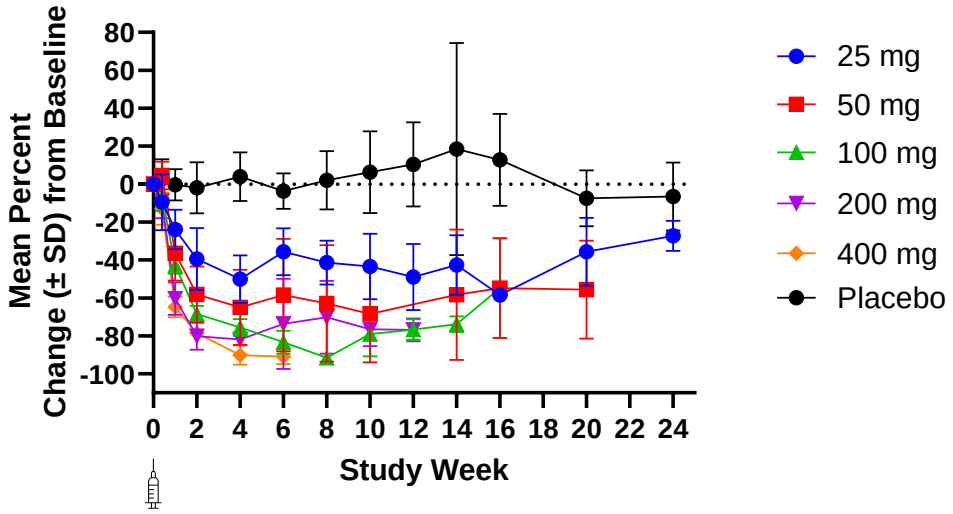
Parameter (SD)	Pooled Placebo (N=16)	Pooled Active (N=32)	
Age (years)	34.4 (8.6)	32.8(8.7)	
Sex (M/%)	4 (25.0%)	14(43.8%)	
BMI (kg/m2)	26.6 (4.6)	26.7(3.0)	Reference Ranges
CFB (mg/dL)	40.0(10.0)	38.5(8.9)	27 – 73 mg/dL
AH50 (U/mL)	133.4 (31.1)	114.8 (21.8)	76 – 176 U/mL
Wieslab AP (%)[1]	84.9 (19.1)	76.3 (22.0)	16 – 110%

[1] Wieslab results were calculated per the assay manufacturer's recommended PC/NC (Positive Control/Negative Control) Ratio.

Interim data cutoff: 15 November 2024

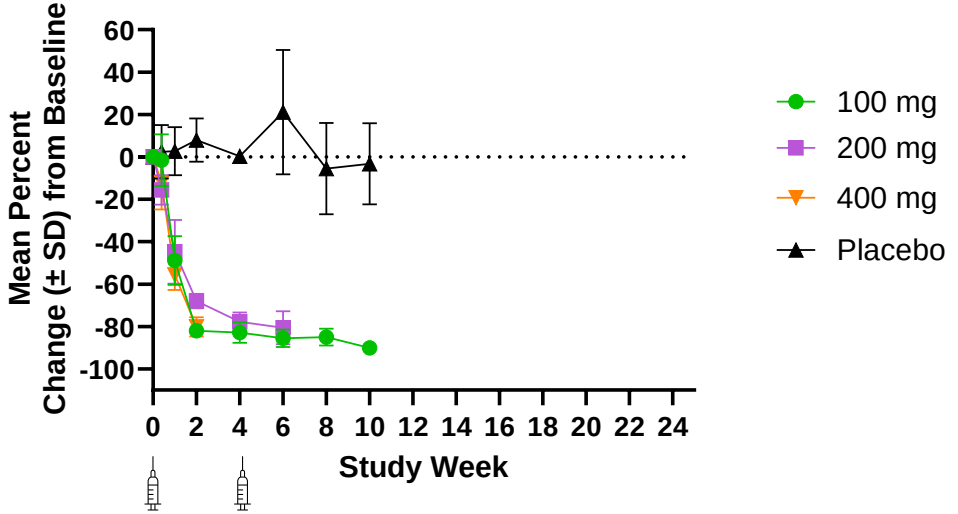
ARO-CFB rapidly reduces mean circulating CFB protein by up to 90% with >3 months duration after single dose

