



Interim Phase 1 Study Results of ADX-038: A Novel siRNA Against Complement Factor B, and Next Steps in IgAN and C3G Glomerulopathy (C3G)

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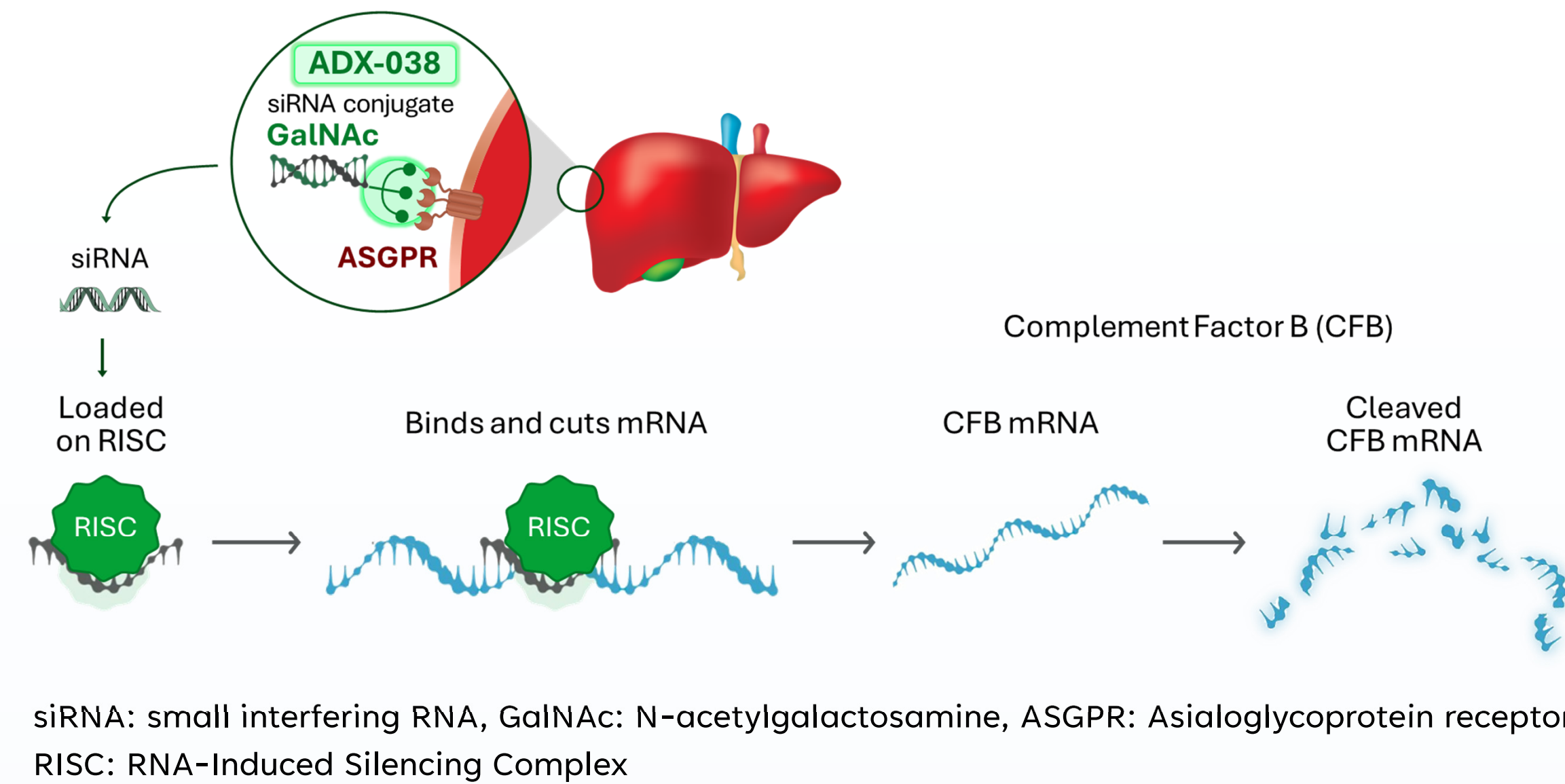
Background

IgA Nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. This serious, progressive autoimmune disease can lead to significant loss of kidney function, with 20–40% of patients requiring renal replacement therapy.

