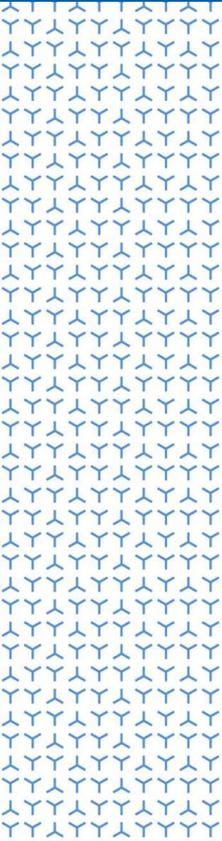




AveXis, a Novartis Company



# Zolgensma<sup>®</sup> clinical data

American Academy of Neurology Annual Meeting  
May 8, 2019



# Disclaimer

This presentation contains forward-looking statements, including "forward-looking statements" within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "expected," "will," "planned," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Zolgensma, or regarding potential future revenues from this product. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Zolgensma will be submitted or approved in any market, or at any particular time. Nor can there be any guarantee that Zolgensma will be commercially successful in the future. In particular, our expectations regarding this product could be affected by, among other things, regulatory actions or delays or government regulation generally; the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data, as well as the planned clinical trials of these products, and the length of time such planned clinical trials may take; the particular prescribing preferences of physicians and patients, including uncertainties as to whether physicians and patients would adopt Zolgensma into their treatment regimens; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; general economic and industry conditions, including the effects of the persistently weak economic and financial environment in many countries; safety, quality or manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this presentation as of this date and does not undertake any obligation to update any forward-looking statements contained in this presentation as a result of new information, future events or otherwise.

# Introduction to our speakers



## **Paul Hudson, CEO, Novartis Pharmaceuticals**

Paul Hudson has been CEO of Novartis Pharmaceuticals since 2016. He is a member of the Executive Committee of Novartis. Mr. Hudson holds a degree in economics from Manchester Metropolitan University (MMU) in the UK and a diploma in marketing from the Chartered Institute of Marketing in the UK. In 2018, he was awarded an honorary doctorate in business administration from MMU. He is a board member of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and vice chair of the Innovation Board Sponsored Committee of EFPIA.



## **David Lennon, Ph.D., President, AveXis**

Dr. Lennon has served as the president of AveXis since June 2018. Since then, he has led the organization in its mission to bring gene therapy to patients and families devastated by rare and life-threatening neurological genetic diseases, starting with the company's lead proprietary gene replacement therapy candidate for spinal muscular atrophy, Zolgensma®. Dr. Lennon has been with Novartis since 2005, serving as oncology general manager, Japan, overseeing the company's extensive portfolio in cancer, including hematology, solid tumors and cell and gene therapies. Prior to that, he served as vice president, US solid tumors franchise.



## **Olga Santiago, M.D., Chief Medical Officer, AveXis**

Dr. Santiago has served as the chief medical officer for AveXis since July 2018. Since joining the team, she has championed the clinical development and medical affairs efforts for Zolgensma® and the broader gene therapy pipeline. Before joining the AveXis team, Dr. Santiago held multiple positions at Novartis since 2006, most recently serving as special unit head of global drug development management, where she was responsible for leading a team accountable for aligning strategy across immunology, cardiovascular and oncology disease areas.

# AAN data demonstrate efficacy of Zolgensma® across broad spectrum of SMA

## Presymptomatic



Ph 3, open-label, single-arm, multi-center trial to evaluate safety and efficacy of IV Zolgensma® in pre-symptomatic **SMA patients with 2 or 3 copies of SMN2 <6 weeks**

## Type 2



Ph 1, open-label, dose-comparison, multi-center trial to evaluate safety and tolerability of intrathecal (IT) Zolgensma® in **SMA Type 2 patients 6 months – 5 years**