Serum CFB - SAD Cohorts



80% and **90%** mean week 4 CFB reduction at 200 mg and 400 mg, respectively

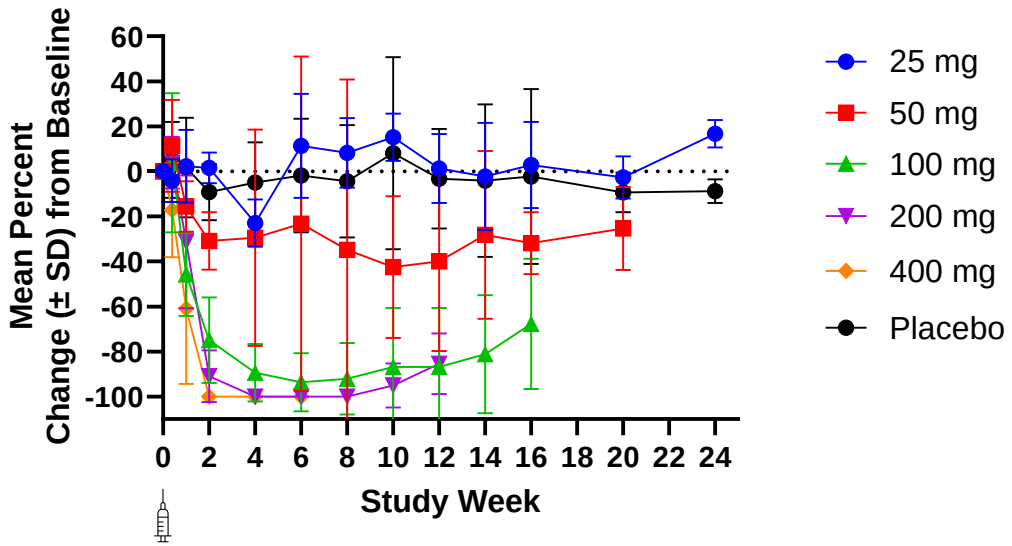
Serum CFB - MAD Cohorts



90% mean reduction in serum CFB by Week 10 after two 100 mg doses

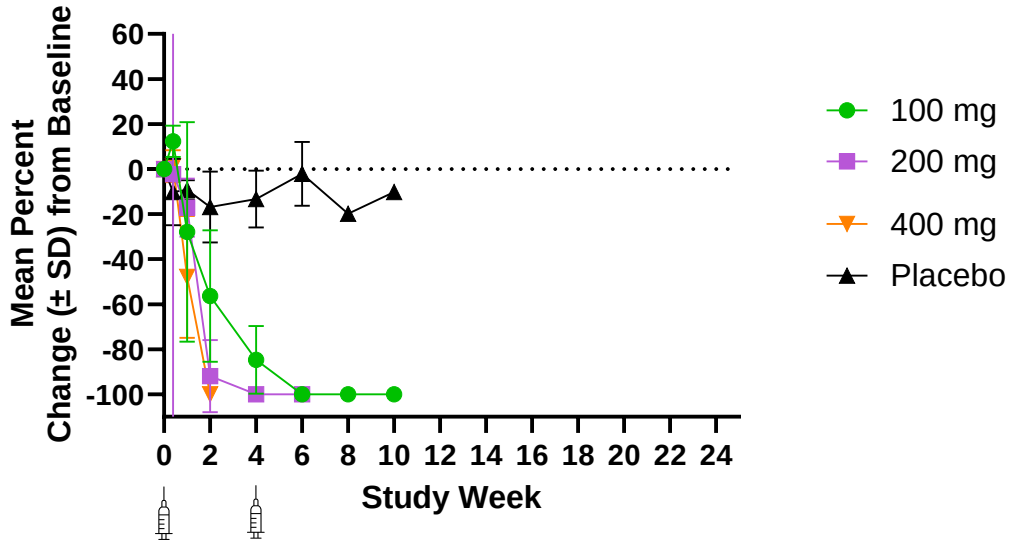
Near complete inhibition of alternative pathway activity based on Wieslab AP after single and multiple doses of ARO-CFB

