

AVXS-101 Clinical Update

Including Motor Milestones as Presented at
the World Muscle Society, October 8, 2016

October 10, 2016



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 and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available 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.

Overview of SMA

SMA is a devastating orphan disease – with no current FDA-approved treatments – 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
- Current treatments limited to palliative care

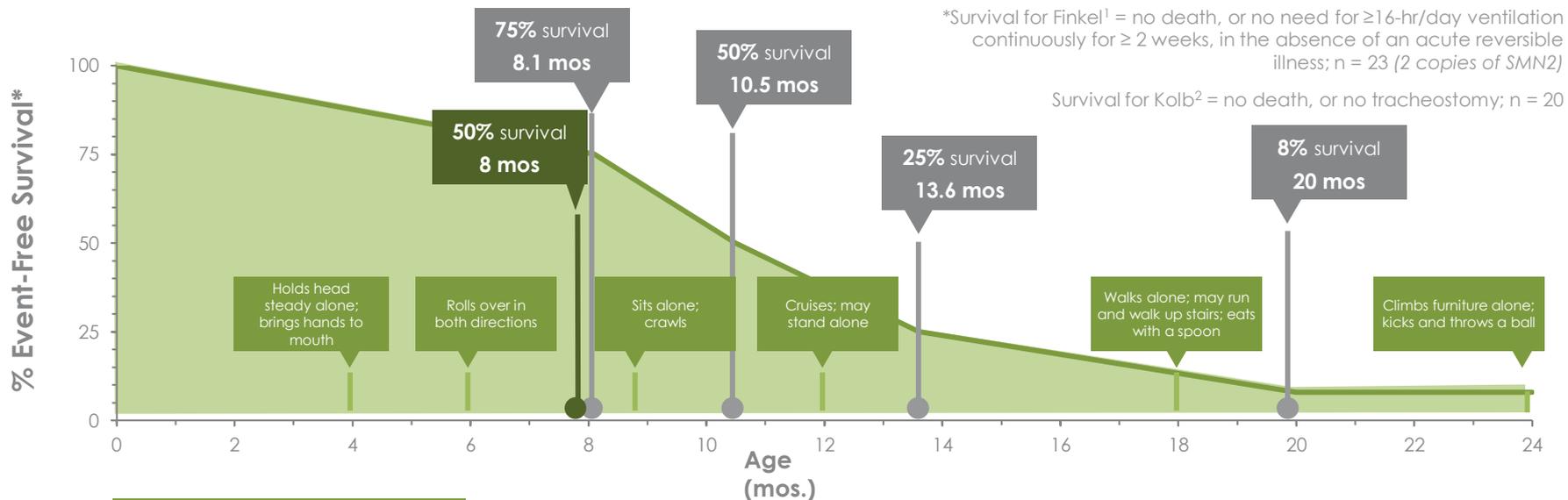
SMA Types: A Devastating Disease

| | 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 | <ul style="list-style-type: none"> • Will never be able to sit without support • Difficulty breathing & swallowing • Can't crawl/will never walk | <ul style="list-style-type: none"> • Will never be able to walk or stand without support | <ul style="list-style-type: none"> • Stand alone and walk but may lose ability to walk in 30s-40s | <ul style="list-style-type: none"> • Stand alone and walk but may lose ability to walk in 30s-40s (Same as Type 3) |
| Survival | <ul style="list-style-type: none"> • <10% Event free* by two years of age | <ul style="list-style-type: none"> • 68% alive at age 25 | <ul style="list-style-type: none"> • Normal | <ul style="list-style-type: none"> • 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 Finkel¹ = 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 Kolb² = 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