## Type 1



Ph 3, open-label, single-arm, single-dose, multi-center trial to evaluate efficacy and safety of IV Zolgensma® in **SMA Type 1 patients <6 months**

## START

Long-term follow-up

Voluntary, ongoing, observational, long-term follow up study in patients from the Ph 1 open-label, single-site trial to evaluate safety and efficacy of IV Zolgensma® in **SMA Type 1 patients <6 months**

# SMA is a rare genetic disease that leads to rapid and irreversible loss of motor neurons, affecting muscle functions

Spinal muscular atrophy (SMA) is caused by a lack of a functional survival motor neuron (*SMN1*) gene<sup>1</sup>  
Severity varies by type and corresponds to the number of copies of the back-up gene (*SMN2*)<sup>2</sup>

## Presymptomatic

Degeneration and loss of motor neurons start shortly before birth and escalates quickly

It is imperative to diagnose SMA and **begin treatment as early as possible** to halt disease progression<sup>3</sup>

## Type 1 (60%)<sup>1,4</sup> 1-2 copies of *SMN2*

**>95% motor neuron loss by 6 months of age<sup>1</sup>**

90% of babies with untreated Type 1 need **permanent breathing support or die by their second birthdays<sup>5</sup>**

## Type 2 (30%)<sup>1,4</sup> 3-4 copies of *SMN2*

Symptoms are disabling and appear between **six and 18 months of age<sup>6</sup>**

**More than 30% will die by age 25<sup>7</sup>**

## Type 3 (10%)<sup>1,4</sup> 3-4 copies of *SMN2*

Symptoms typically appear in **early childhood to early adulthood<sup>6</sup>**

They may **lose the ability to stand or walk without support<sup>6</sup>**

1. Finkel RS, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014;83(9):810-7. 2. Lorson CL, et al. Spinal muscular atrophy: mechanisms and therapeutic strategies. *Hum Mol Genet*. 2010; 19(R1): R111-8. 3. Soler-Botija C, et al. *Brain*. 2002;125(7):1624-1634. 4. Ogino S, et al. *American journal of medical genetics*. 2002;110(4):301-307. 5. Anderton RS and Mastaglia FL. Advances and challenges in developing a therapy for spinal muscular atrophy. *Expert Rev Neurother*. 2015;15(8):895-908. 6. Farrar MA, et al. Emerging therapies and challenges in spinal muscular atrophy. *Ann Neurol*. 2017;81(3):355-368. 7. Darras BT, Finkel RS Spinal Muscular Atrophy. Chapter 25 - Natural History of Spinal Muscular Atrophy. October 2016.

The brand name Zolgensma<sup>®</sup> has been provisionally approved by the FDA for the investigational product AVXS-101 (onasemnogene abeparvovec-xioi), but the product itself has not received marketing authorization or BLA approval from any regulatory authorities.



# Zolgensma<sup>®</sup> is a one-time therapy that addresses the genetic root cause of SMA



Provides a functional copy of the human SMN gene to halt disease progression through SMN protein expression<sup>1</sup>



Replaces the function of the missing or defective *SMN1* gene, potentially making it an appropriate foundational therapy for SMA<sup>2</sup>

x1

Delivered as a single, one-time dose designed to provide long-term benefit



Administration may provide reduced burden on the caregiver compared to current clinical practice



Clinically transformative impact, showing prolonged survival and achievement of motor milestones never seen in natural history of disease<sup>1,3,4,5</sup>

1. Mendell JR, et al. New Eng J Med. 2017;377(18):1713-1722. 2. Farrar MA, et al. Ann Neurol. 2017;81(3):355-368. 3. Scutiz M, et al. AVXS-101 Gene-Replacement Therapy (GRT) in Presymptomatic Spinal Muscular Atrophy (SMA): Study Update. May 2019. 4. Finkel R, et al. Phase 1 Study of Intrathecal Administration of AVXS-101 Gene-Replacement Therapy (GRT) for Spinal Muscular Atrophy Type 2 (SMA2) (STRONG). May 2019 5. Day J, et al. AVXS-101 Gene-Replacement Therapy (GRT) for Spinal Muscular Atrophy Type 1 (SMA1): Pivotal Phase 3 Study (STR1VE) Update. May 2019.

