

Agazisiran, a potent complement Factor B siRNA, provides deep and prolonged inhibition of the alternative pathway

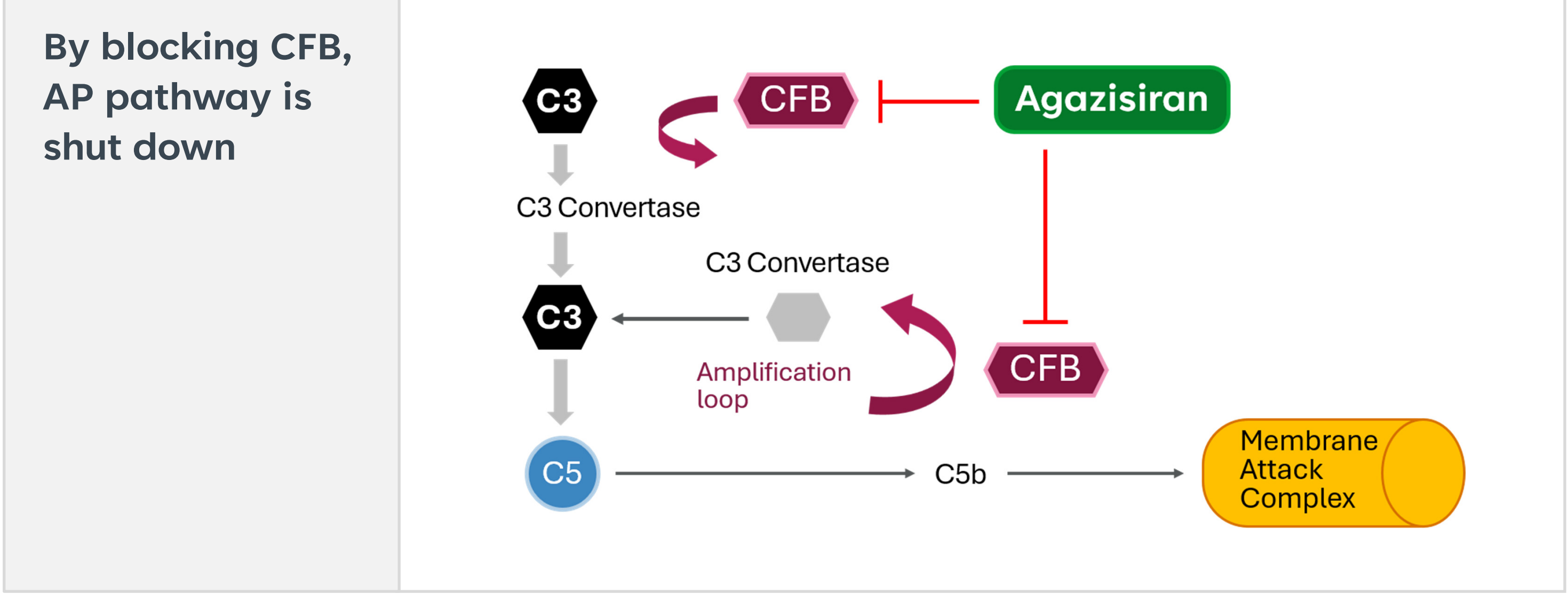
Chee Kay Cheung MD¹, Zhen Li PhD², A. Robert Macleod PhD², Andrew Seacat PhD², Aditya R. Patel MD MBA², Donald Fong MD MPH², Arezoo Mirad MD MS², Lian Li MD²
1. Leicester General Hospital, Leicester, UK; 2. ADARx Pharmaceuticals, San Diego, CA

