AVXS-101, a clinical phase gene replacement therapy for spinal muscular atrophy

Petra Kaufmann MD FAAN

VC R&D Translational Medicine, AveXis

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Financial Disclosures

- Petra Kaufmann is an employee of AveXis, Inc.
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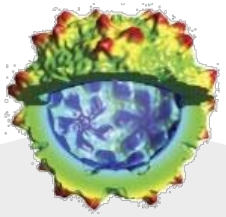
Onasemnogene Abeparvovec (AVXS-101) Is an Investigational One-Time Gene-Replacement Therapy That Treats the Genetic Root Cause of SMA

Able to deliver across the blood-brain barrier and into the spinal cord



Recombinant AAV9 Capsid Shell

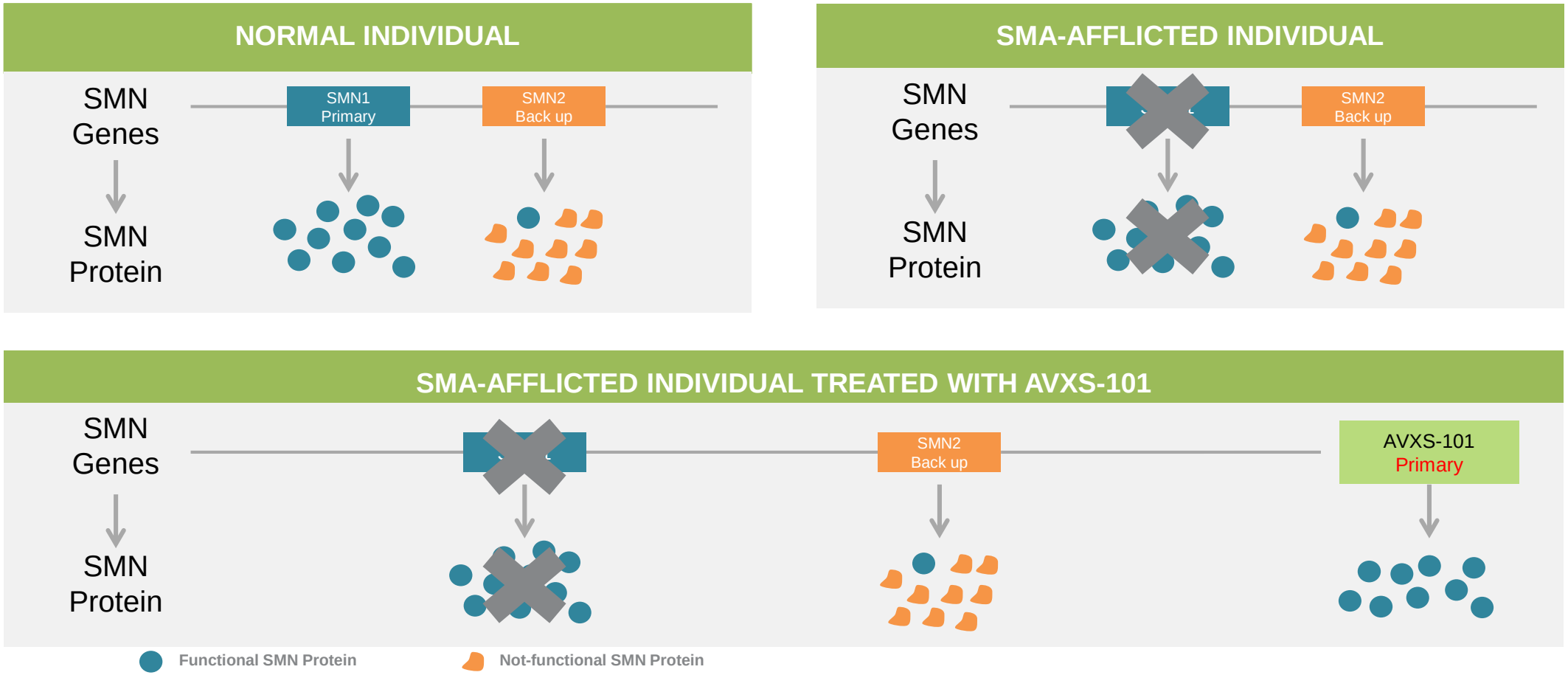
Designed not to integrate into genome of the patient

Continuous Promoter	Human *SMN* Transgene	scAAV ITR
• Hybrid CMV enhancer and CB promoter activates the transgene to allow for continuous and sustained SMN protein expression	• Full copy of a stable, functioning human *SMN* gene that is introduced into the cell's nucleus	• The scAAV ITR increases the speed at which the double-stranded transgene is transcribed and the resulting protein is produced

AAV2, adeno-associated virus serotype 2; AAV9, AAV serotype 9; BGH Poly A, bovine growth hormone polyadenylation; CB, chicken β-actin; cDNA, complementary DNA; CMV, cytomegalovirus; ITR, inverted terminal repeat; scAAV, self-complementary AAV; SMA, spinal muscular atrophy; SMN, survival motor neuron; SV simian virus.

Figure redrawn from Powel SK, et al. *Discov Med*. 2015;19:49–57.