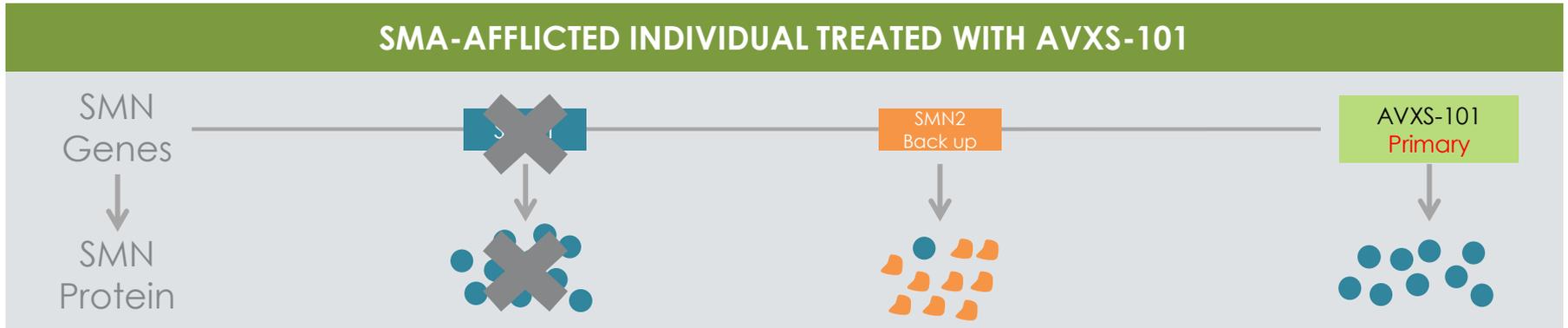
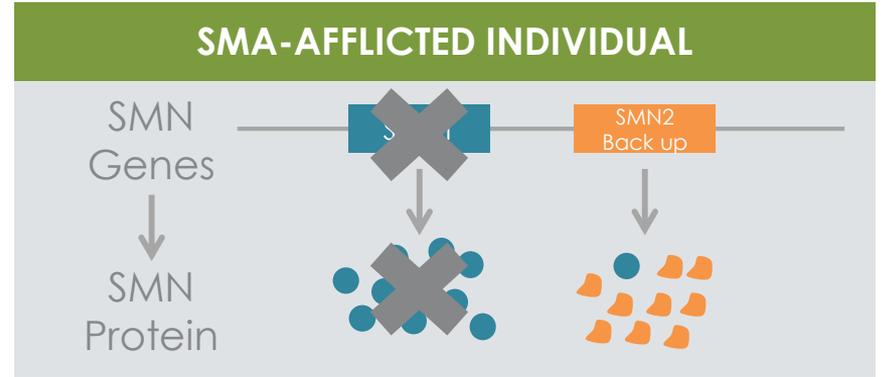
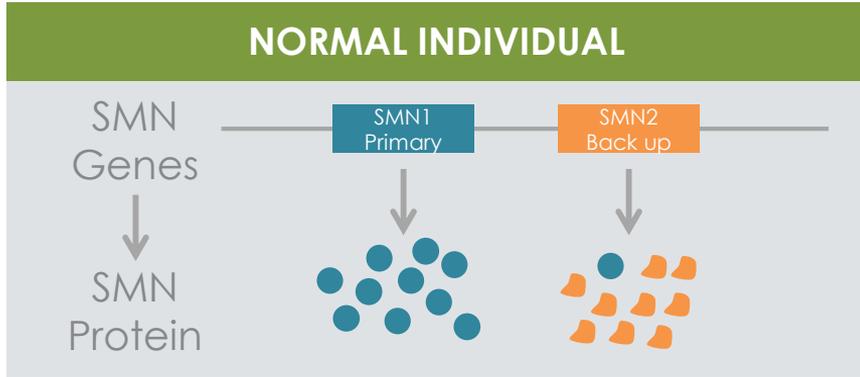
loss of motor function:

- 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 Finkel¹
- SMA Type 1 survival rate per Kolb²

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

AVXS-101 Targets the Primary SMN Gene



● Functional SMN Protein

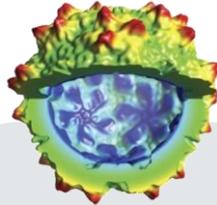
● Not-functional SMN Protein

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

Recombinant AAV9 Capsid Shell

scAAV ITR (Self-complementary DNA technology)

Continuous Promoter

Human SMN Transgene

PURPOSE

- 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.
- Enables rapid onset of effect which is key in a quickly deteriorating population
- Activates the transgene to allow for continuous and sustained SMN expression
- 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.

Phase 1 Trial Design

TRIAL OVERVIEW



Principal Investigator
Jerry R. Mendell, M.D.

Trial Design
Open-label, dose-escalation

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 age¹ and younger at day of vector infusion with SMA Type 1 as defined by the following features:

- **Bi-allelic SMN1 gene mutations (deletion or point mutations)**
- **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 with positive pressure)* 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 for the last six patients.