Background

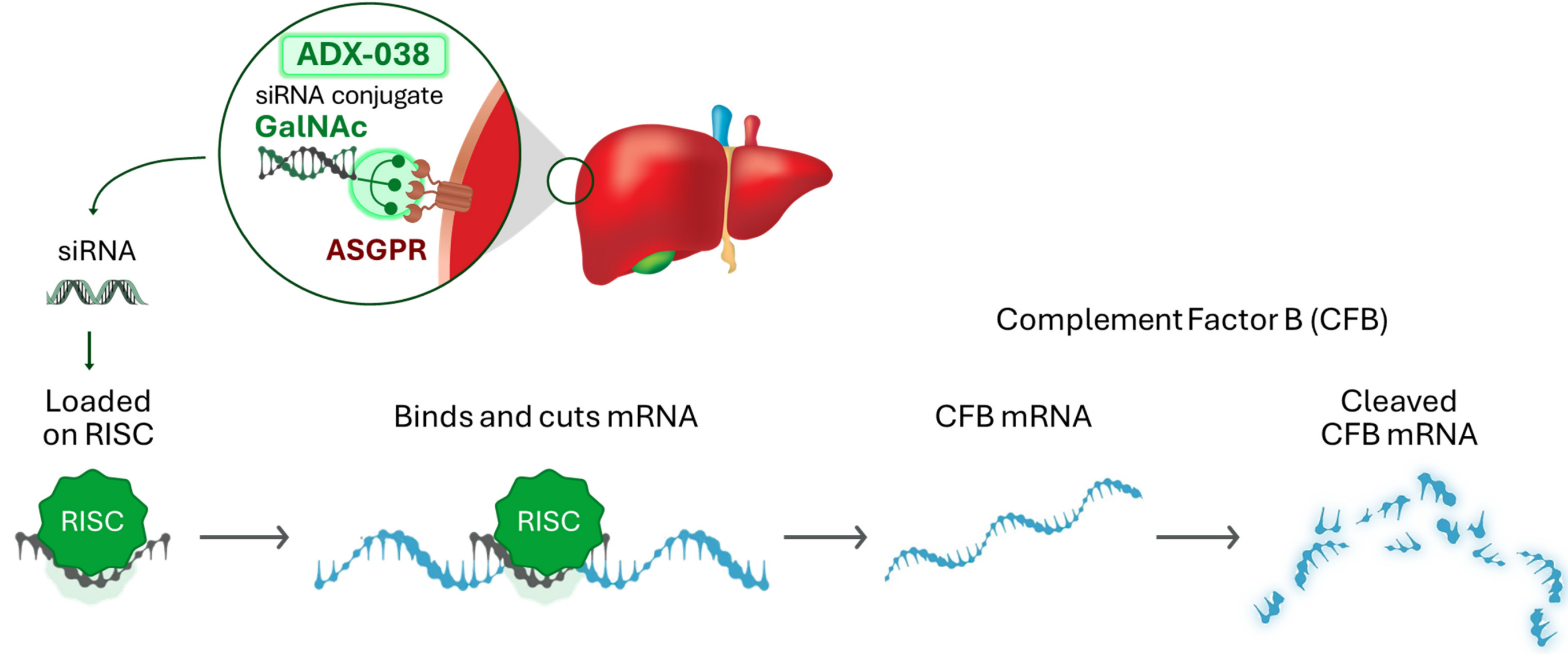
IgA Nephropathy (IgAN) and Complement 3 Glomerulopathy (C3G) are two lifelong complement mediated nephropathies. Inhibition of C3 convertase formation and function and the alternative pathway (AP) has been demonstrated to slow disease progression. However, unmet needs remain with regards to treatment burden and potential disease stabilization or reversion.

One approach for inhibition of AP C3 convertase (C3bBb) is through suppression of complement factor B (CFB), an essential component of C3 convertase.

Reduction of CFB effectively inhibits AP C3 convertase production and the alternative pathway.



Agazisiran Mechanism of Action



- Agazisiran (ADX-038) is a GalNAc-conjugated small interfering RNA (siRNA) designed to suppress CFB levels.
- siRNA loaded into RISC forms a highly potent and stable catalytic machinery that degrades all CFB mRNA.
- Agazisiran has the potential to provide prolonged suppression of CFB and support infrequent subcutaneous dosing.