Mutations in SMN1 are the primary cause of 5q SMA

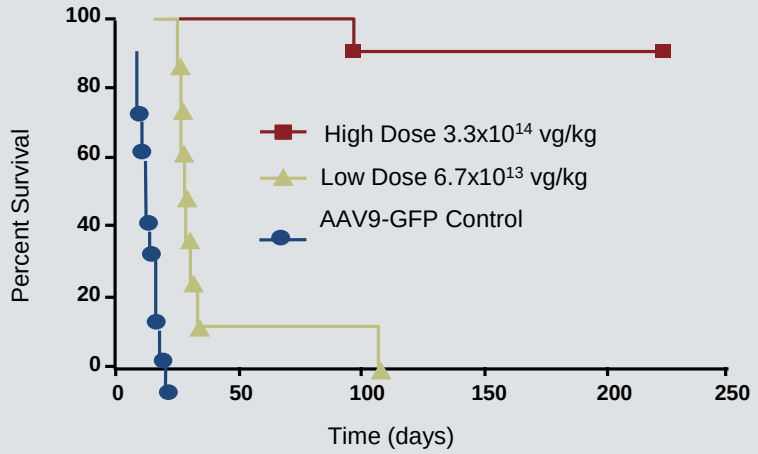


IV Preclinical Proof-of-Concept

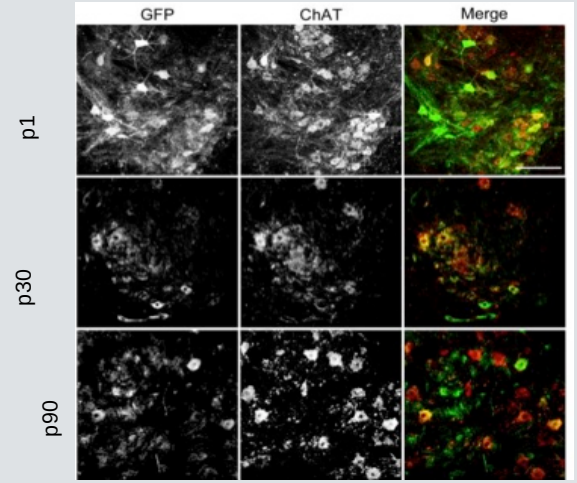
THE HIGHLIGHTS

- In the severe SMA mouse model, a single IV injection of scAAV9-SMN increased survival and **improved motor function**.
  - **Median survival was 265 days** in this cohort. More than 30% survived 400 days. [1]
- Therapeutic benefit is dose- and time-dependent
- scAAV9-GFP led to widespread, sustained transgene expression in motor neurons in non-human primates[2]

DOSE-RESPONSE FOR SURVIVAL[1]



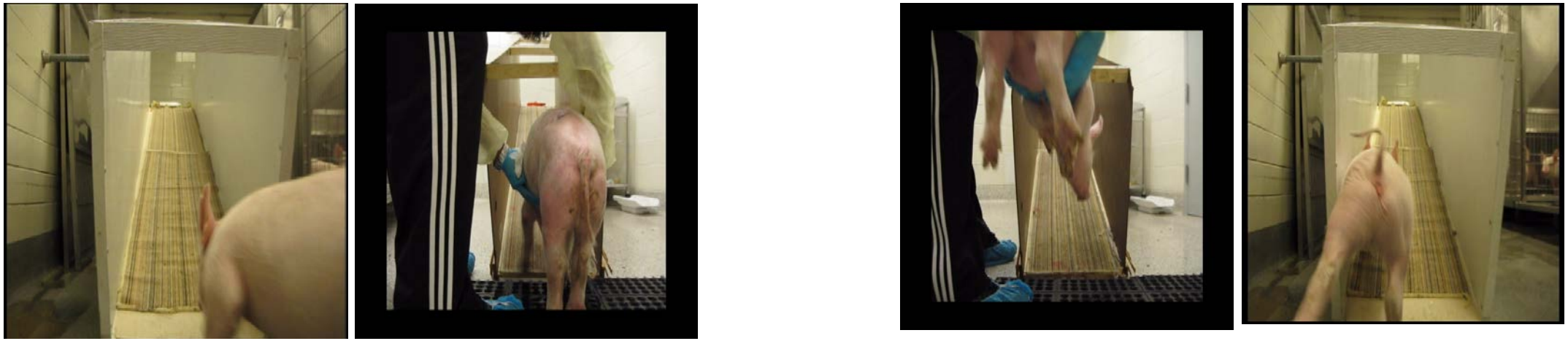
MOTOR NEURON TARGETING* IN NHP



1, Foust et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. *Nat. Biotechnol.* March 2010.
2. Bevan et al. Systemic Gene Delivery in Large Species for Targeting Spinal Cord, Brain, and Peripheral Tissues for Pediatric Disorders. *Mol. Ther.* November 2011.

FAVORABLE OUTCOMES WITH EARLY PRE-SYMPTOMATIC TREATMENT IN LARGE ANIMAL MODEL DEMONSTRATES THE IMPORTANCE OF EARLY THERAPEUTIC INTERVENTION IN SMA[1]

Control **No rescue** **Early rescue** **Late rescue**



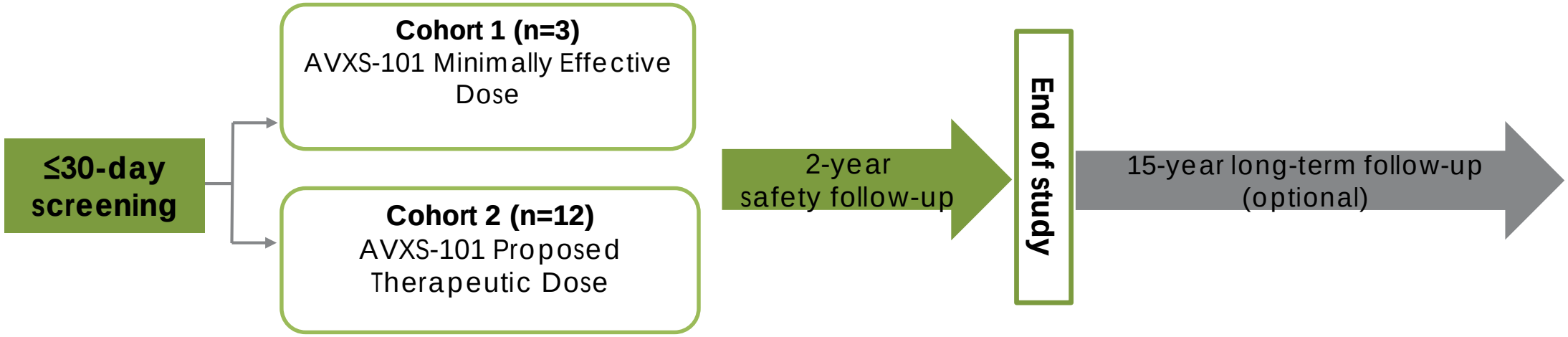
Duque et al. Ann Neurol. 2015;77(3):399–414.

Duque et al. Ann Neurol. 2015;77(3):399–414 [supplementary information video 1]. Available at: https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fana.24332&file=ana24332-sup-0002-suppvideo1.mp4 accessed October 2018.

Duque et al. Ann Neurol. 2015;77(3):399–414 [supplementary information video 3]. Available at: https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fana.24332&file=ana24332-sup-0004-suppvideo3.mp4 accessed October 2018.

Duque et al. Ann Neurol. 2015;77(3):399–414 [supplementary information video 4]. Available at: https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fana.24332&file=ana24332-sup-0005-suppvideo4.mp4 accessed October 2018.