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**

Additional

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

Exploratory

- Ability Captured Through Interactive Video Evaluation-mini (**ACTIVE-mini**)
- Comp Motor Action Pot (**CMAP**)
- Motor Unit Number (**MUNE**)
- Electrical Impedance Myography (**EIM**)

Event-Free Survival Data – Ongoing Phase 1 Trial

Age (months*)

* A month is defined as 30 days

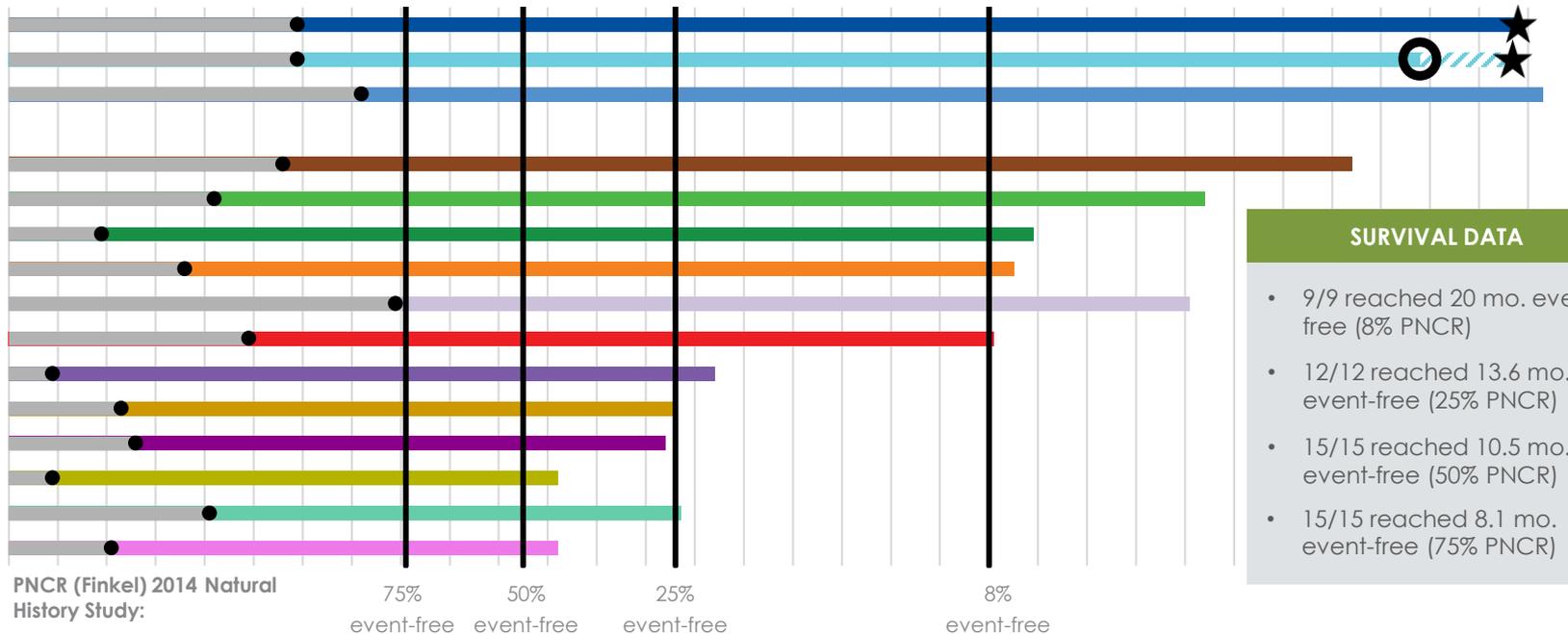
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Cohort 1

6.7E13 vg/kg

Cohort 2

2.0E14 vg/kg



SURVIVAL DATA

- 9/9 reached 20 mo. event-free (8% PNCr)
- 12/12 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)