GalNAc: N-acetylgalactosamine, siRNA: small interfering RNA, RISC: RNA-Induced Silencing Complex

Methods/Rationale

Preclinical	Pharmacodynamic analysis of CFB levels was conducted in cynomolgus monkeys following administration of ADX-038 with subcutaneous doses for 10 months as part of a 40-week GLP toxicity study with a 13-week recovery period. Profound reduction of CFB at supratherapeutic doses was observed, without any adverse effects.
Phase 1	Healthy adults (41) were randomized and administered a single subcutaneous dose of agazisiran, ranging from 0.4 mg/kg to 6.0 mg/kg. Safety, as well as pharmacokinetic and pharmacodynamic measures, were monitored.
Phase 2	Dosing patients with IgAN and C3G at 300 mg every 3 months or 400 mg every 6 months. Actively recruiting. NCT06989359.

Results

Preclinical study:

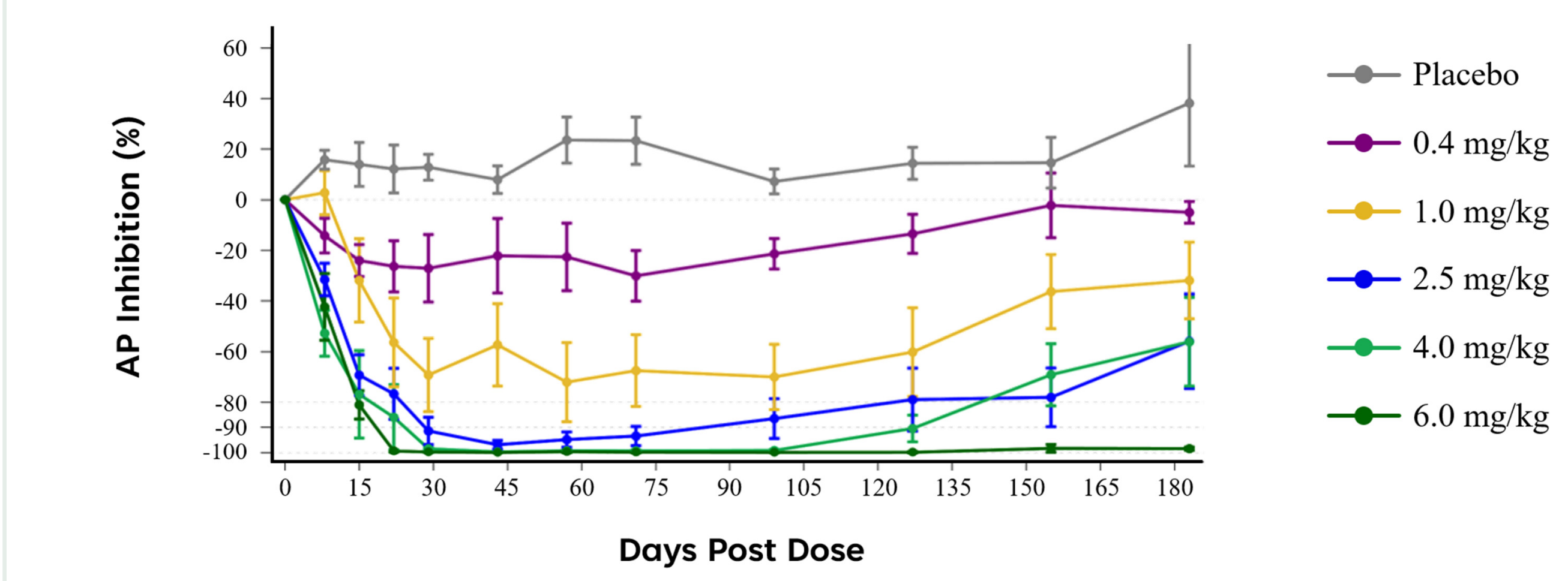
- GLP toxicology studies* demonstrate excellent safety and wide therapeutic index. Both chronic and acute GLP toxicology studies (100 mg/kg and 96 mg/kg, respectively) were defined as the NOEL.
- In 40-week NHP studies, serum CFB protein levels post-treatment with agazisiran showed 94-98% reduction through day 281, demonstrating excellent safety over a long treatment period.