AVXS-101-CL-101: Phase 1, open-label, one-time IV administration, single-site, dose-escalation study to evaluate safety and efficacy of AVXS-101 as a treatment of SMA Type 1



KEY ENROLLMENT CRITERIA

Inclusion
- 9 months/6 months of age[1] or younger at infusion
- Bi-allelic SMN1 gene deletions or point mutations
- **2 copies of SMN2**
- Onset of disease at birth to 6 months of age

Exclusion
- Patients with Anti-AAV9 antibody titers >1:50 by immunoassay

KEY OBJECTIVES

Primary
- Safety and Tolerability

Secondary
- **Time from birth until death or time to ≥16-hour ventilation**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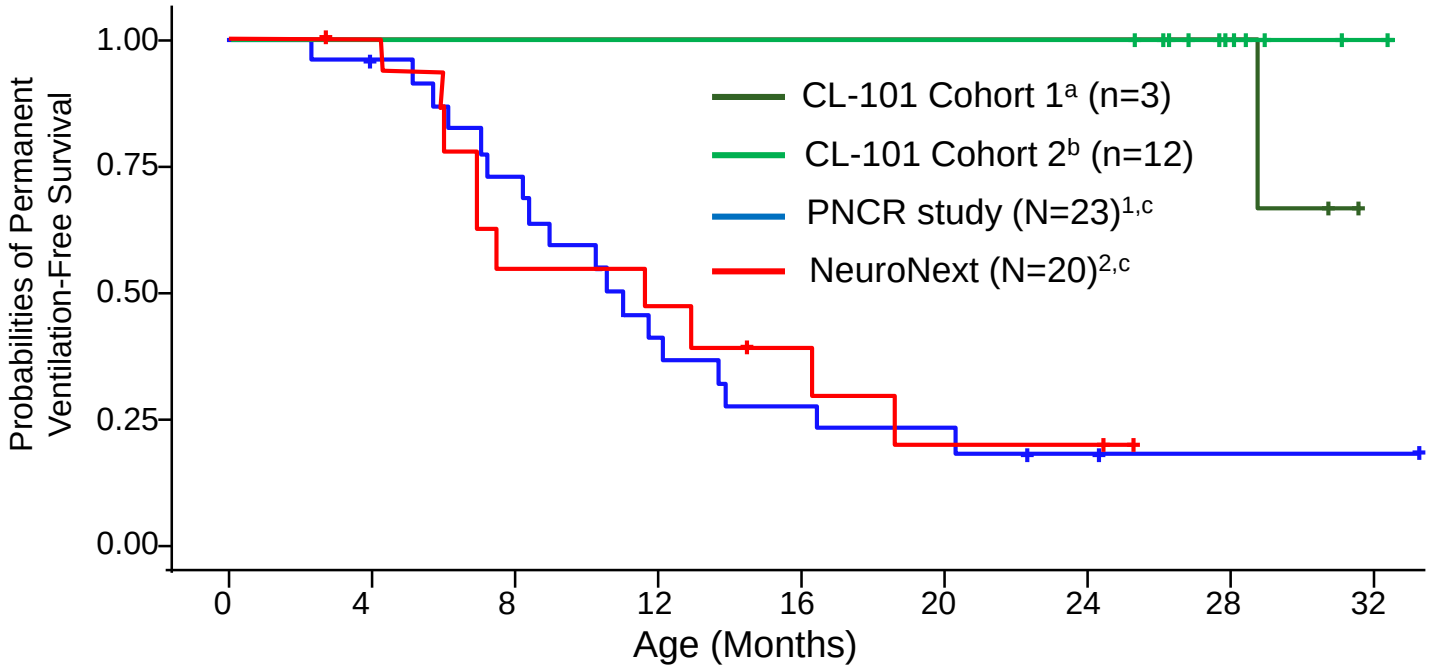
Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

Patients With SMA1 Treated With AVXS-101 in the Phase 1/2a (CL-101) Study Had Improved Survival, Motor Function, and Motor Milestone Achievements

All patients in the CL-101 study were clinically symptomatic at study entry and genetically confirmed to have biallelic *SMN1* mutations and only 2 copies of *SMN2* without the c.859G>C mutation.



At 24 months of follow up:

All patients were alive and without need for permanent ventilation

Patients treated with the proposed therapeutic dose had early and rapid motor function improvements

Eleven of 12 patients (92%) could sit without assistance for ≥5 seconds

Two children crawled, pulled to a stand, stood, and walked independently

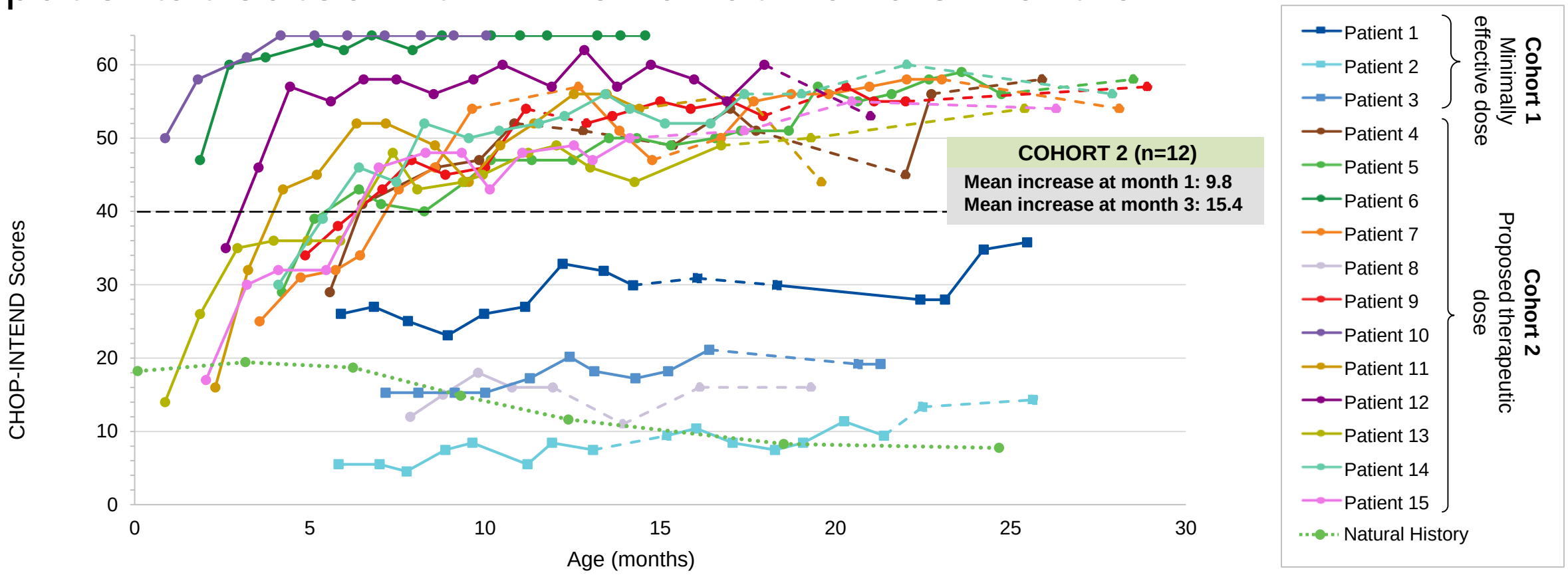
At long-term follow-up (post-24 months):

