AVXS-101 Clinical Update

As Presented at the American Academy of Neurology 2017 Annual Meeting

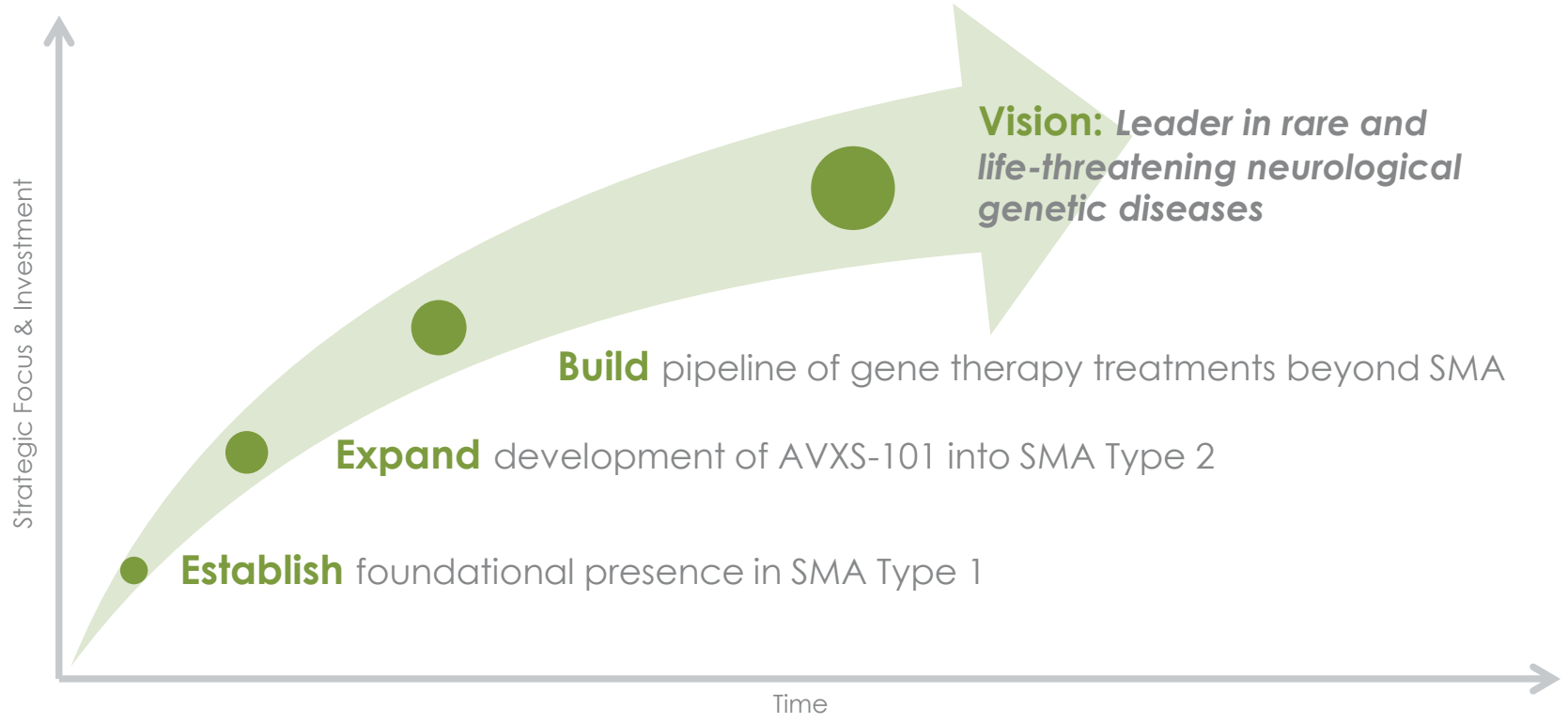
April 25, 2017

Disclaimers

Forward-Looking Statements

This presentation contains forward-looking statements, including statements about: the timing, progress and results of preclinical studies and clinical trials for AVXS-101, including statements regarding the timing of initiation of studies or trials and related preparatory work, our expectations regarding timing for meetings with regulatory agencies, our manufacturing strategy and developments, key regulatory and development milestones and our research and development programs. These statements involve substantial known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this presentation.

