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Development of Exon Editors of *ABCA4* RNA in Human Retinal Explants and Non-Human Primate Retina for the Treatment of Stargardt Disease

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Background: RNA Exon Editing is a strategy that utilizes RNA trans-splicing activity of endogenous spliceosomes to rewrite mutated RNA and thereby correct the underlying genetic causes of disease. These molecules can be designed to carry correct coding sequences of multiple exons and target a specific region of mutated pre-mRNA. This approach enables replacement of RNA exons at the kilobase scale, addresses multiple mutations with a single therapy, and maintains native gene expression without changes to DNA. Here we will describe the discovery of ACDN- 01 that is designed to specifically transduce retinal cells and replace 22 exons in the 5' half of the *ABCA4* coding sequence. Mutations in *ABCA4* are the leading cause of inherited blindness. ACDN-01 has the potential to treat up to 70% of patients carrying *ABCA4* mutations.

Methods: We generated a high-throughput, multiplexed screening platform to design, evaluate, and optimize RNA editing efficiency of thousands of Exon Editors. ABCA4 exon editors were evaluated in multiple preclinical models including *in vitro* in an ABCA4 KO cell line, *ex vivo* in human retinal explants, and *in vivo* in non-human primates (NHP).

Results: We demonstrated durable and well-tolerated exon editing at therapeutically relevant levels in ABCA4 KO cells, human retinal explants, and non-human primate retina following a single treatment of AAV-encoded ABCA4-targeting Exon Editors. Full-length protein translated from ACDN-01 edited *ABCA4* mRNA retained functional ATPase activity. ACDN-01 achieved stable vDNA transduction and Exon Editor RNA expression in NHP retina at 3-months post dosing and persisted up to 6-months post-dosing.

Conclusion: In summary, ACDN-01 can provide robust and durable *ABCA4* exon editing in the NHP retina at well tolerated doses. These results were used to facilitate the design of an ongoing clinical trial (STELLAR, NCT06467344) evaluating the safety and efficacy of ACDN-01 for the treatment of Stargardt disease and other ABCA4-related retinopathies.