* rats, rabbits and non-human primates (NHP); NOAEL: No Observed Adverse Effect Level

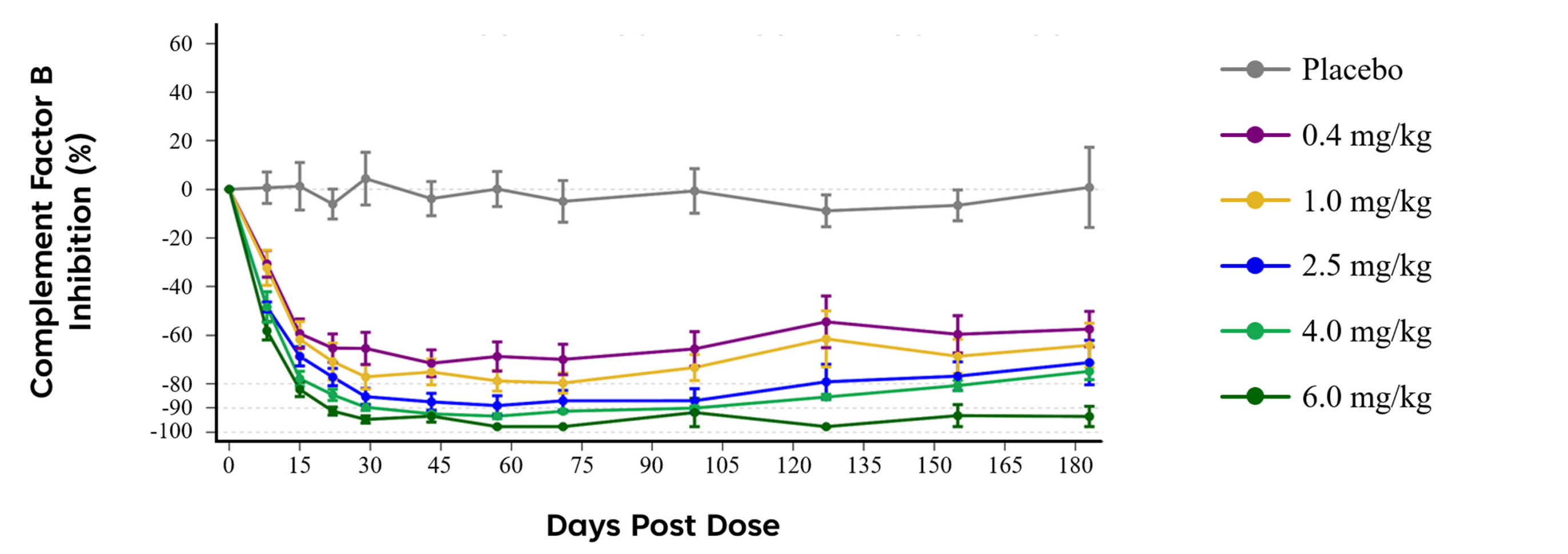
Clinical data:

In the Phase 1 trial, dose-dependent reductions in CFB protein levels and inhibition of AP activity were observed.

Change from Baseline in Complement Alternative Pathway Activity
Percent change from baseline in AP activity data points are expressed as mean (standard error)