As of Sep 2018, no previously attained milestone has been lost

[a]Cohort 1 patients were treated with low-dose AVXS-101. [b]Cohort 2 patients were treated with the proposed therapeutic dose of AVXS-101. [c]Survival for PNCR[1] = no death, or no need for ≥16-h/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness; n=23 (2 copies of *SMN2*); survival for NeuroNext[2] = no death, or no tracheostomy; n=20PNCR; Pediatric Neuromuscular Clinical Research; SMA1, spinal muscular atrophy type 1.

1. Finkel RS, McDermott MP, Kaufmann P et al. *Neurology.* 2014;83:810–7; 2. Kolb SJ, et al. *Ann Neurol.* 2017;82:883–91; 3. Mendell JR, et al. *N Engl J Med.* 2017;377:1713–22.

Results: Rapid and sustained CHOP-INTEND increase observed in patients treated with AVXS-101 at 1 and 3 months



COHORT 1 (n=3)	COHORT 2 (n=12)
Mean CHOP-INTEND Increase: 7.7 points	Mean CHOP-INTEND Increase: 25.4 points

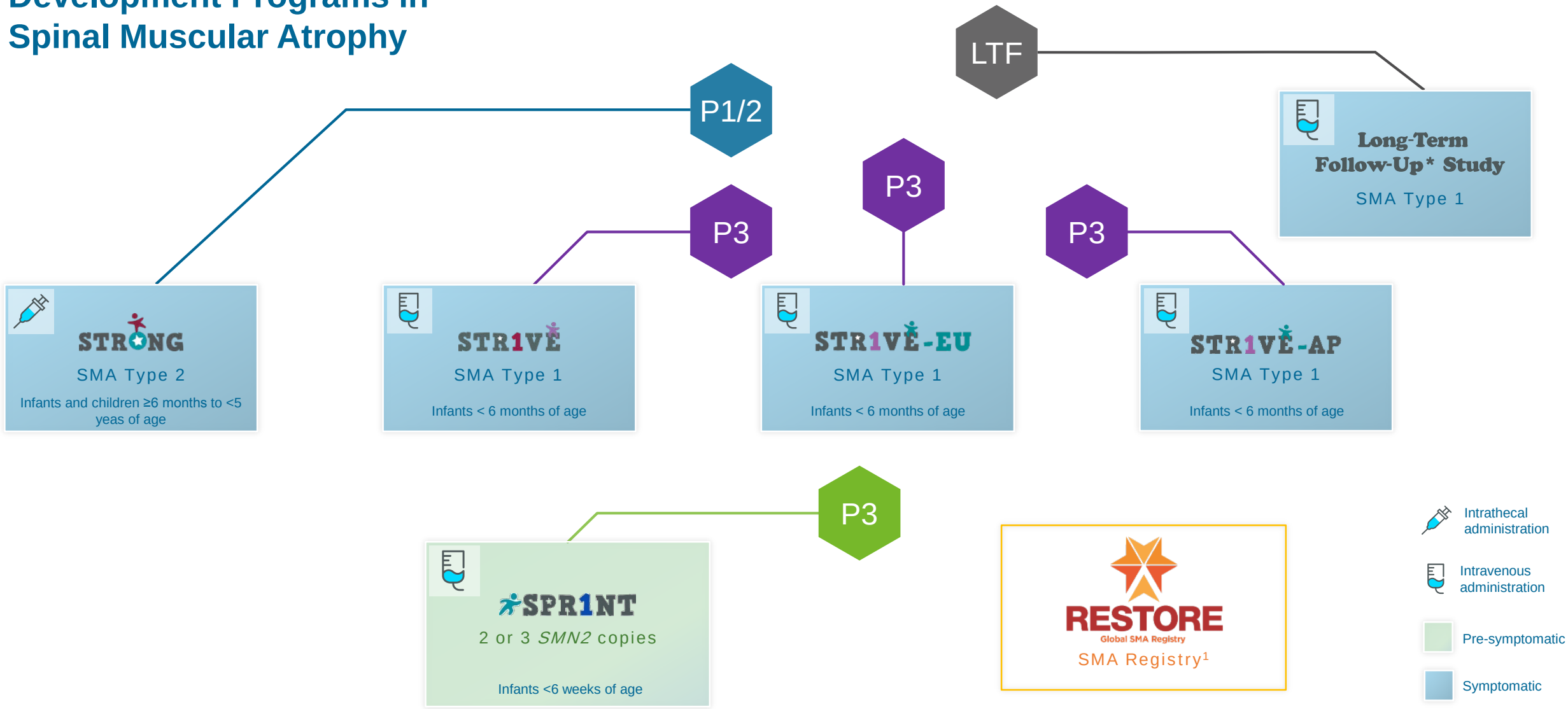
Dashed line denotes missed or partial CHOP-INTEND assessments

Black dashed line: According to natural history, SMA1 children do not achieve/maintain CHOP-INTEND scores >40 points[1]

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Dysfunction; SMA1, spinal muscular atrophy type 1.

1. Finkel RS, et al. *Neurol*. 2014;83:810-7. 2. Kolb SJ, et al. *Ann Neurol*. 2017;82:883-91.

AVXS-101 Clinical Development Programs in Spinal Muscular Atrophy



AP, Asia Pacific; EU, Europe; LTF, Long-term follow-up; P1/2, phase 1/2; P3, phase 3; SMA, spinal muscular atrophy; SMA1, SMA type 1; SMA2, SMA type 2; SMN, survival motor neuron.