Our Strategy



Overview of SMA

SMA is a devastating orphan disease that results in motor neuron loss and progressive weakness; it is the most common genetic cause of infant death

- Incidence: ~1 in 10,000 live births
- Caused by reduced SMN (survival motor neuron) protein levels from loss of/defective SMN1 gene
- SMA divided into sub-categories, Type 1- 4, with Type 1 being most severe
  - Severity correlates with # of copies of SMN2 backup gene

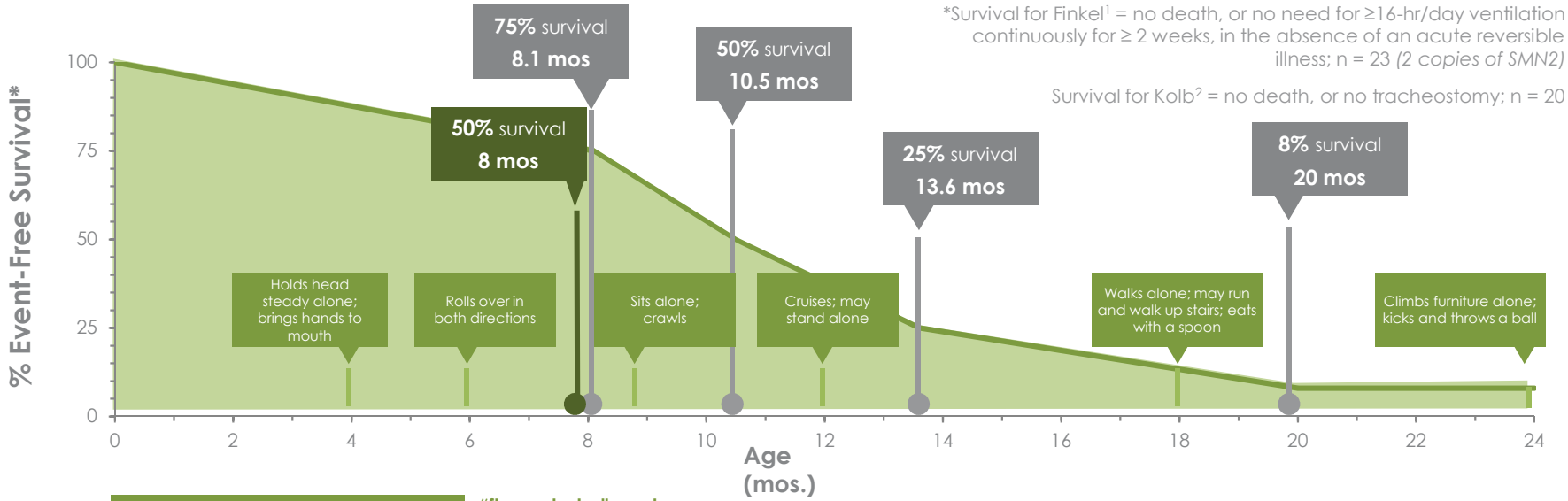
SMA Types: A Devastating Disease

	TYPE 1	TYPE 2	TYPE 3	TYPE 4
SMN2 Copy Number	Two	Three or Four	Three or Four	Four to Eight
Onset	Before 6 Months	6-18 Months	Early childhood to early adulthood (juvenile)	Adulthood (20s-30s) usually after 30
Incidence per Live Birth	Approximately 60%	Approximately 27%	Approximately 13%	Uncommon; limited information available
Developmental Milestones	• Will never be able to sit without support • Difficulty breathing & swallowing • Can't crawl/will never walk	• Will never be able to walk or stand without support	• Stand alone and walk but may lose ability to walk in 30s-40s	• Stand alone and walk but may lose ability to walk in 30s-40s (Same as Type 3)
Survival	• <10% Event free* by two years of age	• 68% alive at age 25	• Normal	• Normal

*Event = Death or ≥16-hr/day ventilation continuously for ≥ 2 wks, in the absence of an acute reversible illness

Natural History of SMA Type 1

More than 90% of SMA Type 1 patients will not survive or will need permanent ventilation support by age 2



*Survival for Finkel[1] = no death, or no need for ≥16-hr/day ventilation continuously for ≥ 2 weeks, in the absence of an acute reversible illness; n = 23 *(2 copies of SMN2)*

Survival for Kolb[2] = no death, or no tracheostomy; n = 20

Onset of SMA Type 1 by 6 months

Symptoms may present

"floppy baby" syndrome
muscle weakness (legs more than arms)
poor head control
belly breathing
bulbar muscle weakness (weak cry, difficulty swallowing, aspiration)
will never sit unsupported
loss of motor function:

- **NeuroNEXT -- CHOP INTEND decrease of 10.5 points/yr.**
- **PNCR -- CHOP INTEND decrease of 1.27 points/yr.**

Milestone for a healthy infant

SMA Type 1 survival rates per Finkel[1]

SMA Type 1 survival rate per Kolb[2]

1. PNCR (Finkel)
2. NeuroNEXT (Kolb)

Children with SMA Type 1 Do Not Reach Any Major Motor Milestones

Developmental Milestones in Type 1 Spinal Muscular Atrophy
De Sanctis et al. *Neuromuscular Disorders, Nov-2016*

