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Treatment effects of nusinersen in longstanding adult 5q-SMA type 3 - a prospective observational study over 10 months

M. Walter [1], J. Stauber [1], M. Hiebeler [1], S. Thiele [1], E. Greckl [1], A. Pechmann [2], J. Kirschner [2], B. Schoser [1]

[1] *Friedrich-Baur-Institute, Munich, Germany;* [2] *Medical Center Univ. Freiburg, Freiburg, Germany*

Spinal muscular atrophy (SMA) is a progressive autosomal recessive motor neuron disease caused by loss of the SMN1 gene. Based on randomized clinical trials in children with SMA type 1 and 2, Nusinersen has been approved as first treatment for all types of SMA, including adults with SMA type 3. Twelve adult SMA3 patients, aged 18 to 54 years with disease duration ranging from 6 to 40 years were treated with intrathecal loading doses at day 1, 14, 28 and 63, followed by maintenance dose every 4 months. Four patients were wheelchair-dependent at baseline. Patients were monitored within SMArtCARE for disease progression, side effects and treatment efficacy by clinical examination, vital capacity, ALS Functional Rating Scale, 6-Minute-Walk-Test, Revised Upper Limb Module, and Hammersmith Functional Rating Scale. Five patients reported back pain and post lumbar-puncture headache following intrathecal administration. Laboratory tests did not reveal nephrotoxicity. At visit 6 (day 300), a clinical benefit of improved endurance, reduced frequency of falls, and better motor function performance in 6MWT and RULM was seen in 11 of 12 patients, while FVC and ALSFR were largely unchanged. This prospective, open-label outcome study shows a favorable treatment response in adults with long-standing SMA3 after 10 months of Nusinersen treatment, which is unexpected in comparison to history natural history data. Outcome measures such as the 6MWT and RULM are sensitive to detect change in adults with SMA type 3 over a 12 month period.

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Investigating an in-home body-weight support harness system to maximize treatment benefit in spinal muscular atrophy

M. Iammarino, L. Alfano, N. Miller, L. Lowes

Nationwide Children's Hospital, Columbus, USA

Novel therapies in spinal muscular atrophy (SMA) have undoubtedly changed the course of the disease. While we understand that earlier treatment significantly affects outcomes, focus has shifted to the optimal dosage of exercise that can maximize therapeutic effect. Early strength deficits in SMA limit mobility and alter the developmental path putting treated children at a disadvantage for learning new skills. Additionally, they are often older and larger before they can start weight-bearing providing less opportunity to practice. In hospital settings, body-weight support harness systems (BWSS) is a modality allowing children with various diagnoses to spend extended periods safely practicing activities in challenging positions, such as standing. We sought to investigate the feasibility of daily in-home BWSS use to maximize therapeutic benefit of treated children with SMA. Twenty children were enrolled; all received treatment with nusinersen or AVXS-101, had 2 or 3 copies of SMN2, had upright head control, and weighed under 50 pounds. Mean age at enrollment was 3.5 ± 2.1 years and mean time since initiation of treatment was 1.9 ± 1.4 years. Caregivers were encouraged to use the BWSS for two hours a day over six months and document the frequency of use. Evaluation of gross motor skill was completed at baseline, 3, and 6-months. Preliminary findings suggest reduced fatigue and improved tolerance to exercise as average use increased 50% from baseline; current reported average of 10.2 hours of use per week. Parents report high satisfaction with BWSS. Improvements have been noted in total weight-bearing with 20% of patients transitioning to the counter-weight system, requiring reduced assistive support. Updated functional data will be presented at time of meeting. Daily in-home use of BWSS is feasible, safe, well-tolerated, and importantly provides the opportunity to practice building strength and endurance in challenging functional positions in treated children with SMA.

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Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy: interim results from the phase 2 NURTURE study

M. Ryan [1], D. De Vivo [2], E. Bertini [3], W. Hwu [4], T. Crawford [5], K. Swoboda [6], R. Finkel [7], J. Kirschner [8], N. Kuntz [9], J. Parsons [10], R. Butterfield [11], H. Topaloğlu [12], T. Ben Omran [13], V. Sansone [14], Y. Jong [15], F. Shu [16], R. Foster [17], I. Bhan [18], S. Fradette [18], W. Farwell [18]

[1] *Royal Children's Hospital, Melbourne, Australia;* [2] *Columbia University, New York, USA;* [3] *Post-Graduate Bambino Gesù, Rome, Italy;* [4] *National Taiwan Univ Hospital, Taipei, Taiwan;* [5] *Johns Hopkins University, Baltimore, USA;* [6] *Center for Genomic Medicine, Boston, USA;* [7] *Nemours Children's Hospital, Orlando, USA;* [8] *University Hospital Bonn, Bonn, Germany;* [9] *Ann & Robert H. Lurie, Chicago, USA;* [10] *Children's Hospital Colorado, Aurora, USA;* [11] *University of Utah, Salt Lake City, USA;* [12] *Hacettepe University, Ankara, Turkey;* [13] *Weill Cornell Medical College, Doha, Qatar;* [14] *Neuromuscular Omniservice, Milan, Italy;* [15] *Institute of Clinical Medicine, Kaohsiung, Taiwan;* [16] *David Geffen School of Med, Los Angeles, USA;* [17] *Biogen, Maidenhead, UK;* [18] *Biogen, Cambridge, USA*

Nusinersen is the first approved treatment for spinal muscular atrophy (SMA). We present interim results from the ongoing NURTURE study (NCT02386553) examining efficacy/safety of intrathecal nusinersen, initiated prior to symptom onset, in infants with 2 or 3 *SMN2* copies. Enrolled infants were age ≤6 weeks at first dose, clinically presymptomatic, and genetically diagnosed with SMA. Primary endpoint is time to death or respiratory intervention (≥6 hours/day continuously for ≥7 days or tracheostomy). As of 15 May 2018, 25 infants (2 copies *SMN2*, n=15; 3 copies, n=10) were enrolled. Median age at last visit was 26.0 (range 14.0–34.3) months. All infants were alive and none required permanent ventilation. Median time to death or respiratory intervention could not be estimated because of too few events. Four infants (all with 2 *SMN2* copies) required respiratory intervention for ≥6 hours/day continuously for ≥7 days, with all cases initiated during acute, reversible illness. All infants achieved the WHO motor milestone sitting without support and 22/25 (88%) achieved walking with assistance; 17/22 (77%) were walking alone. Phosphorylated neurofilament heavy chain levels rapidly declined during the nusinersen loading phase and then stabilized. AEs occurred in all infants; 20/25 had AEs mild/moderate in severity; 9 had SAEs. No new safety concerns were identified. Results from a new, Spring 2019 interim analysis, including additional assessments, will be presented. These findings demonstrate there was continued benefit to infants who initiated nusinersen before symptom onset, emphasizing the value of early treatment and newborn screening. Updated analyses will provide further information.

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Type I spinal muscular atrophy patients treated with AVXS-101 have greater health outcome improvements and lower use of ventilatory support, hospitalization, and associated costs contrasted to those treated with nusinersen

R. Arjunji [1], R. Dean [2], I. Jensen [2], B. Miller [2], M. Menier [1], D. Sproule [1], D. Feltner [1], M. Droege [1], F. Khan [1], O. Dabbous [1]

[1] *AveXis, Inc., Bannockburn, USA;* [2] *Precision Xtract, Boston, USA*

Spinal muscular atrophy type 1 (SMA1) is a rapidly progressing, debilitating, genetic neuromuscular disease that causes loss of motor muscle function and death/permanent ventilation by 2 years of age. This cross-study