With adoption of newborn screening, all incident SMA will be identified at birth – goal for treatment becomes outcomes closer to normal development

## Phase 3 study of Zolgensma® in pre-symptomatic SMA

- 2 or 3 copies of *SMN2*
- <6 weeks of age at dosing

## Primary efficacy outcomes

- 2 copies of *SMN2*: functional independent sitting for ≥30 seconds at 18 months
- 3 copies of *SMN2*: standing without support for ≥3 seconds at 24 months

**1 infant (4.2%) had exclusionary antibody titers during screening**

	2 copies of <i>SMN2</i> (n=8)	3 copies of <i>SMN2</i> (n=9)
Median duration of follow-up at datacut (range)	5.4 months (1.1 - 8.7)	2.2 months (0.4 - 4.8)
Median age at last follow-up (range)	6.1 months (1.7 - 9.1)	3.2 months (0.8 - 6.0)
Patients ≥6 months of age, n (%)	4 (50)	1 (11)

"AVXS-101 Gene-Replacement Therapy in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update," K. Strauss, et al. AAN, 2019.

Motor neuron loss can begin prenatally, rapid loss continues after birth

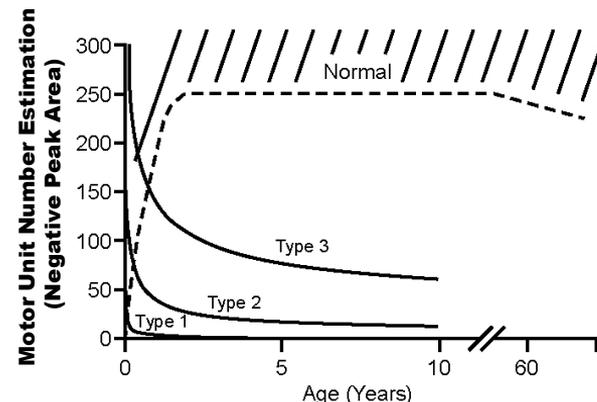
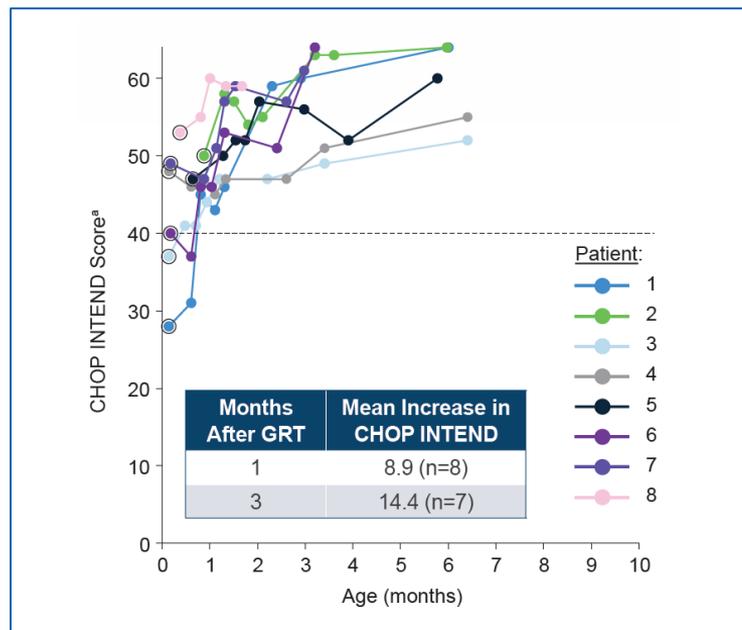