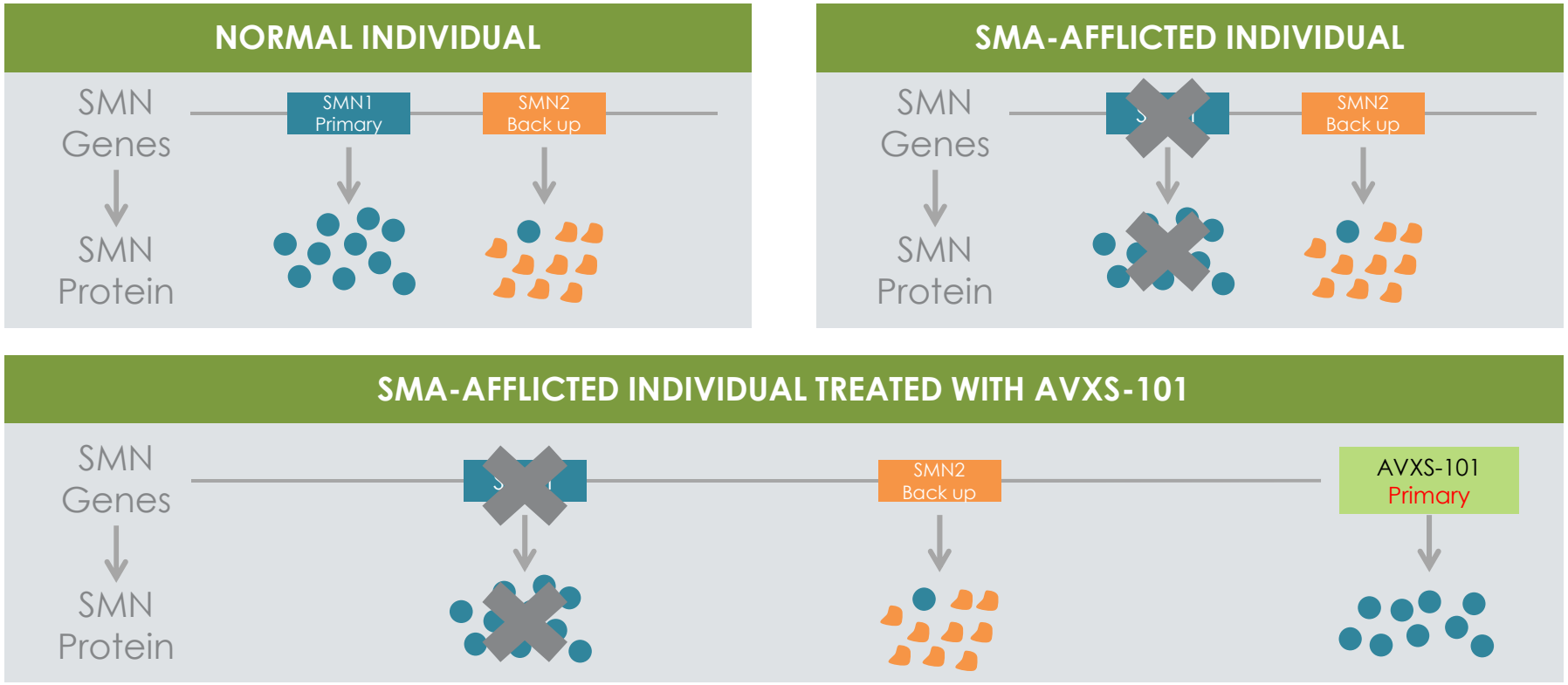
DESIGN

- Retrospective Study from large multi-center datasets (US and EU)
- Patients (n=33) have **genetically confirmed homozygous deletion of exon 7 in SMN1 gene**; categorized according to Dubowitz's decimal classification (confirmation of SMN1 status and clinical observations)
- Study visits at baseline, every 2-3 months until the age of 12 months, and every 6 months thereafter, when possible
- Hammersmith Infant Neurological Examination (HINE) used to assess intermediate steps leading to full achievement of milestones

CONCLUSIONS

- **Prolongation of survival with supportive care does not impact achievement of motor milestones** in SMA Type 1 infants
- SMA Type 1 infants with **symptom onset <6 months**:
  - **Will not reach any major motor milestones, such as sitting, crawling, standing, and walking**
  - Any early intermediate milestones in 1B patients will be quickly lost
- The **highest milestone achieved is seen in the child's first visit followed by a rapid decline**
- **Any improvement or achievement of milestones not usually achieved in a child with SMA Type 1** in a drug intervention trial **can be attributed to the drug** and not due to survival or enhanced standard of care

AVXS-101 Targets the Primary SMN Gene

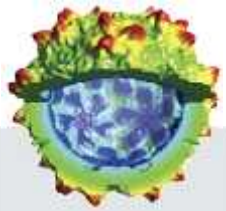


Our Solution: AVXS-101

An Innovative Treatment Approach for SMA

Gene therapy is the right approach for SMA: Monogenic mutation that drives the pathology

Recombinant AAV9 Capsid Shell



scAAV ITR	Continuous Promoter	Human SMN Transgene	scAAV ITR

KEY COMPONENTS	PURPOSE
Recombinant AAV9 Capsid Shell	• Ability to deliver across the blood brain barrier (BBB) and into the spinal cord - Avoids the need for intrathecal delivery when treating infants • Non-replicating virus does not modify the existing DNA of the patient.
scAAV ITR (Self-complementary DNA technology)	• Enables rapid onset of effect which is key in a quickly deteriorating population
Continuous Promoter	• Activates the transgene to allow for continuous and sustained SMN expression
Human SMN Transgene	• Full copy of a stable, functioning SMN gene that is introduced into the cell's nucleus

Rendering adapted from DiMattia et al. Structural Insight into the Unique Properties of Adeno-Associated Virus Serotype 9. J. *Virol*. June 2012.

