complement, prior transduction with the novel vector expressing anti-hC5-scFv01 resulted in a dose-dependent reduction in formation of terminal complement complex (TCC) on the cell surface. These results support further preclinical development of our AAV-based approach for treating dry AMD, which combines a novel engineered capsid and anti-C5 scFv transgene to achieve sustained complement inhibition in the eye following a single suprachoroidal injection. Our approach offers the potential of a minimally invasive approach to dry AMD treatment that could reduce the treatment burden and deliver therapeutic molecules directly into the site of AMD pathogenesis.

OR016

Preliminary safety and efficacy of DB-OTO gene therapy in pediatric patients with profound deafness due to otoferlin variants: The CHORD phase 1/2 open-label trial

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Otoferlin is critical for inner hair cell (IHC) signal transmission to auditory nerve fibers. Biallelic otoferlin gene (*OTOF*) variants typically cause severe-to-profound deafness. As per preclinical data, DB-OTO gene therapy promotes IHC-selective otoferlin expression from the human *OTOF* gene, which may instate high-quality hearing. In this first-in-human multicenter, phase 1/2 open-label clinical trial with DB-OTO (CHORD, NCT05788536), safety, tolerability and preliminary efficacy of DB-OTO is evaluated in pediatric patients with profound *OTOF*-related deafness.

DB-OTO is administered by intracochlear injection using a typical facial recess approach through the round window. A 10-month-old female (patient 1), a 4-year-old male (patient 2) and an 18-month-old female (patient 3) received a single intracochlear injection of DB-OTO (7.2×10^{12} vector genomes) unilaterally into the inner ear perilymph. A cochlear implant (CI) was placed in the contralateral ear for patients 1 and 2. At baseline, patients 1 and 2 had no detectable hearing by behavioral pure tone audiogram (PTA) or auditory brainstem response (ABR) at maximum tested stimulus levels. Patient 3 responded to very loud sounds (>100 dB).

Through week 24 (patient 1), week 6 (patient 2), and week 2 (patient 3), no dose-limiting toxicities or DB-OTO related adverse events were reported, including absence of vestibular manifestations. Cervical vestibular evoked myogenic potential responses were present at baseline for all 3 patients and remained present post-treatment.

Hearing improvements assessed by PTA and ABR were noted in patients 1 and 2 from the first efficacy assessment (Week 4); patient 3 efficacy assessments have not yet been completed.

At 24 weeks post-treatment, hearing improvement was confirmed in patient 1 with PTA hearing thresholds within normal range at key speech frequencies. Hearing (PTA assessed) was improved by an average of 80 dB across all tested frequencies (baseline thresholds absent at 100 dB, maximum air conduction intensity tested, 250–4000 Hz). These improvements were corroborated by ABR showing thresholds of 45–85 dB through week 24. No improvement from baseline was observed in the untreated ear. Parents and audiologist reported that patient 1 could progressively hear loud then softer sounds when the CI in the contralateral ear was turned off at week 24, consistent with PTA and ABR findings. Global auditory skill development was observed on parent reports and as assessed by the LittlEARS Auditory Questionnaire.

In patient 2, hearing thresholds improved from profound deafness at baseline to severe-to-profound hearing levels at week 6 post-treatment. Hearing improved by an average of 16 dB across all tested frequencies, similar to patient 1 at that timepoint. A present ABR was observed through week 6 (thresholds of 75–90 dB) in the DB-OTO treated ear. Parents reported that patient 2 responded when called by name when the CI in the contralateral ear was turned off.

Updated data for patients 1 and 2, and initial efficacy data for patient 3 will be presented.

These results demonstrated an early overall positive safety and tolerability profile and suggest that DB-OTO gene therapy may significantly improve hearing in patients with profound deafness due to *OTOF* variants.

OR017

Safety and expression of intein-based Dual AAV8.ABCA4 in the non-human primate retina

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We recently demonstrated that split intein-mediated protein trans-splicing can expand AAV transfer capacity and enable the efficient reconstitution of the large ATP-binding cassette subfamily A member 4 (ABCA4) which is defective in Stargardt disease (STGD1), the most common form of inherited macular degeneration.

Starting from this observation, we showed that subretinal administrations of Dual AAV8.ABCA4 (AAVB-039) improves the phenotype of a STGD1 mouse model.

To further evaluate the translational potential of AAVB-039, a 13-week long non-GLP, ocular safety and expression study was conducted in non-human primates (NHPs). NHPs received a subretinal injection of either vehicle (control, CTR) or AAVB-039 at one of two relevant doses, as well as a unique anti-inflammatory regimen.

Ocular inflammation showed a dose-dependent severity, gradually decreasing over time. Anterior inflammation disappeared by week 5, while vitreous cells returned to control levels by week 9 in most eyes.

Electroretinography indicated a mild, dose-dependent reduction in amplitude at week 5, with no abnormalities observed by the study end, except for a borderline reduction in one eye treated at the high dose. Histopathological examination revealed slight to minimal ocular findings, mainly focal and localized to the dosing site, and improving over time. Ocular imaging corroborated these findings.

BaseScope analysis showed nearly total photoreceptor co-expression of mRNAs encoding both ABCA4.intein halves across an extended retinal region, while Simple Western analysis confirmed human ABCA4 protein reconstitution at levels 50% over the endogenous macaque protein.