*15 years. 1. Data on file. SMA registry. AveXis. 10/2018.

https://clinicaltrials.gov/ct2/show/NCT03381729; https://clinicaltrials.gov/ct2/show/NCT03505099; https://clinicaltrials.gov/ct2/show/NCT03306277; https://clinicaltrials.gov/ct2/show/NCT03461289; https://clinicaltrials.gov/ct2/show/NCT03421977; https://clinicaltrials.gov/ct2/show/NCT03837184.

The usages mentioned are investigational only and have not been approved for use by the US Food and Drug Administration or by any other health authority.

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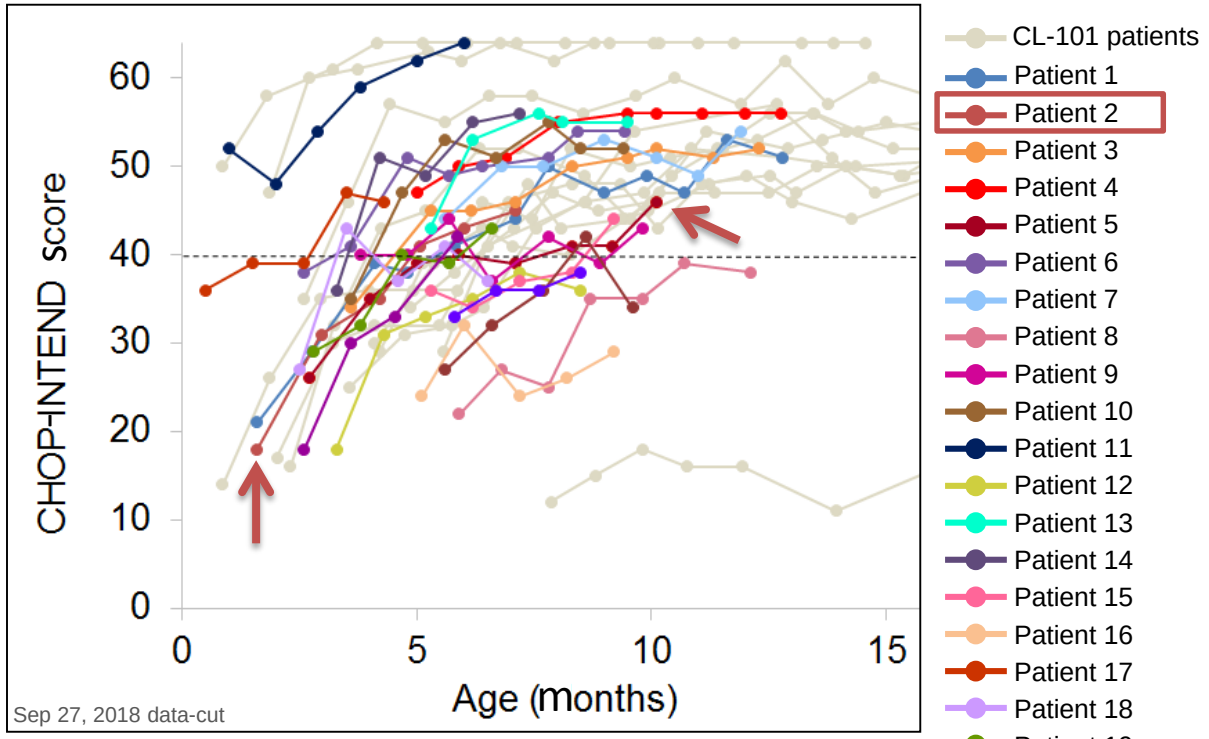
Motor Function Improvements Similar Between Patients in the Phase 1/2a and Phase 3 Studies of AVXS-101

Phase 3 study (STR1VE) of AVXS-101 in SMA1 infants

- **Key inclusion criteria:**
  - Up to 180 days old at dosing
  - Genetic confirmation of *SMN1* mutations and 1-2 copies of *SMN2* (inclusive of the *SMN2* gene modifier mutation; c.859G>C)
- **Key exclusion criteria:**
  - Anti-AAV9 antibody titer >1:50
- **Primary objectives:**
  - Achievement of independent sitting for at least 30 seconds
  - Event-free survival as defined by avoidance of death and permanent ventilation*

All patients in the phase 3 and phase 1/2a studies were clinically symptomatic at study entry and genetically confirmed to have biallelic *SMN1* mutations and only 2 copies of *SMN2* without the c.859G>C mutation.

Patients in the phase 3 and phase 1/2a studies showed a similar early CHOP-INTEND response