Wieslab® AP – SAD Cohorts



100% mean reduction in Wieslab® AP by week 4 at both 200 mg and 400 mg

Wieslab® AP – MAD Cohorts

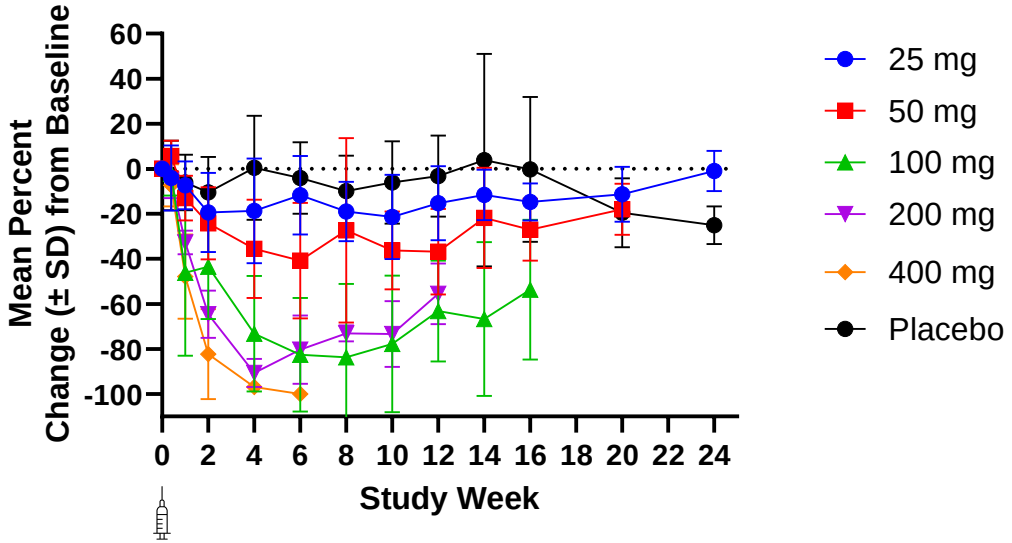


92% and **100%** mean reduction in Wieslab® AP achieved with 100 mg and 200 mg x2 doses

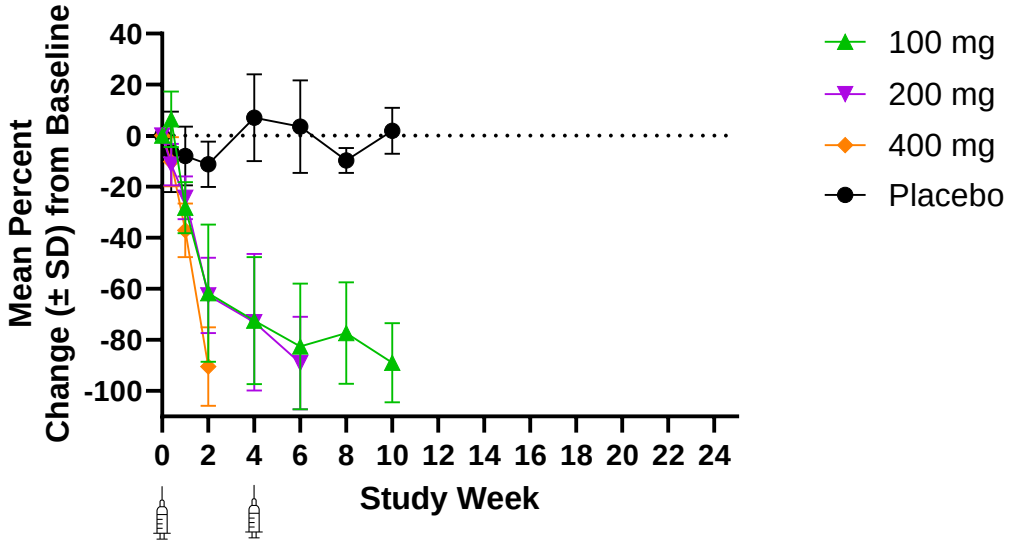
Wieslab results were calculated per the assay manufacturer's recommended PC/NC (Positive Control/Negative Control) Ratio

Near complete inhibition of alternative pathway hemolytic activity (measured by AH50) after single and multiple doses of ARO-CFB

