Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ARO-CFB, an Investigational RNAi Therapeutic Targeting Complement Factor B in Adult Healthy Volunteers

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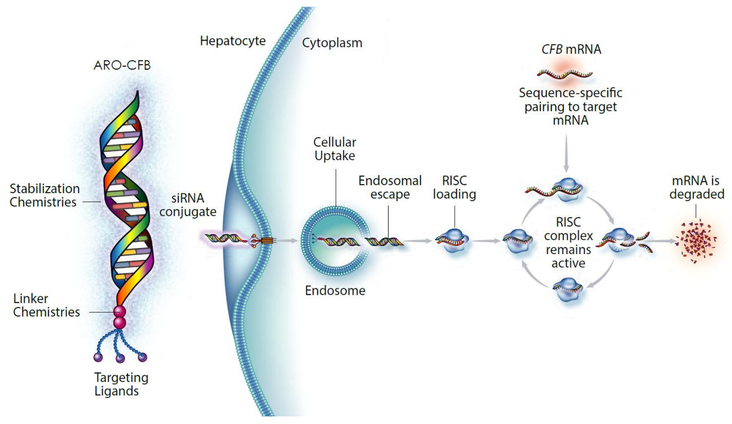
INTRODUCTION

- Complement dysregulation has been implicated in the pathogenesis of various glomerular diseases, including IgA Nephropathy (IgAN).
- Despite increasing recognition of the role of complement in mediating renal injury and disease progression in these conditions, few therapies targeting complement have been approved to treat renal diseases.
- ARO-CFB is an RNA-interference therapeutic that reduces hepatic expression of complement Factor B (FB).

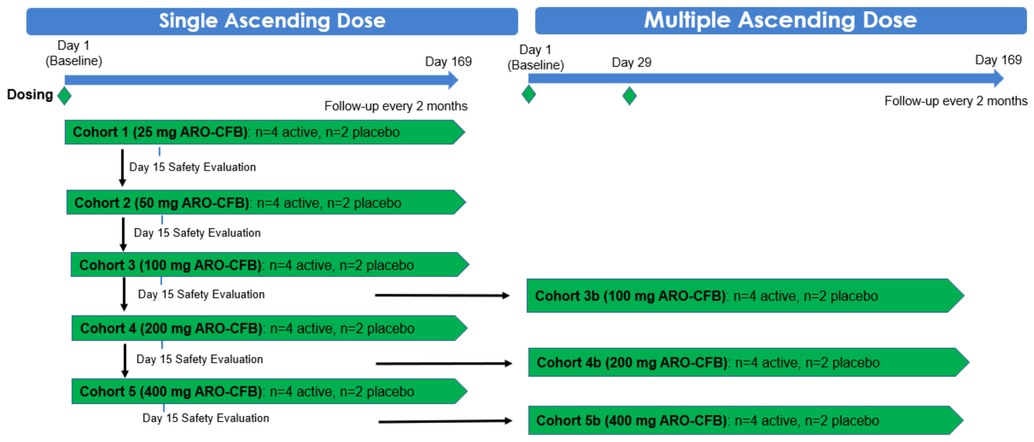


AIM

- The aim of the ongoing AROCFB-1001 Phase 1/2a dose-escalating study (NCT06209177) is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ARO-CFB, in healthy volunteers (HV) and patients with IgAN.

METHODS

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



- 49 adult HVs were randomized to receive ARO-CFB (n=33) or placebo (n=16).
- **Assessments:** Safety – [adverse events (AEs) and lab results] and PD parameters, including changes in serum FB, its breakdown products (Ba and Bb), and measures of alternative pathway (AP) activity (including AH50 and Wieslab® Alternative Pathway [WAP] assays) were assessed over a 24-week follow-up period. PK parameters were assessed up to 48 hours post-dose.
- **Data cut:** 08 April 2025

RESULTS

Table 1. Baseline HV Characteristics

	Pooled Placebo (N=16)	Pooled Active (N=33)[2]
Age (years)	34.4 (8.6)	32.8(8.6)
Sex (M/%)	4 (25.0%)	14(42.4%)
BMI (kg/m2)	26.6 (4.6)	26.6(3.1)
C3 (mg/dL)	40.0(10.0)	38.2(8.8)
AH50 (U/mL)	133.0 (33.3)	115.2 (23.0)
Wieslab AP (%)[1]	87.9 (18.3)	85.1 (23.1)

[1] Wieslab AP results calculated per the assay manufacturer's recommended PC/NC (Positive Control/Negative Control) ratio
2 One subject in Cohort 3b (MAD 100mg) dropped out of study for non-safety reasons and was replaced

Pharmacokinetics

- Plasma exposure of ARO-CFB was dose-dependent and there is no systemic accumulation observed with monthly dosing **[Fig 1]**.
- The overall mean values of renal clearance and fraction excreted unchanged in urine are 5.81 L/h and 32.4%, respectively, suggesting renal clearance is comparatively minor elimination pathway.