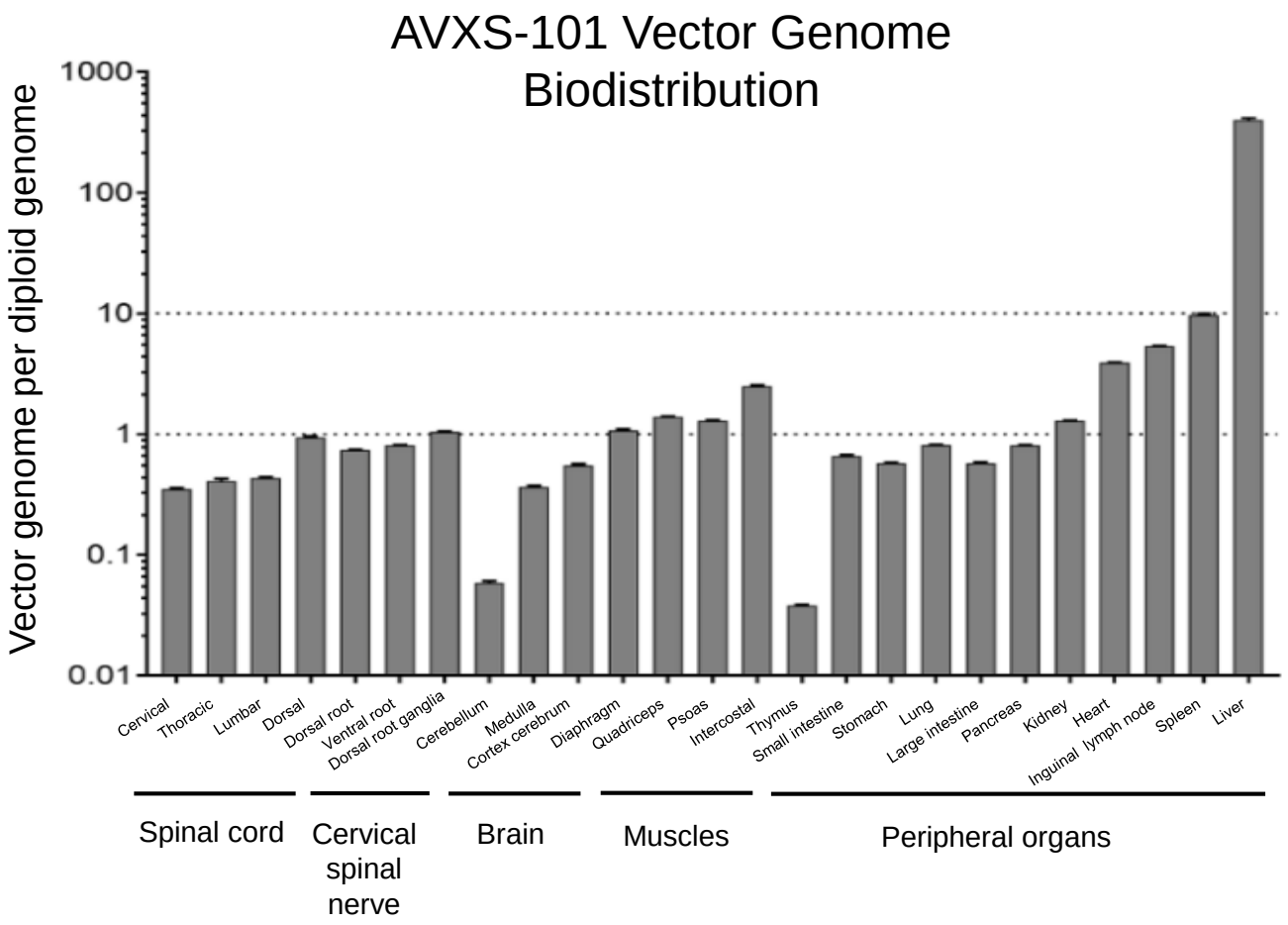


Mean Increase in CHOP-INTEND Score From Baseline		
Month	Phase 3	Phase 1/2a[†,1]
1	7.0	9.8
3	11.8	15.4

[†]Data from the phase 1/2a trial only includes patients treated with the proposed therapeutic dose of AVXS-101 (cohort 2; n=12).

AAV, adeno-associated virus; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA1, spinal muscular atrophy type 1; SMN, survival motor neuron; STR1VE, Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1. *permanent ventilation as defined by tracheostomy or ≥16 hours of respiratory assistance per day for ≥14 consecutive days) in the absence of an acute reversible illness, excluding perioperative ventilation.1. Mendell JR, et al. *N Engl J Med*. 2017;377:1713-1722.

AVXS-101 Vector Genomes Were Detected in All Tissues Evaluated, Including All Regions of the Spinal Cord

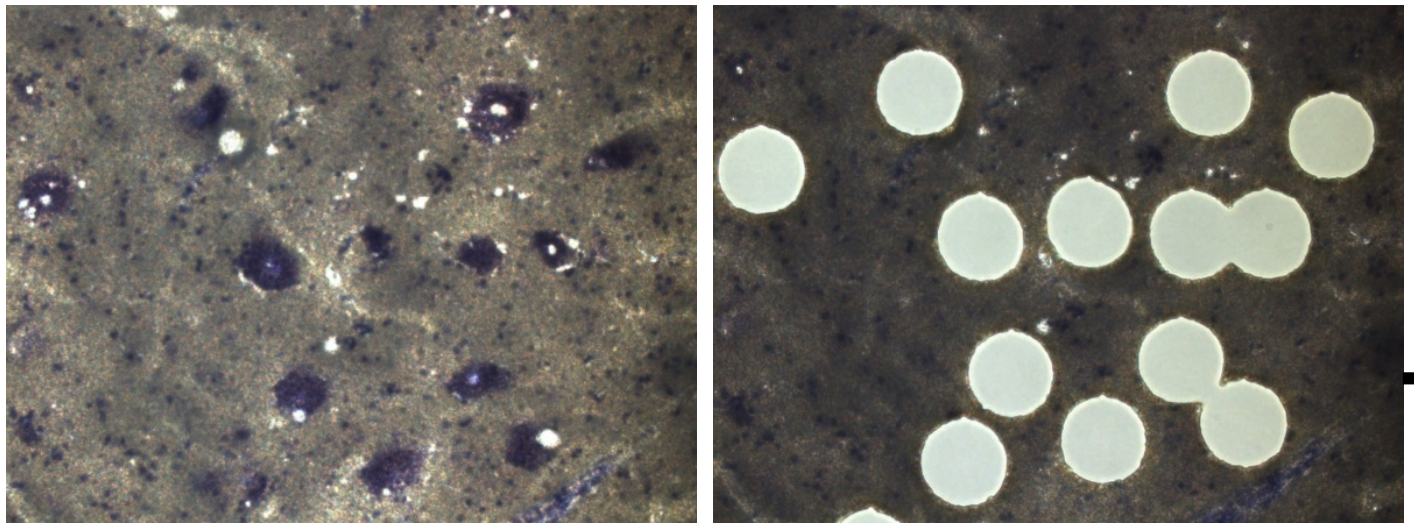


- First-in-human data to show transduction
  - Comparable to what was seen in animal data
- The AVXS-101 genome was broadly distributed
  - Importantly, AVXS-101 genome was detected in all spinal cord regions

Error bars are standard errors between technical replicates

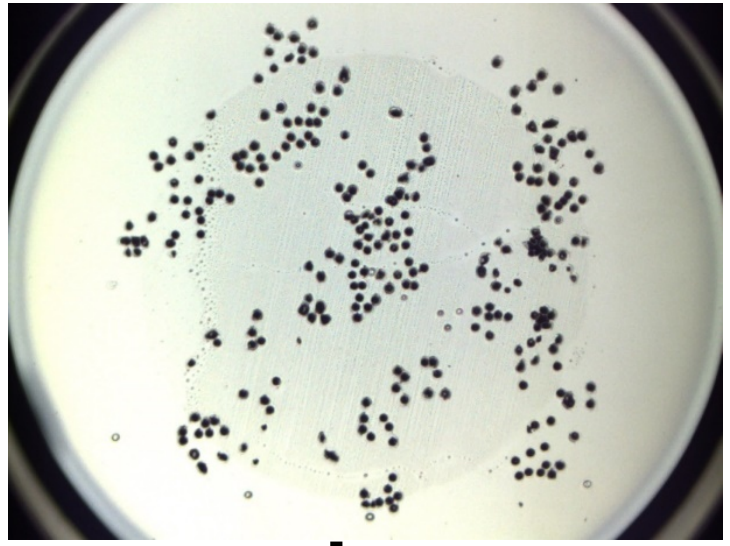
Laser-Capture Microdissection (LCM) of Spinal Motor Neurons for AVXS-101 Vector Genome Quantification