Clinical Study Closeout – January 20, 2017

AVXS-101 PHASE 1 TRIAL OVERVIEW – SMA TYPE 1

Study Site
Nationwide Children's

Principal Investigator
Jerry R. Mendell, M.D.

Trial Design
Open-label, dose-escalation
scAAV9.CB.SMN

Route of Administration
One-time intravenous infusion through peripheral limb vein
Prednisolone 1 mg/kg 1 day Pre-GT

KEY ENROLLMENT CRITERIA

Inclusion

- 9 months of age / 6 months of age[1] and younger at day of vector infusion with SMA Type 1 as defined by the following features:
  - **Bi-allelic SMN1 gene deletion or point mutations**
    - **All enrolled patients carry bi-allelic SMN1 deletions, confirmed by independent laboratory**
  - **2 copies of SMN2**
  - **Onset of disease at birth to 6 months of age**
  - Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints

Exclusion

- Active viral infection (includes HIV or serology positive for hepatitis B or C)
- Use of invasive ventilatory support (tracheotomy)* or pulse oximetry <95% saturation
- Patients with Anti-AAV9 antibody titers >1:50 as determined by ELISA binding immunoassay
- Abnormal laboratory values considered to be clinically significant
- **Patients with the c.859G>C mutation in SMN2 exon 7 (predicted mild phenotype)[2]**

*Patients may be put on non-invasive ventilatory support (BiPAP) for <16 hours/day at discretion of their physician or study staff.
Clinicaltrials.gov Identifier = NCT02122952
[1] Inclusion criteria was 9 months of age and younger for the first nine patients. 6 months of age and younger for the last six patients.
[2] Exclusion criteria related to c.859G>C was confirmed for all patients by an independent laboratory.

OBJECTIVES

Primary

- Safety and Tolerability

Secondary

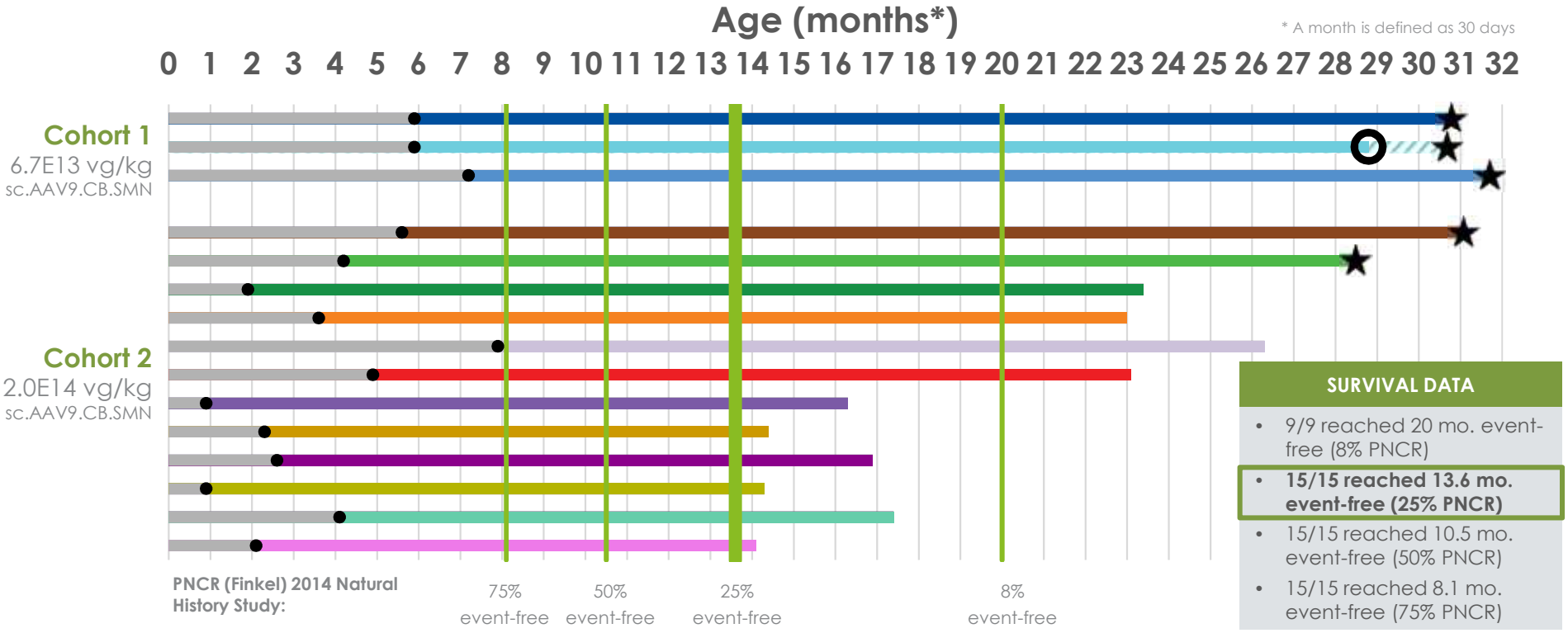
- **Time from birth until death or time to ≥16-hour ventilation continuously for ≥2 weeks** in the absence of an acute reversible illness or perioperatively
- **Video confirmed achievement of ability to sit unassisted***