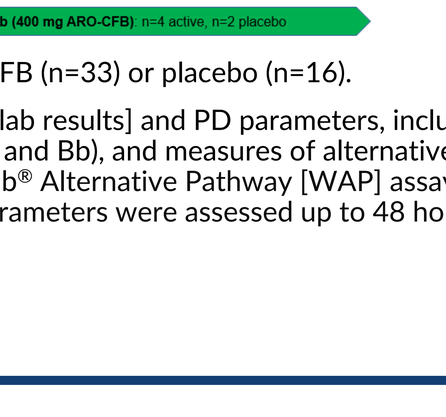


Figure 1. Mean (±SE) ARO-CFB Plasma Concentration-Time Profiles by Cohort on Semi-log Scale Following Subcutaneous Dose(s).

RESULTS

Pharmacodynamics

- ARO-CFB, administered as one or two subcutaneous injections of 25-400mg, resulted in durable, dose-dependent decreases in serum FB levels **[Fig 2, 3]** and AP activity (AH50 and WAP) **[Fig 4]**. No reductions in total complement activity (CH50) were observed.
- Following a single 400mg dose of ARO-CFB, mean(±SD) FB reduction of 90.1±5.1% from baseline was observed at Week 4, with sustained reduction >86% observed through week 12 **[Fig 2a]**. Repeat doses of 200mg and 400mg administered on Day 1 and Day 29 demonstrated similar reductions, due in part to the limitations of the nephelometry assay **[Fig2b]**[1].
- Analysis using an exploratory ELISA-based method demonstrated reductions of up to 97.8±1.2% after two 400mg doses, with sustained reductions >95% through Week 24 **[Fig 3a]**[2]. FB breakdown products Ba **[Fig3b]** and Bb were reduced to undetectable levels.
- Near-complete inhibition of AP complement activity by AH50 and WAP after both single doses of 400mg and multiple doses of either 200-400mg was observed[3,4]. Decreases in AP complement activity were sustained through week 24 **[Fig 4]**.

Figure 2. Serum-based nephelometry measurement of FB in **(a)** single ascending dose (SAD) healthy volunteer cohorts and **(b)** multiple ascending dose (MAD) healthy volunteer cohorts[1].

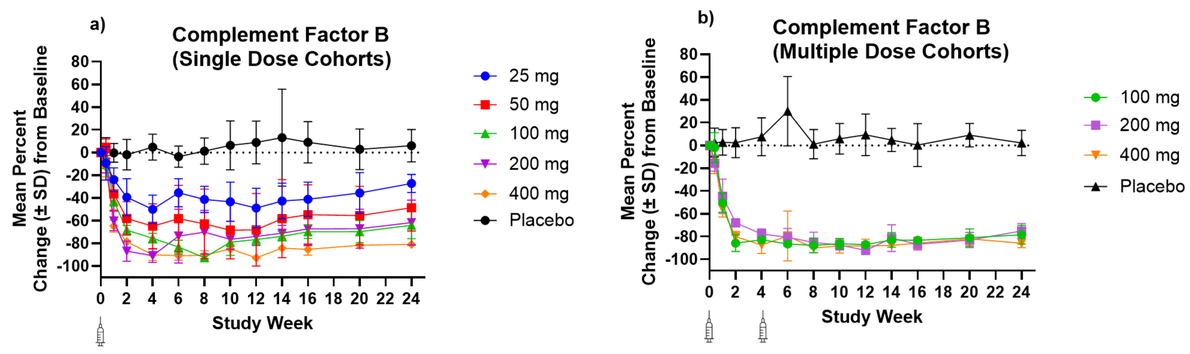


Figure 3. **(a)** Exploratory ELISA-based measurement of FB[2] and **(b)** serum Factor Ba levels in multiple ascending dose (MAD) healthy volunteer cohorts.