AH50 – SAD Cohorts



AH50 – MAD Cohorts



Safety data supportive of further clinical development

Safety Summary

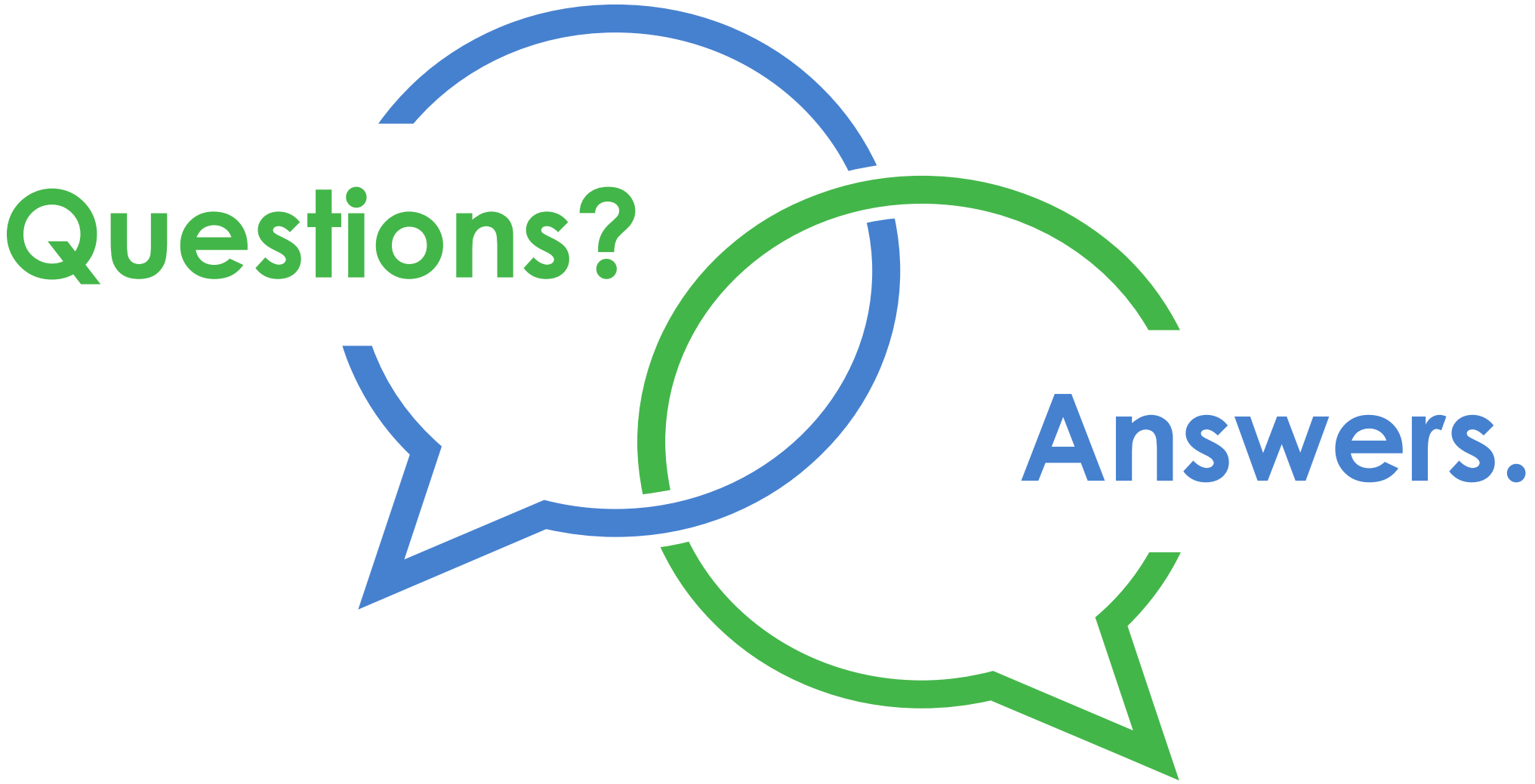
- ARO-CFB was well-tolerated overall.
  - Most TEAEs were mild in severity.
  - No TEAEs led to study or study drug discontinuation.
- No infections with encapsulated organisms.
- One 1 SAE – not drug related, due to motor vehicle collision.

TEAEs Reported in ≥10% Subjects

Adverse Event	Pooled Placebo, N=16 n (%)	Pooled Active, N=32 n (%)
Upper respiratory tract infection	4 (25.0)	9 (28.1)
Headache	5 (31.3)	7 (21.9)
Injection Site AEs	1 (6.3)	7 (21.9)
Dry skin	2 (12.5)	0
Gastroenteritis	2 (12.5)	0
Mouth ulceration	2 (12.5)	0
Vessel puncture site bruise	2 (12.5)	0

Summary

- Healthy volunteer enrollment complete
- Safety profile supportive of continued development
- ARO-CFB achieved mean serum CFB knockdown of 90% after a single 400 mg dose
- ARO-CFB achieved near complete inhibition in hemolytic activity and functional activity of alternative pathway that should be competitive with other AP-targeted therapeutics.
- Duration of effect supportive of at least Q3-Q4 mo SC dosing regimen



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