***key developmental milestone achievements assessed and adjudicated by external independent reviewer**

Additional

- CHOP INTEND
- Bayley Motor Scales of Infant/Toddler development – Gross Motor

Event-Free Survival Data – January 20, 2017



SURVIVAL DATA

- 9/9 reached 20 mo. event-free (8% PNCR)
- **15/15 reached 13.6 mo. event-free (25% PNCR)**
- 15/15 reached 10.5 mo. event-free (50% PNCR)
- 15/15 reached 8.1 mo. event-free (75% PNCR)

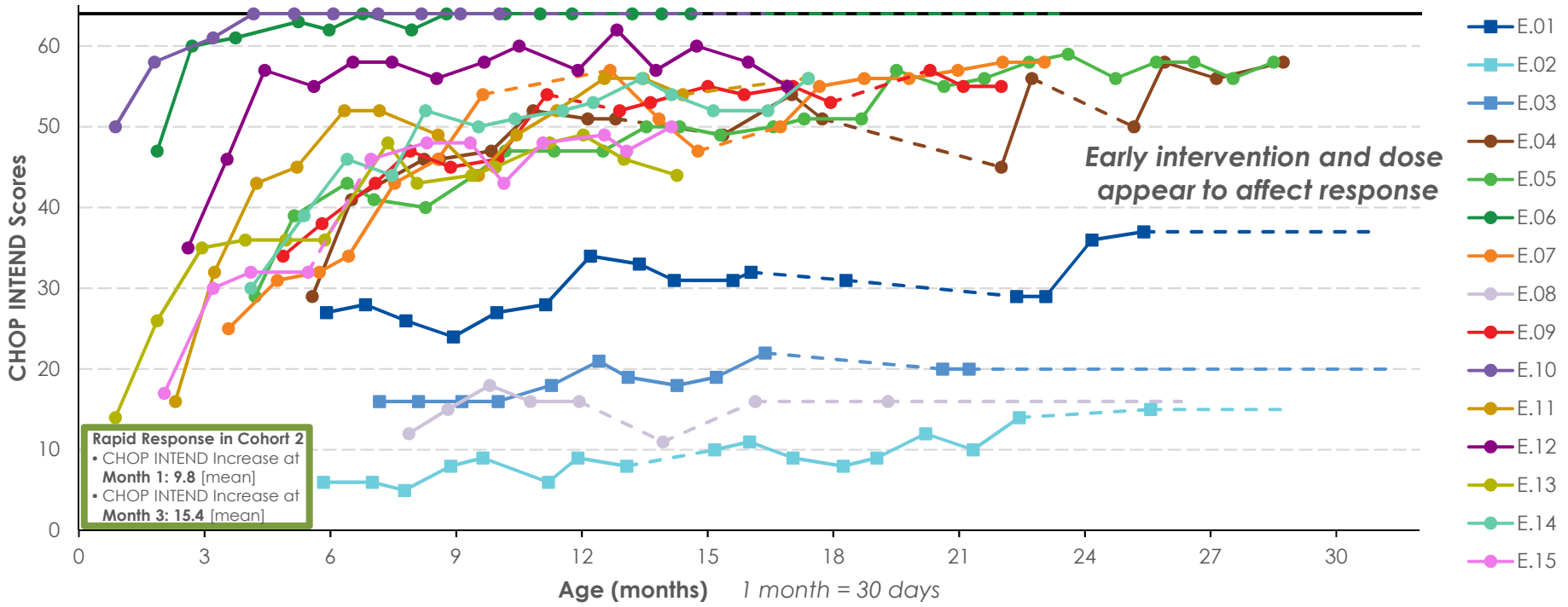
Age at Last Follow-up

Cohort 1*:	30.8 months (median)	30.4 months (mean)
Cohort 2*:	20.2 months (median)	20.7 months (mean)

**reflects age at Last Trial Visit or most recent pulmonary assessment, E.02's age at Pulmonary Event*

● Day of Gene Transfer ★ Last Trial Visit – Age Fixed ○ Pulmonary Event – Age Fixed