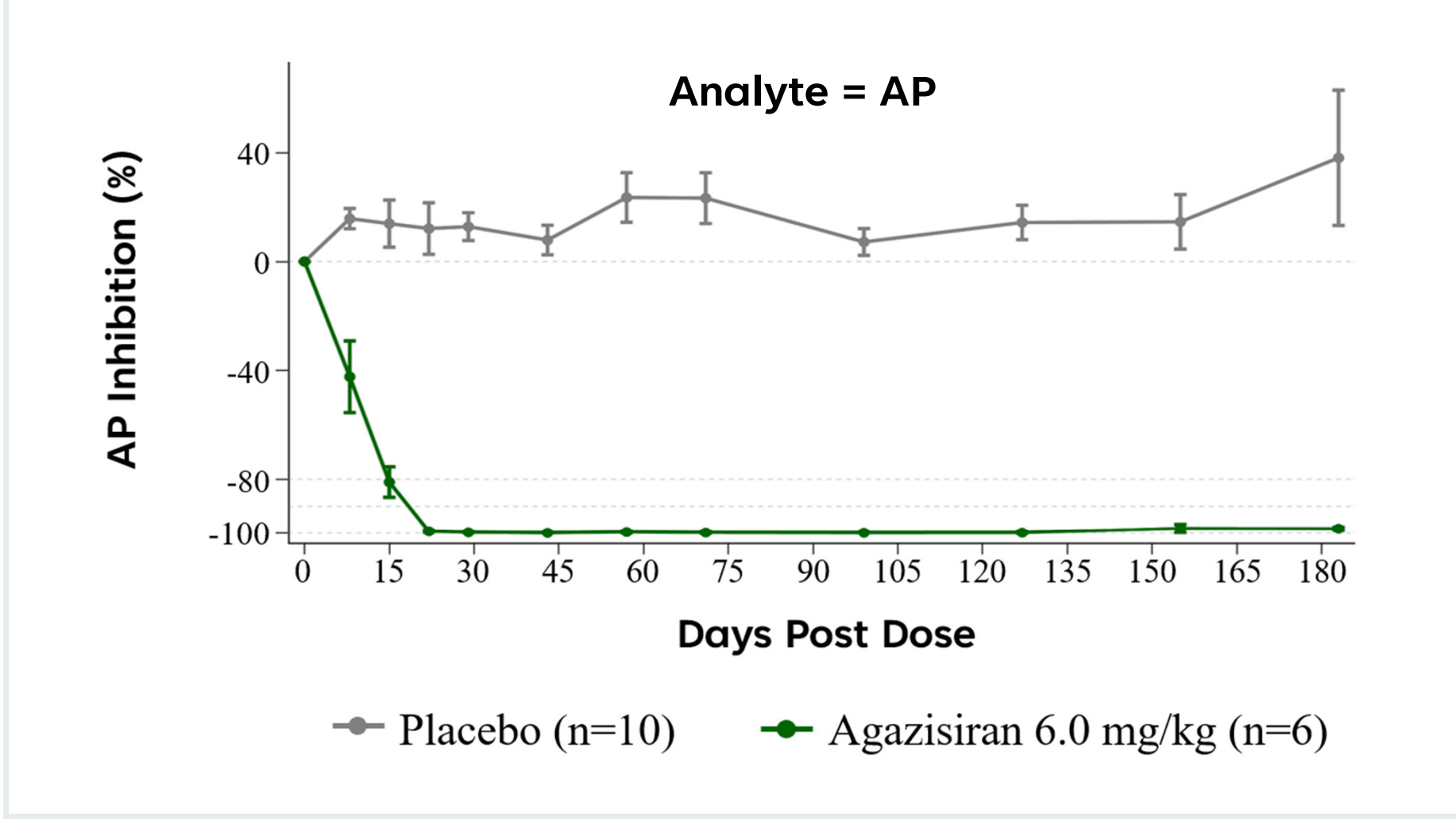


Change from Baseline in Complement Factor B (CFB) levels
Percent change from baseline in CFB data points are expressed as mean (standard error)