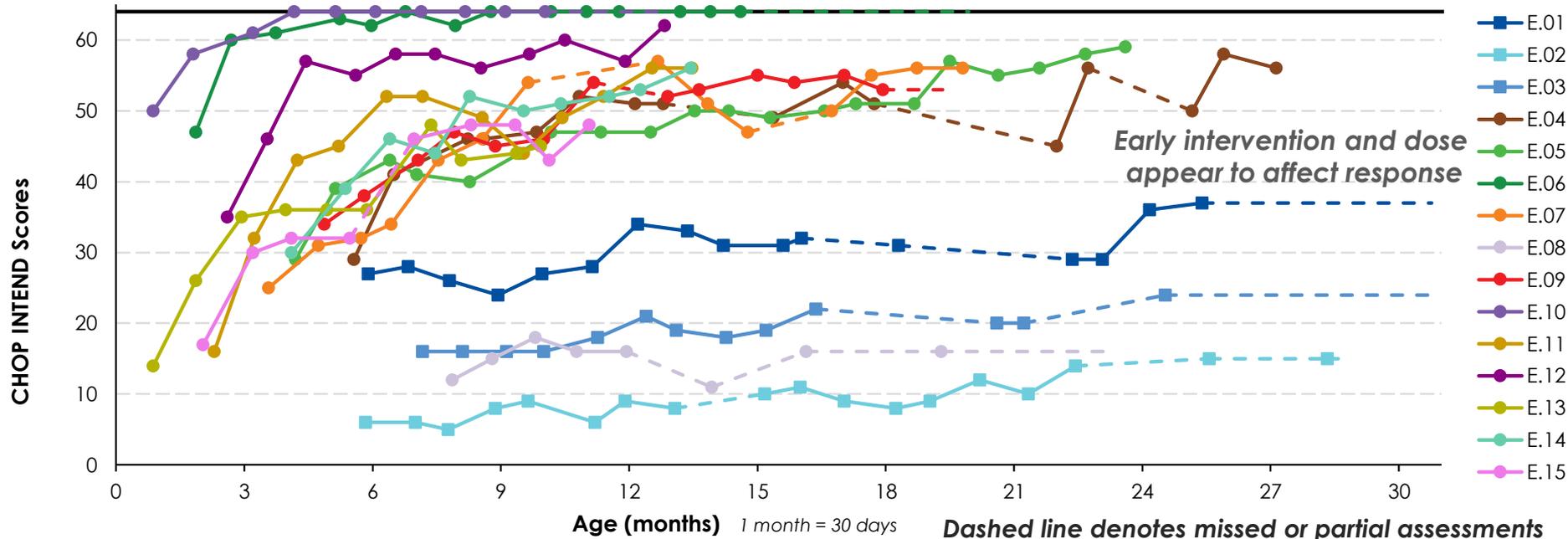
Age at Last Follow-up

| | | |
|------------|----------------------|--------------------|
| Cohort 1*: | 30.8 months (median) | 30.3 months (mean) |
| Cohort 2: | 17.3 months (median) | 17.9 months (mean) |

*reflects E.01's age at Last Trial Visit, E.02's age at Pulmonary Event

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

CHOP INTEND vs. Age



COHORT 1 (n=3)

Baseline Age (months): 5.9 [median], 6.3 [mean]
 Current Age* (months): 30.8 [median], 30.3 [mean]
 Mean CHOP INTEND Increase: 9.0 points

COHORT 2 (n=12)

Baseline Age (months): 3.1 [median], 3.4 [mean]
 Current Age (months): 17.3 [median], 17.9 [mean]
 Mean CHOP INTEND Increase**: 24.8 points

* reflects E.01's age at Last Trial Visit, E.02's age at Pulmonary Event

** Calculation includes 2 patients who achieved max score



Safety Data – Ongoing Phase 1 Trial

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 observed to date
 - Treatment-related SAEs and AEs were **clinically asymptomatic** elevated liver function enzymes (LFEs) **resolved with prednisolone treatment***
 - 2 were SAEs experienced by 2 patients (SAEs defined on the basis of laboratory tests showing elevated LFEs)
 - 3 were AEs experienced by 2 patients
- A total 118 AEs (34 SAEs and 84 non-serious AEs) have been reported

*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 Achievement in Proposed Therapeutic Dose (Interim Data)

| Cohort 2 2.0e14 vg/kg | Age at GT (mos) | Motor Milestone Achievement | | | | | Sitting unassisted |
|-----------------------------|--------------------|-----------------------------|--------------|-------------------------|--------------------------|----------------------------|-----------------------|
| | | Brings hand to mouth | Head control | Rolls over (partial) | Rolls over (complete) | Sitting with assistance | |
| E.04 | 6 | ✓ | ✓ | ✓ | | ✓ | ✓ |
| E.05 | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E.06 | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E.07 | 4 | ✓ | ✓ | ✓ | | ✓ | ✓ |
| E.08 | 8 | ✓ | | | | | |
| E.09 | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E.10 | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E.11 | 2 | ✓ | ✓ | ✓ | | ✓ | ✓ |
| E.12 | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E.13 | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | |
| E.14 | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | |
| E.15 | 2 | ✓ | ✓ | | | ✓ | |