CHOP INTEND vs. Age – January 20, 2017



COHORT 1 (n=3)	COHORT 2 (n=12)
Baseline Age (months): 5.9 [median], 6.3 [mean]	Baseline Age (months): 3.1 [median], 3.4 [mean]
Current Age (months): 30.8 [median], 30.4 [mean]	Current Age (months): 20.2 [median], 20.7 [mean]
Mean CHOP INTEND Increase: 7.7 points	Mean CHOP INTEND Increase: 24.7 points

Dashed line denotes missed or partial CHOP-INTEND assessments 1 2

SMA Type 1 Children Typically Require Significant Nutritional and Respiratory Supportive Care By 12 Months Of Age

NATURAL HISTORY FOR SMA TYPE 1		
NUTRITIONAL SUPPORT	**RESPIRATORY SUPPORT**	**BULBAR MUSCLE FUNCTION**
• Nearly all Type 1 patients require nutritional support by 12 mos of age[1]	• Most Type 1 patients require respiratory support by 12 mos of age1	• Most patients are not able to swallow or speak effectively

COHORT 2 RECEIVING THE PROPOSED THERAPEUTIC DOSE OF AVXS-101		
NUTRITIONAL SUPPORT STATUS OF PROPOSED THERAPEUTIC DOSE COHORT	**RESPIRATORY SUPPORT STATUS OF PROPOSED THERAPEUTIC DOSE COHORT**	**BULBAR MUSCLE FUNCTION OF PROPOSED THERAPEUTIC DOSE COHORT**
• **6 of 7 (86%)** that did not require feeding support before dosing **continue without nutritional support**	• **7/10 (70%)** that did not require BiPAP support before dosing **continue without any BiPAP** • **No** children hospitalized for respiratory illnesses required a tracheostomy or prolonged invasive ventilation.	• **11/12 (92%) patients are feeding orally**, including 6 exclusively fed by mouth • **8/12 (67%) patients are able to speak**

1. Finkel et al. Observational Study of Spinal Muscular Atrophy Type I and Implications for Clinical Trials. *Neurology*. August 2014.

Safety Data – January 20, 2017

AVXS-101 appears to have a favorable safety profile and appears to be generally well-tolerated in patients studied to date

SAFETY AND TOLERABILITY OBSERVATIONS

- **No new treatment-related SAEs or AEs observed**
- As previously reported, a total of **5 treatment-related AEs in 4 patients** have been reported following monitoring and source verification
  - Treatment-related SAEs and AEs were **clinically asymptomatic** elevated liver function enzymes (LFEs) assessed under CTCAE on the basis on laboratory values and **resolved with prednisolone treatment***
    - 2 were SAEs experienced by 2 patients
    - 3 were AEs experienced by 2 patients
- **A total 256 AEs** (5 treatment-related AEs and **251 non-treatment related AEs**) have been reported following monitoring and source verification
  - 52 SAEs and 204 non-serious AEs
  - 65 AEs have occurred since September 15, 2016
    - 10 disease-related SAEs in 3 patients have occurred since September 15, 2016

*No drug-induced liver injury (DILI) as defined by Hy's Law

Children with SMA Type 1 Never Sit Unassisted

The Natural History of SMA Type 1 is marked by the inability to achieve or maintain developmental milestones

DISEASE CHARACTERISTICS

- Disease onset <6 months
- Hypotonia and weakness
- Bulbar muscle weakness
- Difficulty breathing and swallowing
- Inexorable progression to nutritional failure
- Inexorable progression to respiratory failure

DEVELOPMENTAL MILESTONE PROGNOSIS

- Progressive decline in motor function soon after birth
- Rapid loss of any early milestones (e.g. head control, hands to mouth)
- Will never be able to sit unassisted
- Will never be able to roll
- Will never be able to crawl, stand, or walk

Motor Milestone Achievements in Cohort 2

Cohort 2 2.0e14 vg/kg	Age at GT (mos)	Motor Milestone Achievement							
		Brings hand to mouth	Head control	Partial Roll[a]	Roll[b]	Sitting with assistance	Sitting Unassisted		
							≥ 5 seconds[c]	≥ 10 seconds[d]	≥ 30 seconds[e]
E.04	6	a	a	a	a	a	a		
E.05	4	a	a	a	a	a	a	a	a
E.06	2	a	a	a	a	a	a	a	a
E.07	4	a	a	a	a	a	a	a	
E.08	8	a							
E.09	5	a	a	a	a	a	a	a	a
E.10	1	a	a	a	a	a	a	a	a
E.11	2	a	a	a	a	a	a	O	O
E.12	3	a	a	a	a	a	a	a	a
E.13	1	a	a			a	a	a	O
E.14	4	a	a	a	a	a	O	O	O
E.15	2	a	a			a			

Two children crawl, pull to a stand, and stand and walk independently.