Dysregulated activation of the alternative complement pathway is a key factor in the progression of complement-mediated kidney diseases, such as IgAN.

ADX-038 is a siRNA that targets complement factor B (CFB) mRNA, being developed for diseases whose pathogenesis is driven by activation of the complement alternative pathway (AP).

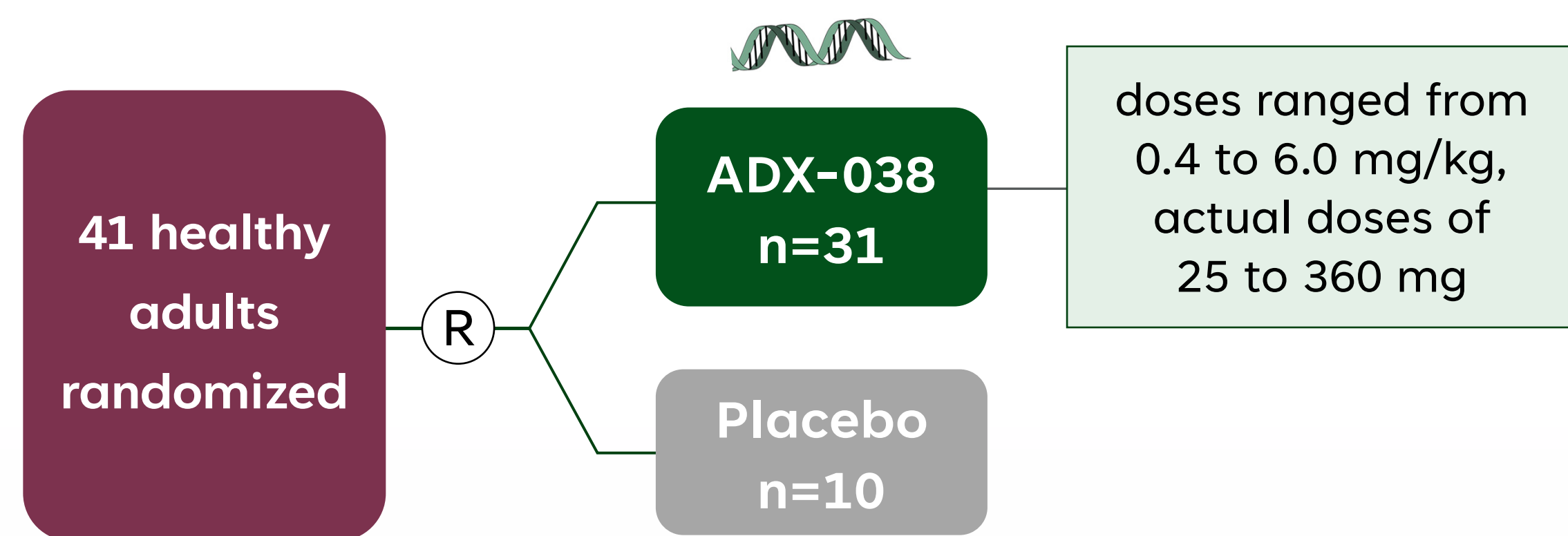
ADX-038 Mechanism of Action



The effects of ADX-038 on CFB protein knockdown on the complement AP and classical pathway (CP) activity in healthy volunteers are reported here with the discussion of the Phase 2 study in IgAN and C3G.

Methods/Rationale

As of 2/2025:



Changes in CFB protein levels, and AP and CP (Weislab) activity were quantitatively measured.

Clinical safety was based on adverse events (AEs) and monitoring of clinical lab tests, physical exams (PE).