- 7 patients are feeding themselves
- 5 patients are speaking (1 bilingual)
- 2 patients are crawling
- 4 patients are standing with support
- 2 patients are standing alone
- 2 patients are walking independently

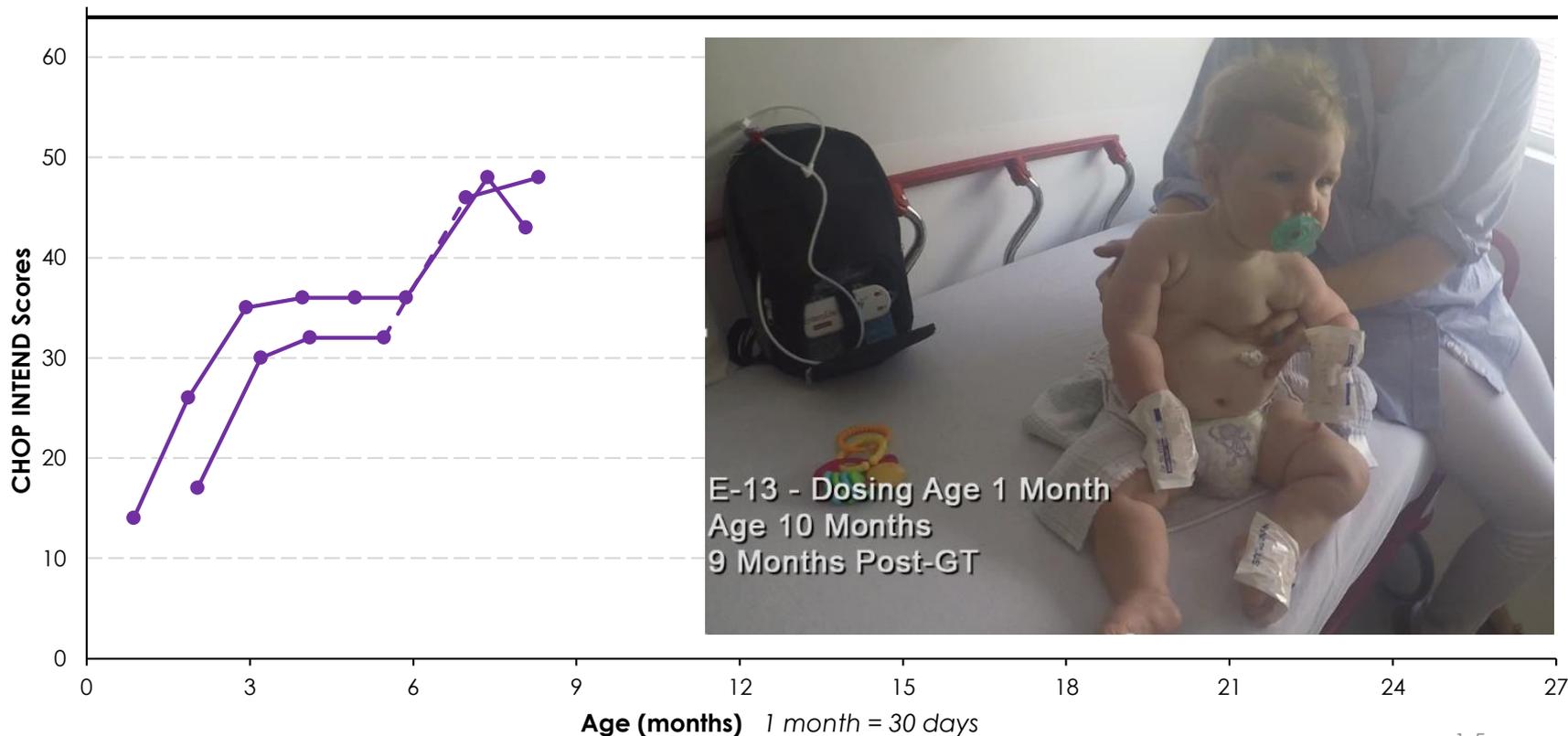
E.11 sitting unassisted and standing with support, E.10 walking independently, E.12 standing with support, and E.15 feeding self were confirmed with video evidence after September 15, 2016.