*Milestone achievements as of January 20, 2017, except those indicated by O, which were achieved after the January 20, 2017 cutoff.

a. Bayley Scales of Infant and Toddler Development, item #20, rolls a minimum 180° from back in only one direction.
b. Bayley Scales of Infant and Toddler Development, item #20, rolls a minimum 180° from back to both left and right.
c. Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 in the Bayley Scales of Infant and Toddler Development – gross motor subtest and surpasses the three second count used as a basis for sitting (test item 1) in the Hammersmith Functional Motor Scale – Expanded for SMA (HFMSE).
d. Sitting unassisted for ≥10 seconds is in accordance with the criteria in the World Health Organization – MultiCentre Growth Reference Study.
e. Sitting unassisted for ≥30 seconds defines functional independent sitting and is in accordance with the criteria of item 26 in the Bayley Scales of Infant and Toddler Development – gross motor subtest.

Cohort 2 Achieved Motor Milestones Not Seen in the Natural History of SMA Type 1

CSF Delivery of AAV9-mediated Gene Therapy for SMA

A Dose-response Study in Mice and Nonhuman Primates data regarding a dose-response study for the CSF delivery of AVXS-101
Brian Kaspar, PhD, Senior Vice President and Chief Scientific Officer

DESIGN

- AVXS-101 was delivered via Intracerebroventricular (ICV) injection in the mouse model for SMA (SMND7 mouse) to evaluate phenotypic rescue
- The scAAV9-Green Fluorescent Protein (scAAV9-GFP) was used to evaluate transgene/AAV9-biodistribution and was delivered via ICV injection in mice and intrathecal sacral infusion incynomolgus macaques

CONCLUSIONS

- **ICV delivery of AVXS-101 in mice demonstrate improved survival in the SMA mouse**
- **CSF delivery of gene therapy utilizing the AAV9 viral vector combined with tilting (Trendelenburg position) allows widespread transgene transduction in the brain, brain stem, cerebellum and upper spinal cord segments of nonhuman primates**
- **Tilting resulted in an increase in the transduction of motor neurons in the brain stem, cerebellum and upper spinal cord segments**
- **These data offer insight into vector distribution and its correlation with transgene expression and provides guidance for future AAV9-based clinical trials in SMA, as well as other neurodegenerative disorders**

Experience with Preexisting Anti-AAV9 Antibody in the SMA Type 1 Population

AVXS-101 Phase 1 Gene Therapy Clinical Trial in SMA Type 1: Experience with Preexisting Anti-AAV9 Antibody in the SMA1 Population

Douglas Sproule, MD, Vice President of Clinical Development and Medical Affairs

CONCLUSIONS

- **Most patients (13/16) did not exhibit elevated antibody titers prior to gene replacement therapy**
  - Consistent with the literature, AAV9 antibody seropositivity under the age of 10 appears rare
  - When positive in young children, titers are typically low
  - AAV9 seropositivity increases after age 40, especially in women
- **2 of 3 patients with initial titers >1:50 were retested and able to participate in the clinical trial**
  - In the uncommon instance where both mother and child expressed antibodies against AAV9, breast-feeding was discontinued
  - A decrease in antibody titers to 1:50 or less was seen on retesting
- **Data suggest pre-existing antibodies to AAV9 are quite uncommon in the pediatric population, and will not impact use of gene therapy for the vast majority of SMA Type 1 patients**

Correlation between CHOP-INTEND and Motor Milestone Achievements

AVXS-101 Phase 1 Gene Therapy Clinical Trial in SMA Type 1: Correlation between CHOP-INTEND & Motor Milestone Achievements

Linda Lowes, PT, PhD, Director of Clinical Therapies Research and a member of the Center for Gene Therapy at the Research Institute of Nationwide Children's Hospital

CONCLUSIONS

- **Regardless of age at dosing and baseline motor function, most of Cohort 2 has achieved the ability to sit unassisted**
- **In Cohort 2 (proposed therapeutic dose), 11/12 patients have surpassed a CHOP-INTEND score of 40, 10/12 have surpassed a score of 50, and 2/12 have achieved the max score**
  - Natural History studies documented that by 6 months of age, almost no SMA1 child achieves a CHOP-INTEND Score of 40
- **Rapid improvements in CHOP-INTEND scores were observed in Cohort 2 at 1 month (9.8 points) and 3 months (15.4 points) post-dosing**
- **Most patients (9/12) in Cohort 2 are sitting unassisted**
  - Untreated children with SMA1 do not achieve major motor milestones, including sitting unassisted
- **The degree of treatment outcomes appear to be influenced by age at dosing and baseline motor function**
  - Two children (proposed therapeutic dose) early in age and early in disease progression achieved sitting unassisted within the range of general developmental timelines
  - These data highlight the potential impact of expeditious treatment upon diagnosis and emphasize the need for newborn screening in SMA