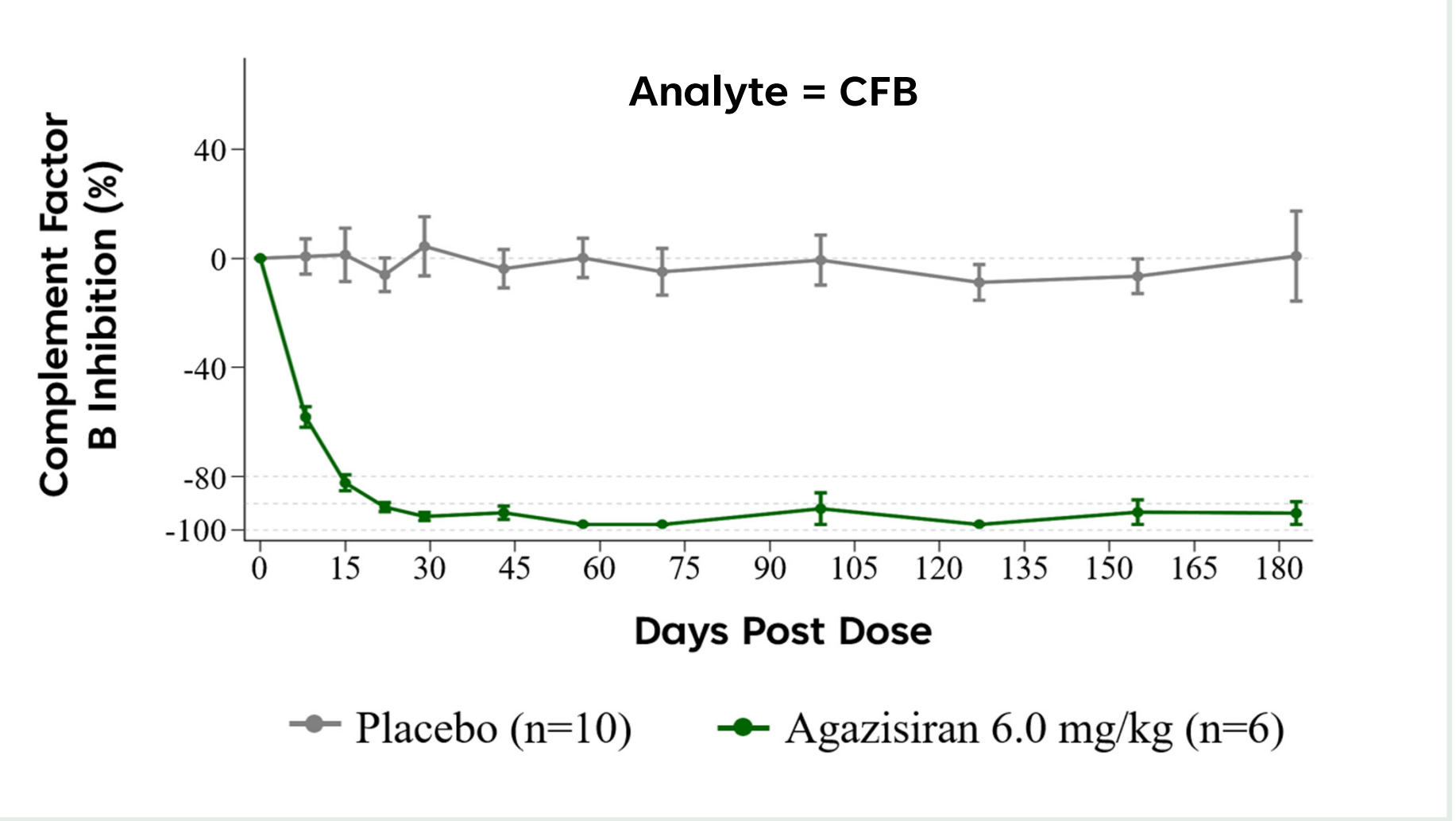


A single 6 mg/kg ADX-038 dose suppressed AP activity by 99.6% at nadir and 98% at Day 180, reduced CFB level to approximately 93.5%, with no significant effect observed in CP from baseline through 6 months.