Results

Dose-dependent reductions in CFB protein levels and inhibition of AP activity were observed (Figures 1 and 2). A single 4 mg/kg or 6 mg/kg dose of ADX-038 suppressed AP activity by 99% from baseline at 3 mos. CP activity was unchanged (Figure 3).

Figure 1:
Change from Baseline in Complement Alternative Pathway Activity

Percent change from baseline in AP activity data points are expressed as mean (standard error).

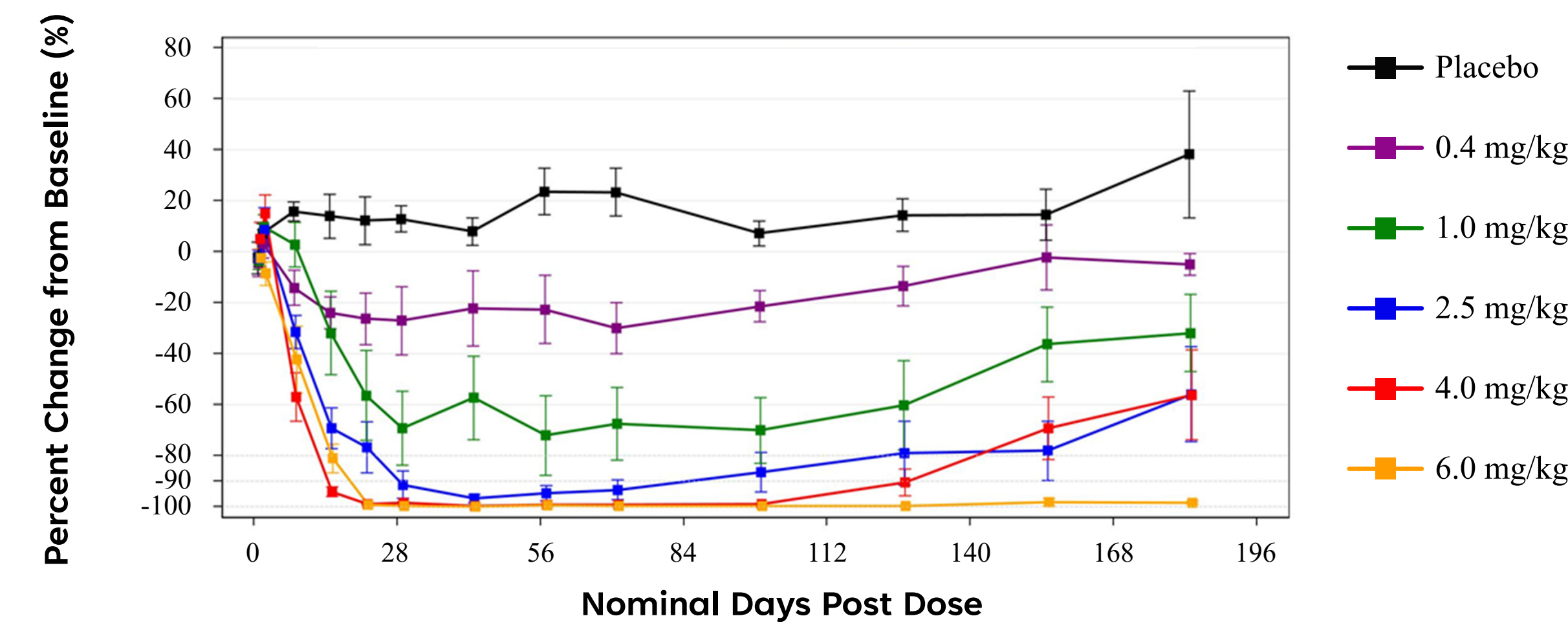


Figure 2:
Change from Baseline in Complement Factor B (CFB) levels

Percent change from baseline in CFB data points are expressed as mean (standard error).