Summary: AVXS-101 Phase 1 Study in SMA Type 1

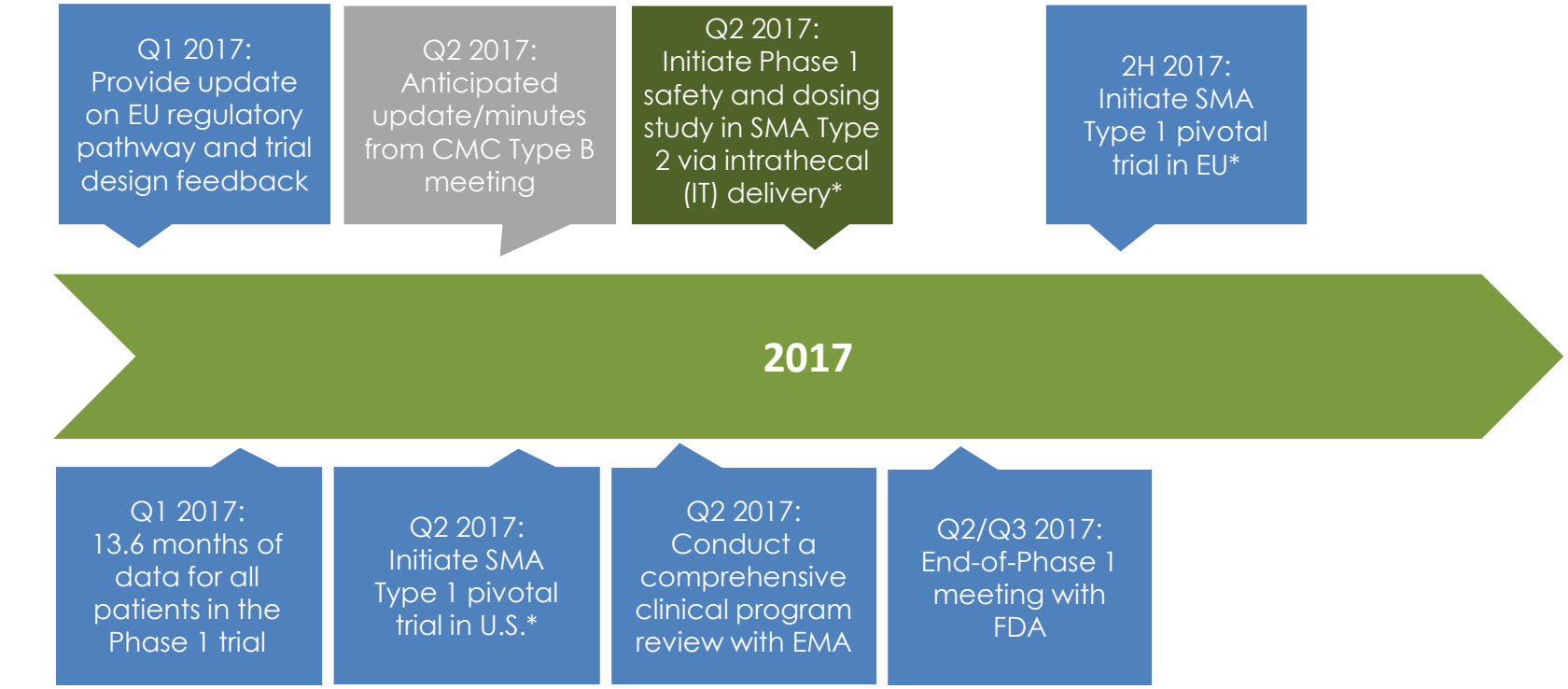
- **All patients are alive and ≥15 mos of age (6 are >2 years old)**
- **All patients reached 13.6 months of age free of permanent ventilation**
  - The published natural history shows that only 25% of SMA Type 1 patients survive to 13.6 months of age without permanent ventilation

- **9 of 12 patients in Cohort 2 sat unassisted and 5 of 12 sat unassisted for ≥30 sec**
  - **Data Update (post-Jan 20): 10 of 12 patients sat unassisted and 8 of 12 sat unassisted for ≥30 sec**
- **11 of 12 patients in Cohort 2 achieved head control and sitting with support**
- **2 patients in Cohort 2 crawled, stood and walked independently**
  - The published natural history shows that no SMA Type 1 patients achieve any major motor milestones

- **11 of 12 patients feed orally, including 6 exclusively fed by mouth**
- **7 of 10 patients that did not require BiPAP support before dosing continue without <u>any</u> BiPAP**
- **8 of 12 patients in Cohort 2 are speaking**
  - The published natural history shows that most SMA Type 1 patients require nutritional support and most require respiratory support by 12 months of age

- **AVXS-101 appears to have a favorable safety profile and to be generally well tolerated**
  - Clinically asymptomatic elevated liver enzymes were the only treatment-related SAEs/AEs and were managed with a prednisolone regimen

Company Milestones



*Assumes positive outcome of CMC Type B meeting

Type 1 Program Type 2 Program Manufacturing

Thank You