Two-thirds of Patients in Cohort 2 are Sitting Unassisted

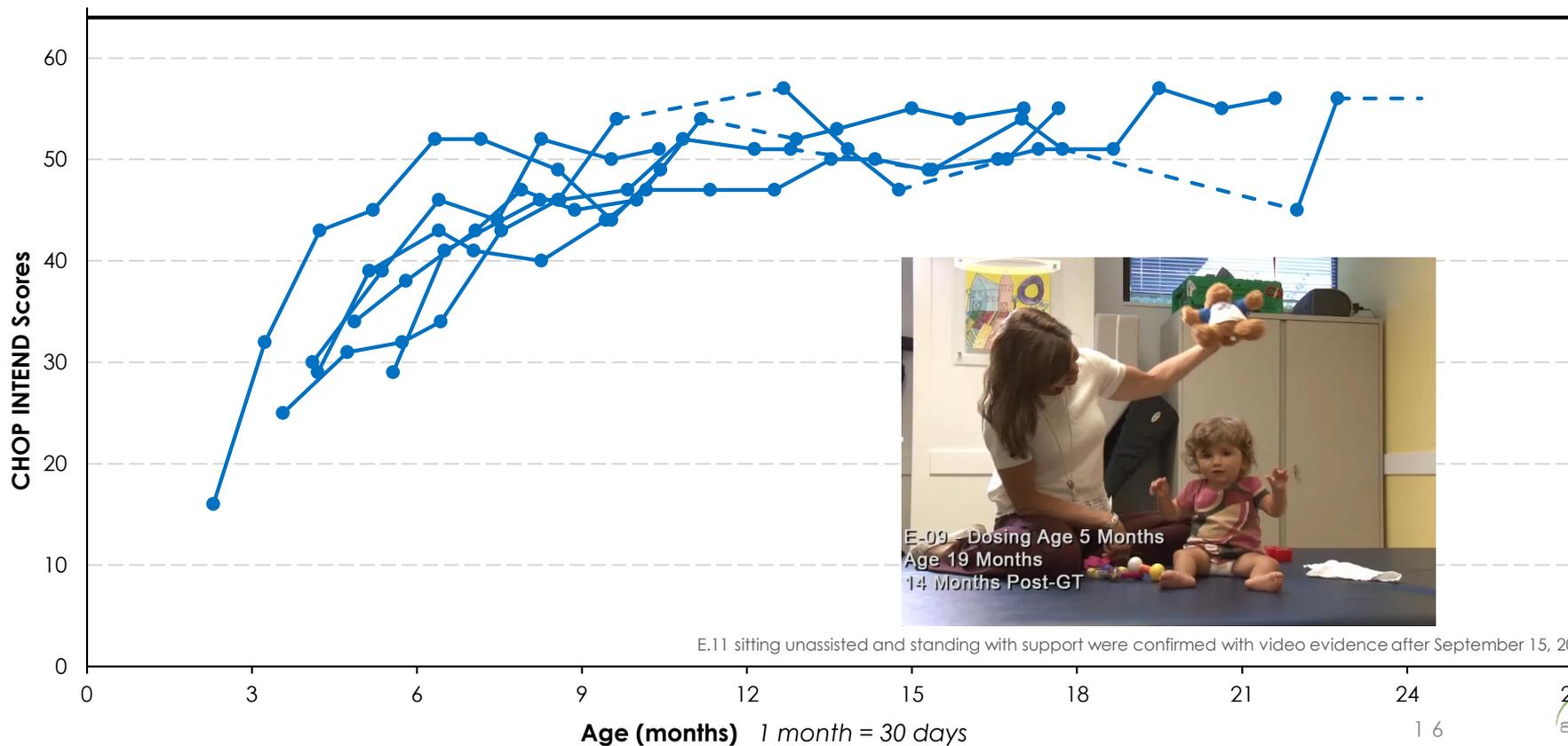
Inability to Sit is the Hallmark Motor Milestone of SMA Type 1



