Phase 1 Study of Intrathecal Administration of AVXS-101 Gene-Replacement Therapy (GRT) for Spinal Muscular Atrophy Type 2 (SMA2) (STRONG)

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Objective: To describe STRONG, a multicenter, open-label, phase 1 study (NCT03381729) of the safety, tolerability, optimal dose, and efficacy of onasemnogene abeparvovec (AVXS-101) in patients with SMA2.

Background: SMA is a rapidly progressing neurodegenerative disease causing loss of motor and respiratory function. The genetic root cause is bi-allelic deletion/mutation of the survival motor neuron 1 gene (SMN1). Disease severity is modified by SMN2 copy number. AVXS-101 comprises an adeno-associated virus serotype 9-encapsulated transcript of human SMN that crosses the blood-brain barrier. In a phase 1 study (NCT02122952) in patients with SMA1, intravenous AVXS-101 demonstrated unprecedented improvements in survival, motor function, and motor milestone achievement.

Design/Methods: In STRONG, SMA2 patients (bi-allelic SMN1 mutations/deletions, 3 copies of SMN2) who could sit but not stand or walk independently were enrolled in 2 cohorts by age (cohort 1: ≥6 to <24 months; cohort 2: ≥24 to <60 months), received one-time intrathecal AVXS-101 at the highest acceptably safe dose, and were followed for 12 months. Three patients in cohort 1 received dose A. Based on demonstrated acceptable safety, three additional patients in cohort 2 received dose B. Given ongoing demonstration of acceptable safety, 13 additional patients in cohort 1 and 9 in cohort 2 were treated with dose B. Primary endpoints were safety/tolerability, optimal dose, ability to stand unsupported ≥3 sec (cohort 1), and Hammersmith Functional Motor Scale-Expanded score (cohort 2).

Results: As of October 12, 2018, 28 patients have been enrolled at 11 sites. Enrollment is complete. To date, no safety or tolerability concerns have been identified. A study update will be provided.

Conclusions: Results from STRONG show intrathecal delivery of AVXS-101 in infants is feasible and well tolerated, with no safety concerns to date, and may support AVXS-101 as a promising treatment option for patients with SMA2.