Spinal cord ventral horn motor neurons: laser captured using Arcturus® LCM System



(Single cell)

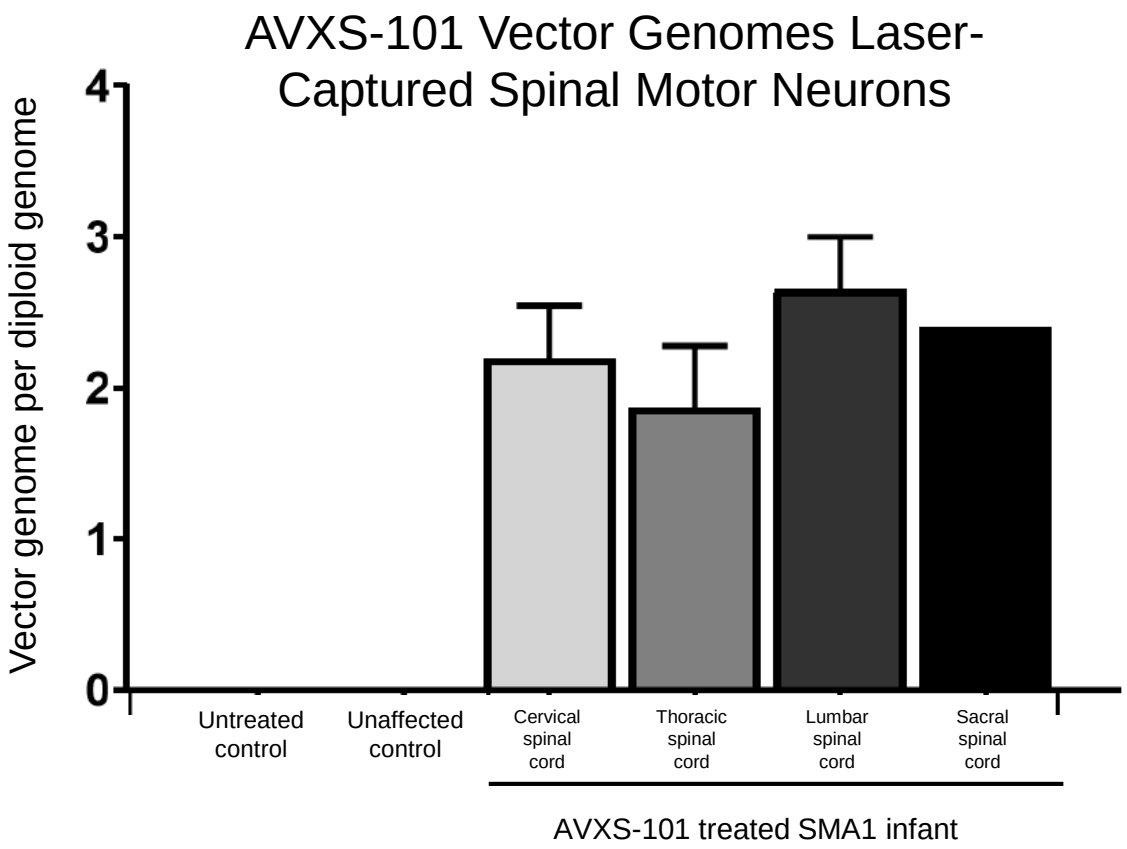
Motor neurons ~250 cells



ddPCR quantification of AVXS-101 vector genomes

ddPCR, droplet digital PCR.

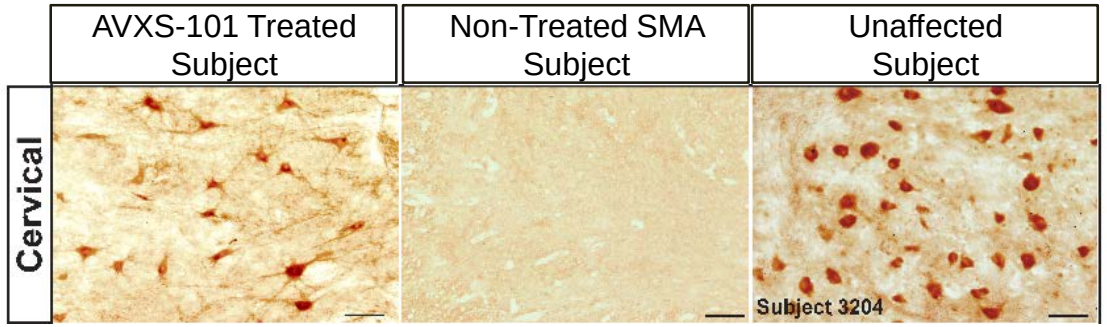
AVXS-101 Vector Genomes Were Detected in Motor Neurons, the Target Cells for SMA