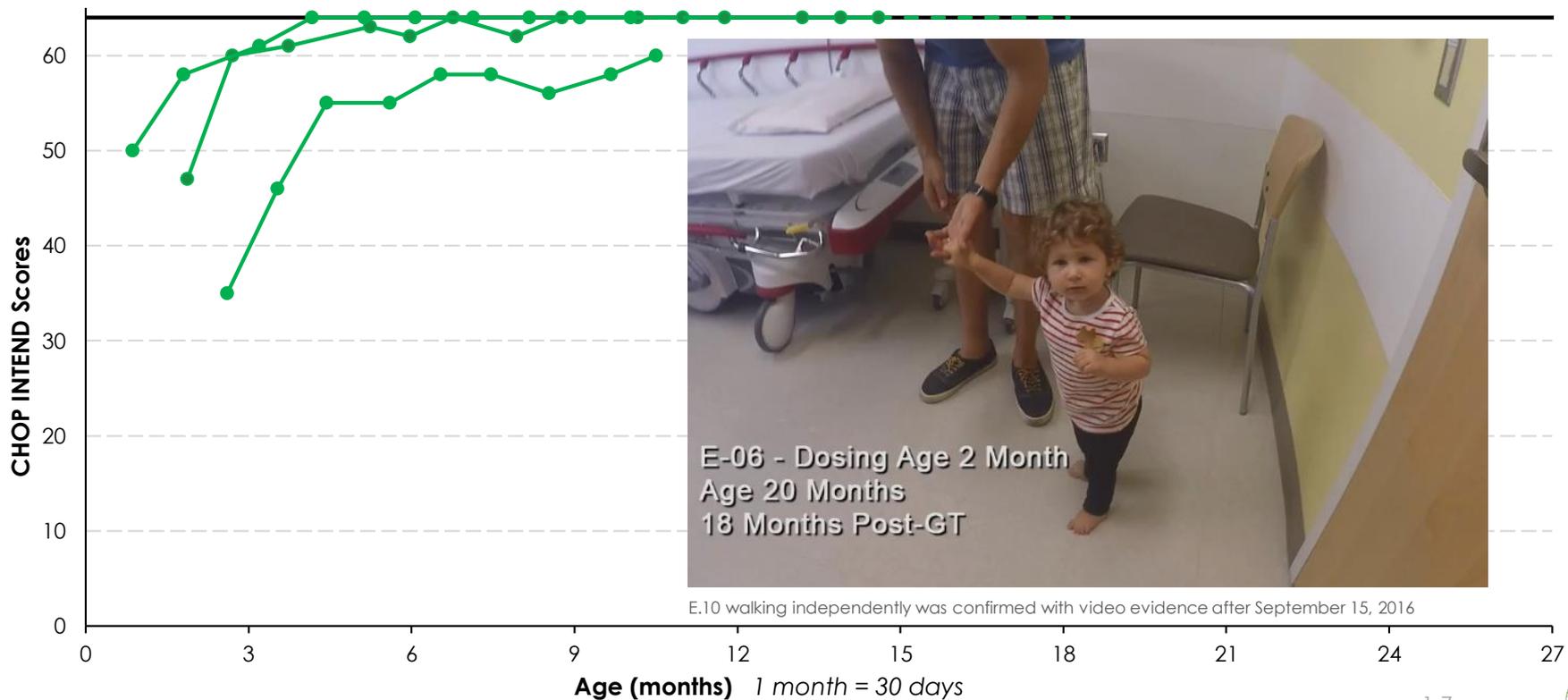
Patients with CHOP INTEND ≥ 40



Patients with CHOP INTEND ≥ 50



Patients with CHOP INTEND ≥ 60

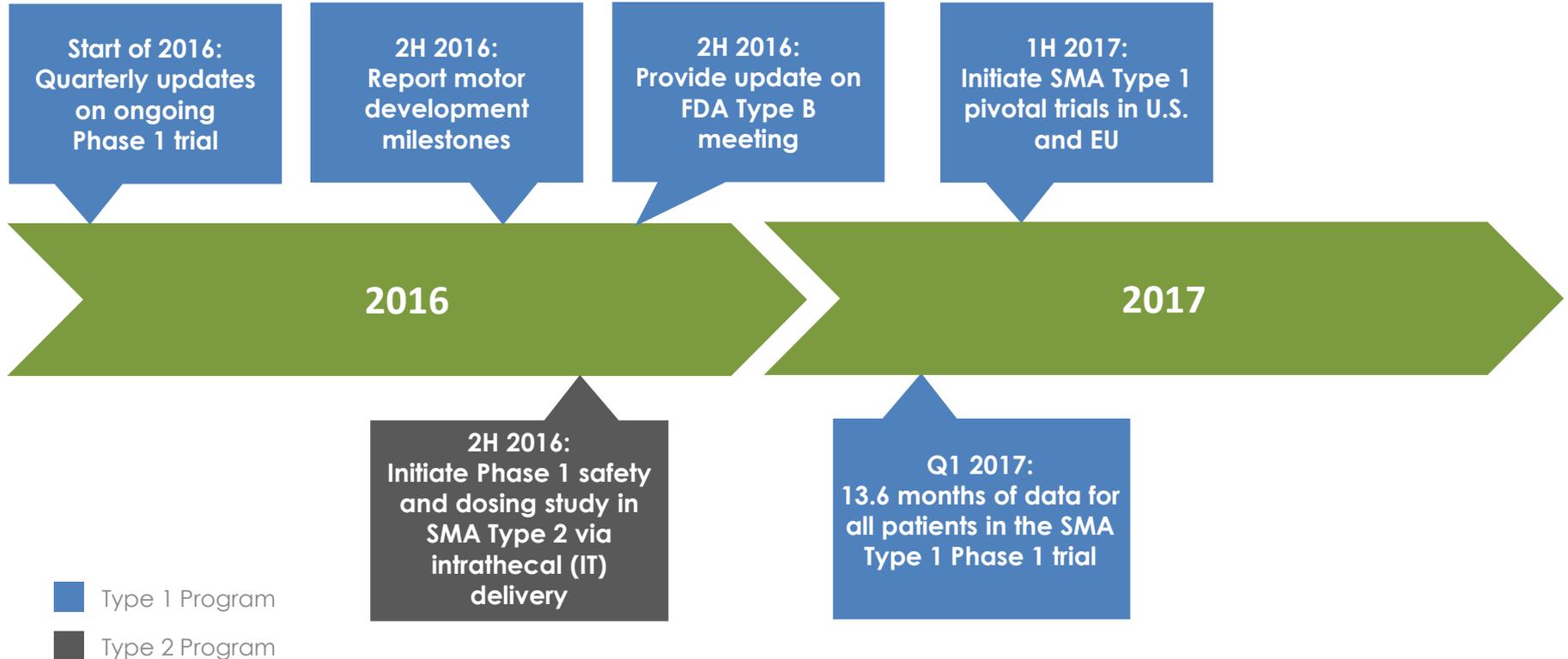


Summary: Ongoing Phase 1 Data

- AVXS-101 appears to have a favorable safety profile and appears to be generally well tolerated
 - A total 118 AEs (34 SAEs and 84 non-serious AEs) have been reported
 - No additional treatment-related AEs have been observed beyond the previously reported five elevated LFEs experienced by 4 patients, two of which were Grade 4 SAEs. All were resolved following prednisolone treatment.
- Significant and sustained increases in motor function appear to be dose-dependent
 - Cohort 1 (n=3) has increased an average of 9.0 points from an average baseline CHOP INTEND score of 16.3 points.
 - Cohort 2 (n=12) has increased an average of 24.8 points from an average baseline CHOP INTEND score of 28.2 points.
 - Finkel 2014 observed no SMA Type 1 patients scoring above 40 points (1 transient exception)
 - 11 out of 12 patients in Cohort 2 reached CHOP INTEND ≥ 40 points
 - 9 out of 12 patients in Cohort 2 reached CHOP INTEND ≥ 50 points
 - 3 out of 12 patients in Cohort 2 reached CHOP INTEND ≥ 60 points
- All patients in Cohort 2 (except E.08) have achieved at least one motor development milestone
 - 11 out of 12 patients can sit with assistance and 8 out of 12 can sit unassisted[†]
 - 7 of 12 patients can roll over completely; 7 of 12 are feeding themselves; 5 of 12 are speaking; 4 of 12 are standing with support
 - 2 patients who are now walking independently[†] have also each achieved crawling, standing with support, standing alone, and walking with support
- AVXS-101 administration has resulted in marked and positive impact on the disease course of SMA Type 1.
 - The median age at last follow-up of all 15 patients is 20.5 months, with the oldest patient at 31.3 months of age.* One patient in Cohort 1 reached Pulmonary Event at 28.8 months of age but has since returned below the 16 hrs/day event threshold.
 - All patients in Cohort 2 are alive and event-free. The median age at last follow-up for Cohort 2 is 17.3 months, with the oldest patient at 27.4 months of age.

*E.01's age is calculated as of Last Trial Visit (May 2016); E.02's age is calculated at Pulmonary Event (July 2016)
†A patient in this group was confirmed to have achieved this milestone with video evidence after Sept 15, 2016

Clinical Development Milestones



Question and Answer Session

October 10, 2016



Thank You