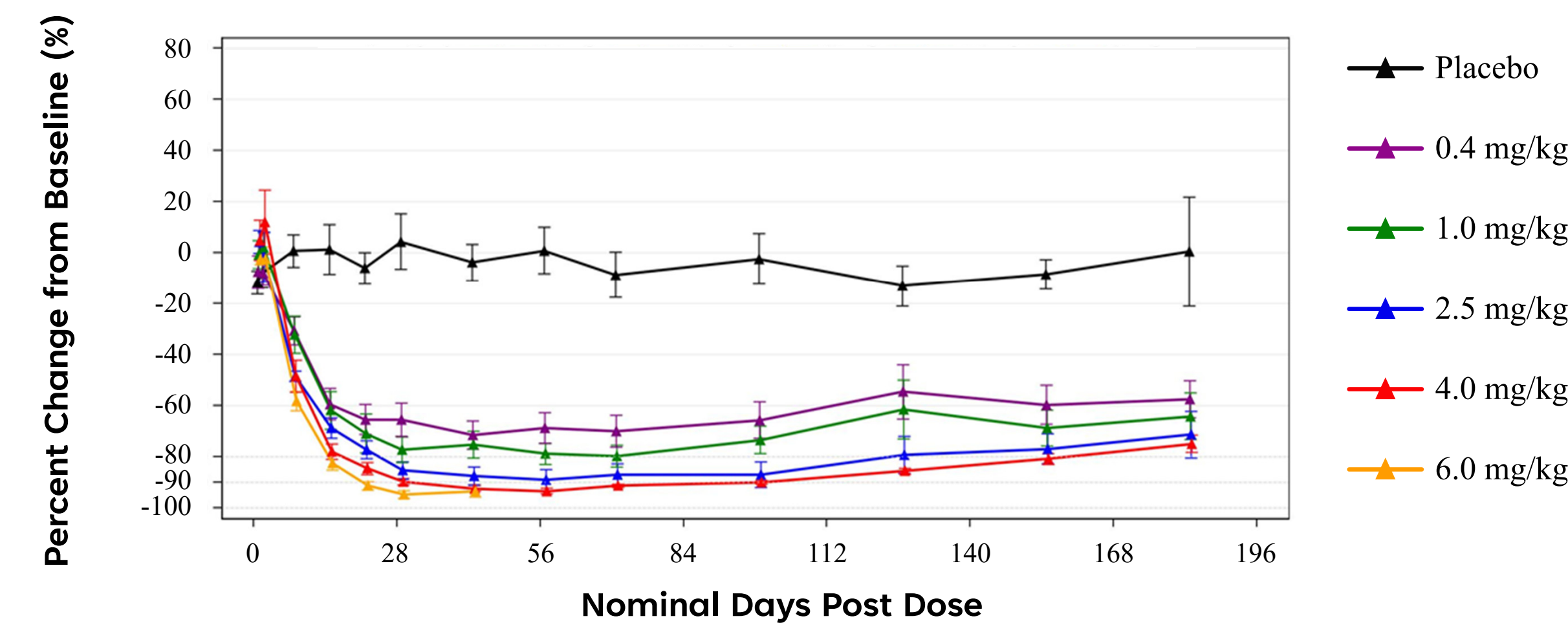
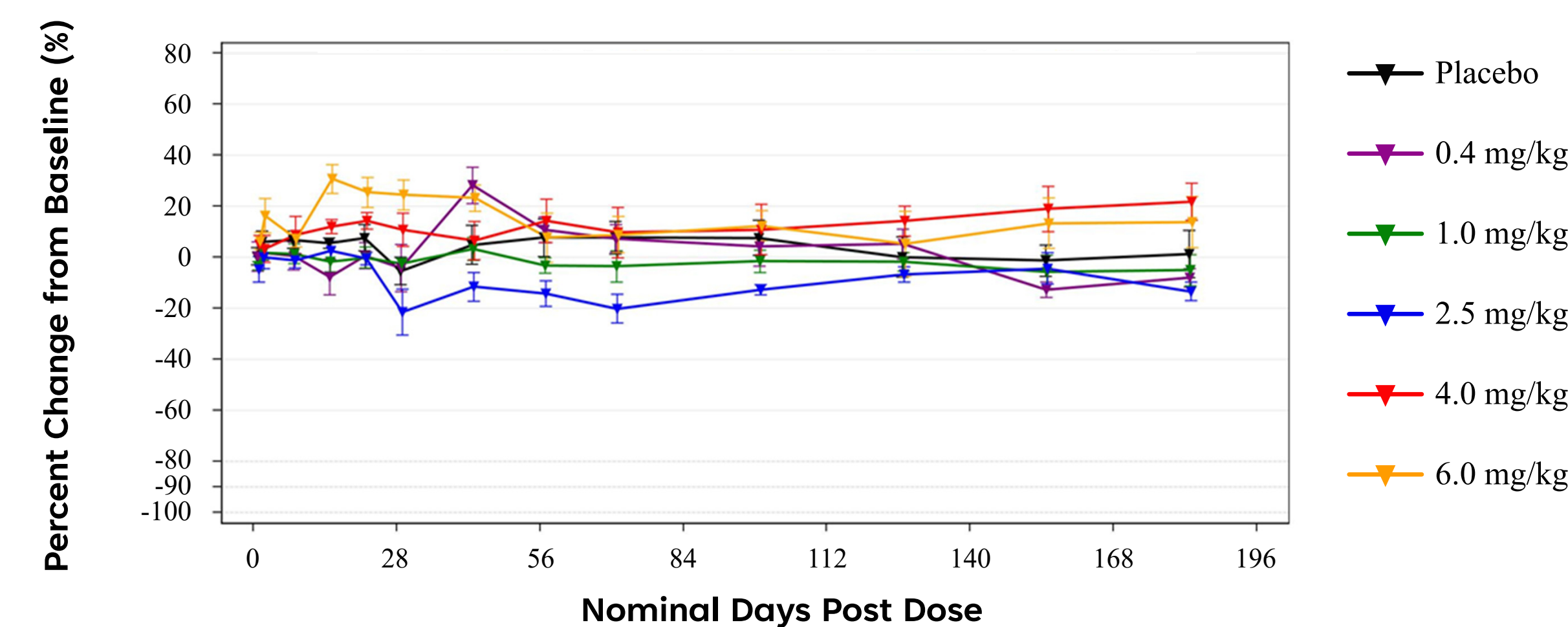