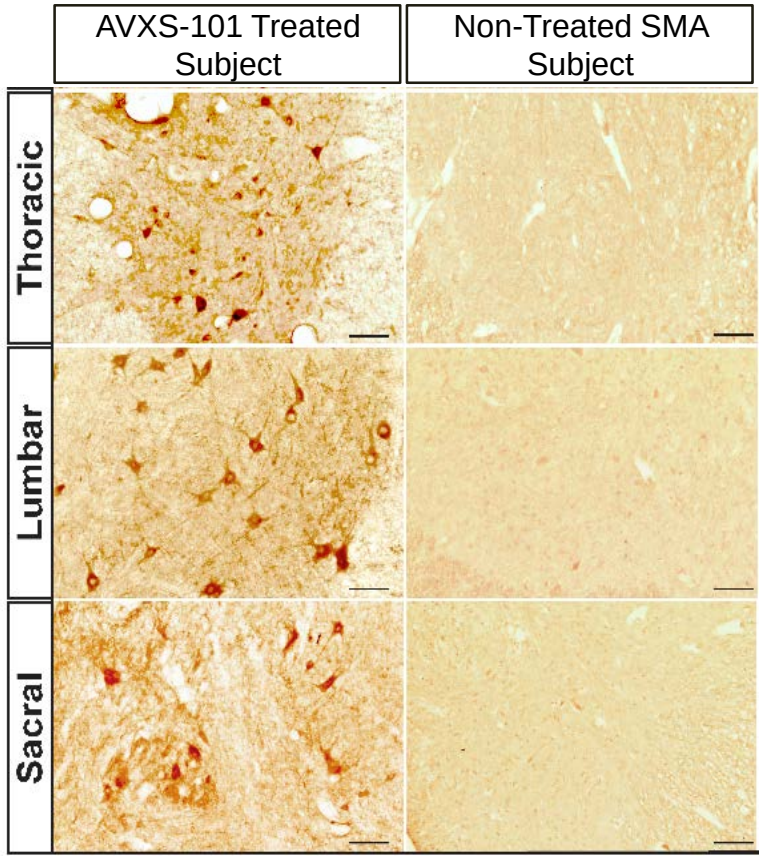


- 2.2, 1.9, 2.7, and 2.4 AVXS-101 vector genomes per diploid genome were detected in motor neurons within the cervical, thoracic, lumbar, and sacral regions, respectively*
- Untreated SMA patients and untreated unaffected controls did not express AVXS-101 genomes

SMA, spinal muscular atrophy.
*Values are calculated as vector genomes per diploid genome and reported as mean with standard error from 3 technical replicates.

SMN Protein Expression Was Detected Along All Regions of the Spinal Cord

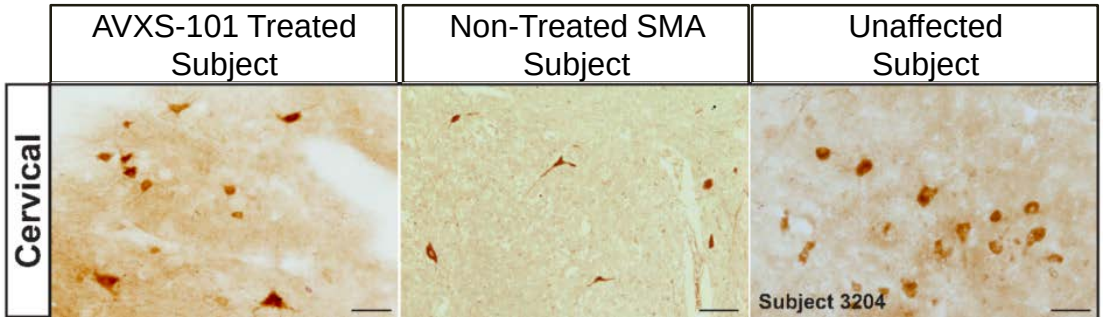


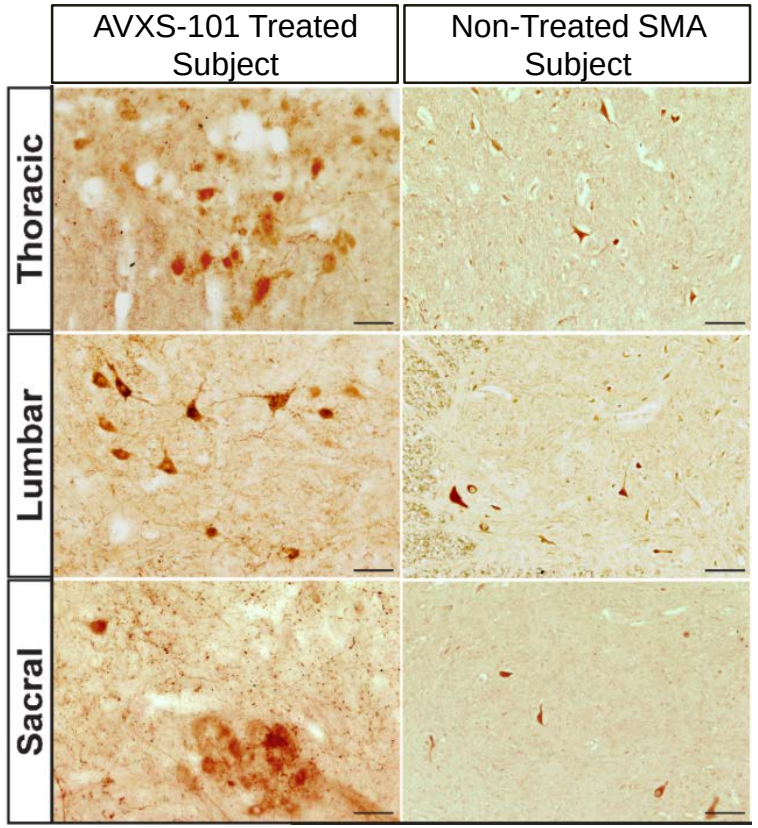


- Strong expression of SMN in AVXS-101 treated patients and unaffected control
- Immunohistochemistry findings were consistent with SMN transduction as measured by laser-capture microdissection
- Little or no detectable SMN staining in the non-treated SMA control

SMA, spinal muscular atrophy; SMN, survival motor neuron.
SMN protein immunohistochemistry. Scale bars = 100 µm.

Motor Neuron Morphology Comparable to Unaffected Control





- Motor neurons were apparent and of normal size and shape in treated patient and unaffected control patient in all regions of the spinal cord
- In contrast, ChAT motor neuron staining in the non-treated SMA patient was less, suggesting these motor neurons were sick and/or dying

ChAT, choline acetyltransferase; SMA, spinal muscular atrophy; SMN, survival motor neuron.
ChAT protein immunohistochemistry. Scale bars = 100 µm.

Conclusions

- Interim data from the multi-center AVXS-101 phase 3 STR1VE confirm AVXS-101 results showing improvements in patients with SMA1:
  - Improved survival
  - Motor function improvements were seen at 1 month post-infusion and motor milestones were achieved over the follow-up period
  - No patient required permanent ventilation
  - No pre-existing AAV9 antibody titer >1:50
- In contrast with the observations from natural history studies and in line with CL-101, these data suggest that AVXS-101 has significant therapeutic benefit in prolonging survival in patients with SMA1
- A patient death enabled a first-in-human biodistribution case study for gene replacement therapy
  - This analysis demonstrates that AVXS-101 is successfully transduced in humans and crosses the BBB to target the CNS, including spinal cord and motor neurons
  - SMN expression is clearly increased in motor neurons in AVXS-101 treated SMA patient compared to untreated patients
- The STRIVE study is progressing well and is on track to confirm the findings from the CL-101 study