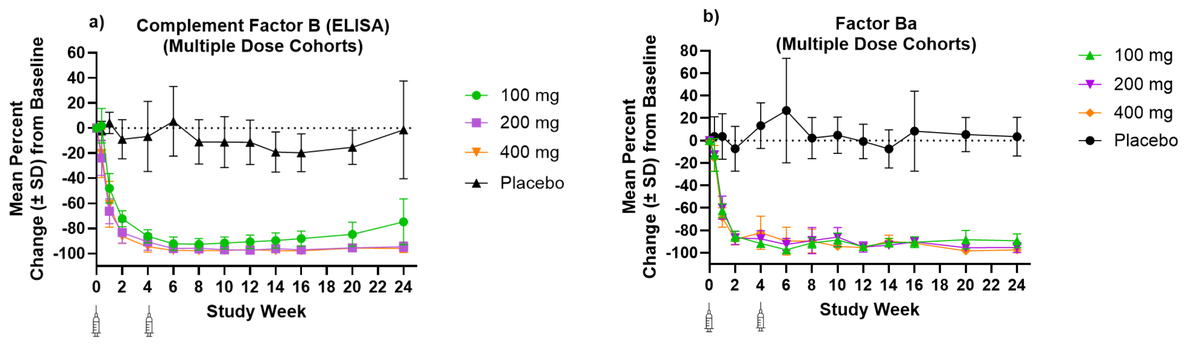
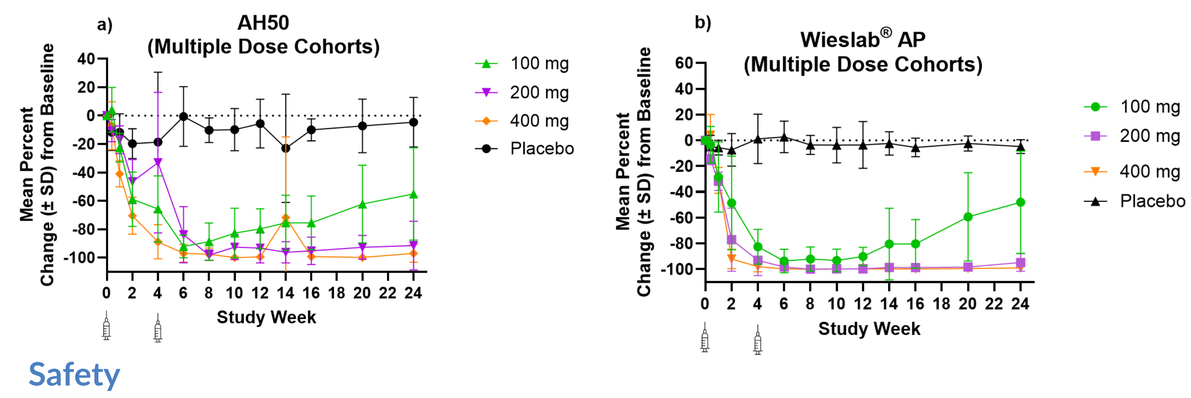


Figure 4. Measures of Alternative Complement Activity in multiple ascending dose (MAD) healthy volunteer cohorts: **(a)** Alternative Pathway Activity (AH50)[3], and **(b)** Wieslab® Alternative Pathway (AP) Activity (PC/NC)[4].



Safety

- ARO-CFB 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 or moderate in severity. Most ISRs were mild, and all resolved without sequelae. No infections with encapsulated organisms were reported.

Table 2. TEAEs Reported in >10% of Subjects

Adverse Event Preferred Term	Pooled Active (N=33)	Pooled Placebo (N=16)
Upper Respiratory Tract Infection	11 (33%)	7 (44%)
Headache	7 (21%)	5 (31%)
Injection Site Reaction	7 (21%)	1 (6%)
COVID-19	4 (12%)	2 (13%)
Gastroenteritis	1 (3%)	3 (19%)

CONCLUSIONS

ARO-CFB is well tolerated and achieves sustained reductions in complement Factor B and suppression of alternative pathway activity after single and repeat subcutaneous doses, supporting a quarterly dosing regimen.

ACKNOWLEDGEMENTS

The study sponsors would like to acknowledge the help and participation of all volunteers who agreed to take part in this study, as well as the work and dedication of the investigators and staff at the clinical sites.

[1] The validated assay range is 12 mg/dL to 2880 mg/dL. Serum CFB concentrations measured as less than 5 mg/dL are reported as 2.5 mg/dL; [2] Not a validated assay. Plasma CFB concentrations measured as less than 3.12 mcg/mL are reported as 1.56 mcg/mL; [3] The validated assay range is 11% - 200%. Data shown includes results outside the validated range; [4] The validated assay range is 27 U/mL – 200 U/mL. Data shown includes results outside the validated range.