Figure 3:
Mean ± SE of Percent Change from Baseline of CP by Actual Dose



Treatment was well-tolerated

- The most common AE were headache and upper respiratory tract infection
- Only one AE related to blinded study drug (vomiting, grade 1, D1, resolved in 24 hours)
- There were no encapsulated bacterial infections
- There were no clinically relevant changes in clinical lab tests, PE or vital signs

Phase 2 study will dose IgAN and C3G patients with ADX-038. The primary objective of the study is to assess the tolerability of ADX-038, with the secondary objective of changes to proteinuria.

Note: One participant in 4.0 mg/kg group was removed from Day 183 analysis due to occurrence of a significant complement activating event starting at Day 130 (unrelated SAE of multiple fractures due to pedestrian motor vehicle accident followed by pulmonary embolism and aspiration pneumonia).

Discussion

A single dose of ADX-038 ranging from 2.5 mg/kg to 6 mg/kg demonstrated potent knockdown of complement pathway and CFB to >95% with no impact to classical pathway.

The novel mechanism of action and durability of effect up to 180 days shows strong proof of concept for complement mediated diseases with opportunity for infrequent dosing.

Conclusion

A single dose of ADX-038 effectively silenced CFB gene expression, resulting in selective and maximal suppression of complement AP.

The durable, potent, and precise on-target PD effects support its potential as an effective therapeutic agent for kidney diseases with a convenient (every 3 months or longer) subcutaneous dosing schedule.

Based on these results, a Phase 2 study has been initiated to assess the safety and efficacy of ADX-038 in patients with complement mediated kidney diseases (e.g., IgAN and C3G) (NCT06989359).

Acknowledgements

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