months follow up. Three patients in cohort 2 have completed at least 30-months observation, and one completed 24 months of observation. Patients were aged between 53 and 76yrs, with 9 males and 2 females. Mean LVEF at baseline was 30.33% (SD 3.88; cohort 1) and 23.28% (SD 5.92; cohort 2). The first 3 participants in Cohort 1, showed clinically meaningful improvements in LVEF, NYHA Class, MLHFQ, Peak VO_2 and 6MWT at 12 months. Of the 3 remaining patients in cohort 1, two have shown initial improvement in NYHA Class, 6MWT and MLHFQ score at 3 months post administration. Among participants in Cohort 2, four of the 5 patients enrolled could be evaluated. Two of 4 patients showed improvements in MLHFQ and NYHA score, and all 4 showed improvements in LVEF at 12 months, compared to baseline. Peak VO2 declined in three but improved in one at 12 months while 6MWT declined in one patient, worsened in one, and was stable in two at 12 months. In support of this encouraging early clinical efficacy signal, left ventricular cardiac tissue was obtained from 1 patient in cohort 2 who underwent left ventricular assist device (LVAD) placement 13 months post-intracoronary gene transfer. AB-1002 demonstrated high myocardial transduction efficiency at 1.19 vg per cardiomyocyte and phosphorylation levels of phospholamban similar to normal hearts. To date AB-1002 has been well tolerated. Over the total follow up time available, 4 of 6 patients experienced 25 treatment emergent adverse events (TEAEs) and 5 patients experienced 56 TEAEs in cohorts 1 and 2 respectively, most of which were mild or moderate in severity. There was 1 fatal event in cohort 2 not considered related to investigational product. We believe our Phase 1 clinical trial demonstrates that AB-1002 is well-tolerated and results in positive efficacy outcomes in patients with non-ischemic HF. Further development of AB-1002 will be conducted in a phase 2 trial of up to 150 patients, GenePHIT, which is currently ongoing.

10. Intracochlear Administration of DB-OTO Gene Therapy in Pediatric Patients with Profound Hearing Loss Due to Otoferlin Mutations: The CHORD Phase 1/2 Open-Label Trial

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Introduction: Biallelic otoferlin gene (*OTOF*) mutations commonly result in auditory neuropathy characterized by severe-to-profound sensorineural hearing loss. In these patients, the auditory brainstem response (ABR) is absent or severely reduced contrasting with normal outer hair cell function. *OTOF* gene replacement may provide instatement of high-quality, physiological hearing and be a more effective and durable treatment than cochlear implants. DB-OTO is a dual adeno-associated virus (AAV1) vector designed for intracochlear delivery of a full-length copy of the human *OTOF* gene under the control of the Myo15 hair-cell specific promoter. In this first-in-human clinical trial with DB-OTO (CHORD, NCT05788536), the safety, tolerability and preliminary efficacy of DB-OTO is being evaluated in pediatric patients with profound hearing loss caused by *OTOF* mutations. **Methods**: CHORD is a global, phase 1/2 trial of DB-OTO enrolling pediatric patients with biallelic pathogenic *OTOF* variants, profound hearing loss, presence of otoacoustic emissions or cochlear microphonic if >2 years. In Part A, the initial unilateral dose escalation phase of the study, DB-OTO is being administered by intracochlear injection using a typical facial recess approach through the round window. A 10-month-old female received a single intracochlear injection of 7.2×10^{12} vector genomes of DB-OTO unilaterally with a cochlear implant placed in the contralateral ear. At baseline the patient had no detectable hearing by behavioral pure tone audiogram (PTA) nor ABR. **Results**: Through week 12 after treatment, no dose-limiting toxicities and no DB-OTO related adverse events (AEs) were reported, including absence of vestibular manifestations. Hearing recovery was detected at 4 weeks post-treatment, with average behavioral PTA thresholds improving to 55 dB in the best frequencies (2, 4 and 8 kHz) at 12 weeks posttreatment. Hearing recovery measured by ABR showed a positive wave V amplitude through week 12 (thresholds of 40-80 dB, no response at 100 dB at baseline) in the DB-OTO treated ear, while no improvement was observed in the untreated ear. According to parental reports, as indicated by the LittlEARS auditory questionnaire, an improvement in the patient's global auditory skill development was also observed at week 12. Parents reported also more natural vocalizations when the patient was not wearing the cochlear implant on the other ear, indicating improved hearing acuity on the DBOTO-treated ear. Additional data from this and other enrolled patients will be presented. **Conclusions**: In this first-in-human gene therapy trial of DB-OTO, an overall positive tolerability profile was reported, with no AEs related to DB-OTO treatment reported. Audiometric data showed improvement in hearing from baseline corroborated by early auditory skills testing and parental reporting. These encouraging results prompt further investigation in other patients with profound hearing loss due to *OTOF* mutations.

New Technologies for Gene Targeting and Gene Correction

11. Efficacy and Integration of a Non-Viral *ABCA4* Transposon in Treating Stargardt Disease: Evidence from Mice and Primate Studies

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