AVXS-101 Gene-Replacement Therapy (GRT) in Presymptomatic Spinal Muscular Atrophy (SMA): Study Update
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Objective: To evaluate efficacy and safety of onasemnogene abeparvovec (AVXS-101), an SMN GRT, for treatment of presymptomatic newborns with SMA.

Background: SMA is a recessive neurodegenerative disease resulting in loss of motor and respiratory function, the genetic root cause of which is biallelic deletion/mutation of SMN1. Genomic copies of a structurally similar gene (SMN2) modify disease severity. In a phase 1 study, AVXS-101 improved survival and motor function of symptomatic SMA type 1 patients (2x SMN2) dosed at ≤6 months of age. Because motor neuron loss can be insidious and disease progression is rapid, early intervention with disease modifying treatment is critical.

Design/Methods:
SPR1NT is a multicenter, open-label, single-arm, phase 3 study enrolling ≥27 SMA patients with 2xSMN2 (cohort 1) or 3xSMN2 (cohort 2). Asymptomatic infants aged ≤6 weeks receive a one-time intravenous infusion of AVXS-101 (1.1x10^14 vg/kg). Safety and efficacy are assessed through study end at 18 or 24 months for patients with 2x or 3xSMN2, respectively. Primary outcomes are independent sitting for ≥30 seconds at 18 months (2xSMN2) or standing with assistance at 24 months (3xSMN2).

Results:
As of September 27, 2018, 7 presymptomatic infants received AVXS-101 (4 female; 6 with 2xSMN2; 1 with 3xSMN2). The first patient was infused April 10, 2018. Age at dosing was 8–37 days (median: 12 days; mean: 21 days); mean CHOP-INTEND score was 41.7 (n=6 with data available). Mean increase from baseline in CHOP-INTEND score was 6.8 at day 14 (n=4), 11.0 at month 1 (n=3), 18.0 at month 2 (n=3), and 22.5 at month 3 (n=2). Additional baseline patient data (weight, motor function, maternal AAV9 antibody titers) and clinical follow-up will be presented.

Conclusions:
Preliminary data from SPR1NT show rapid motor function improvements in presymptomatic SMA patients with 2–3xSMN2, which may be associated with future survival and motor milestone achievement.