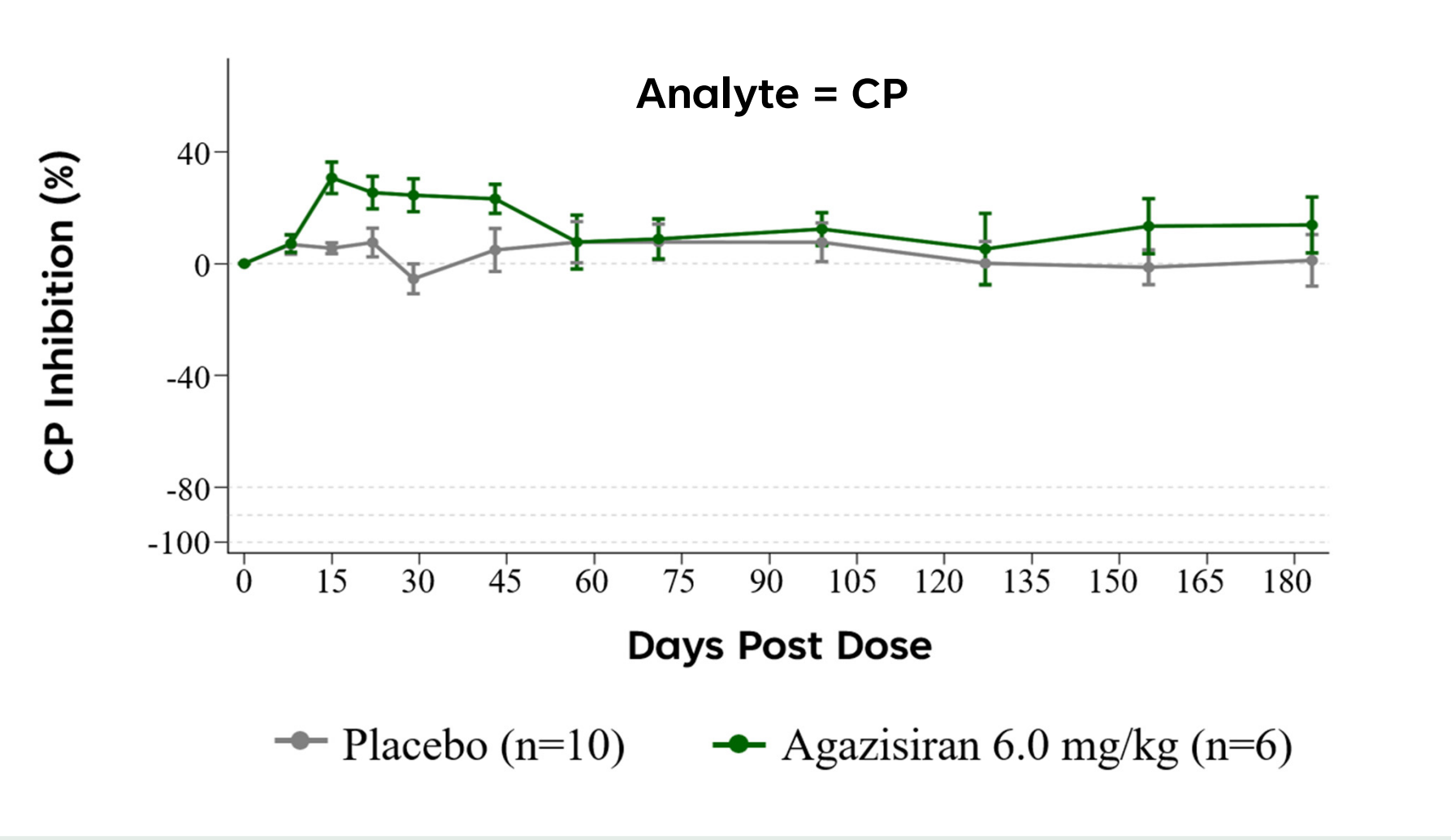
Change from Baseline in Alternative Pathway Activity¹



Change from Baseline in CFB Levels



Change from Baseline in CP Levels



1. AP inhibition reached a mean of 99.9% (99.6% to 100%, median 99.9%) at nadir, with the mean inhibition maintained above 98.3% (95.9% to 100%, median 98.3%) at 6 months

Safety

- Treatment was well-tolerated
- There was one SAE not related to treatment and TEAs were mild to moderate and did not result in any discontinuations

Conclusion

- Agazisiran demonstrated excellent safety, potency and duration of effect in preclinical studies
- A Phase 1 study confirmed prolonged suppression of CFB and AP up to 6 months with no impact on CP following single dose of agazisiran
- A Phase 2 study of agazisiran (ADX-038) (NCT06989359) is actively recruiting and dosing patients with IgAN and C3G

For additional information, please contact: Arezoo Mirad at amirad@adarx.com