Figure redrawn from Swoboda KJ, et al. *Ann Neurol.* 2005;57:704–712

# Patients treated pre-symptomatically show rapid improvement in motor function

Patients with 2 copies of *SMN2* had early increases in mean CHOP-INTEND score from baseline



Increase from baseline  
 CHOP-INTEND +8.9 pts

**All patients with 2 copies of *SMN2* achieved or maintained a CHOP-INTEND score of  $\geq 50$ <sup>b</sup>**

- 6 patients achieved a score of  $\geq 60$  points
- 3 patients achieved maximum score of 64

<sup>a</sup>CHOP INTEND data are presented for patients with 2 copies of *SMN2* only.

<sup>b</sup>Patients are counted as having achieved a score if it is achieved at any post-baseline visit.

"AVXS-101 Gene-Replacement Therapy in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update," K. Strauss, et al. AAN, 2019.

# Patients with 2 copies of *SMN2* are achieving age-appropriate motor milestones

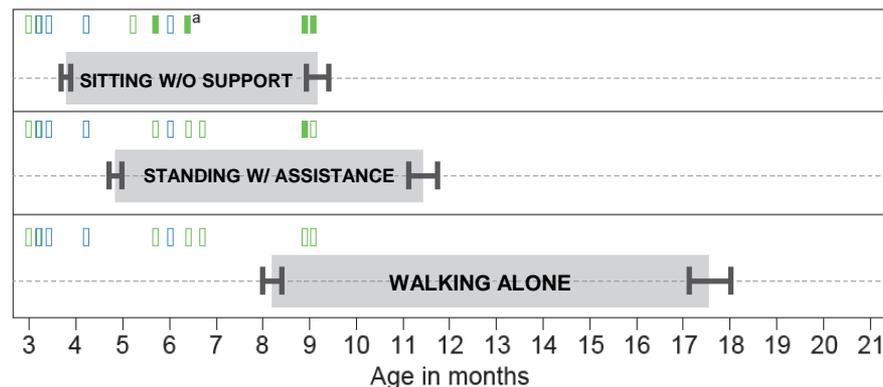
Open label, data as of March 8, 2019  
 2 copies: median 5.4 months of follow-up  
 3 copies: median 2.2 months of follow-up



4 patients  
 could sit without  
 support for  $\geq 30$  secs

1 patient  
 could stand with  
 assistance for  $\geq 2$  secs

## Patients with 2 copies of *SMN2* within WHO windows of normal achievement



■ = 2 copies of *SMN2*      ■ = Age at which patients achieved milestones  
■ = 3 copies of *SMN2*       = Age at last visit for patients who have not yet achieved a given milestone  
 = WHO-MGRS<sup>9</sup> windows of achievement bounded by the 1st and 99th percentiles (bars indicate 95% CIs)

<sup>a</sup>This data point represents 2 patients at 6.4 months of age. One patient reached the milestone at 6.4 months of age and the other, who is 6.4 months of age, has not reached the milestone.

"AVXS-101 Gene-Replacement Therapy in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update," K. Strauss, et al. AAN, 2019.

# All patients alive in SPR1NT, with no new safety signals relative to other Zolgensma<sup>®</sup> studies



- No AEs led to study discontinuation and all patients were alive
- SAEs were deemed unrelated to treatment and resolved
  - croup (n=1), lethargy (n=1) and hypercalcemia (n=1)
- AEs included elevated transaminases, elevated blood creatine phosphokinase MB and elevated troponin

# Preliminary evidence from SPR1NT demonstrates a rapid response in patients treated pre-symptomatically with Zolgensma®

- Rapid, age-appropriate improvement in motor function and milestone achievement
- Supports use of Zolgensma® as a foundational therapy in SMA identified through newborn screening
- Enrollment expected to be completed by July 2019
- Next update anticipated at WMS, October 2019

## Phase 3 study of intravenous Zolgensma® in patients with SMA Type 1

- 1 or 2 copies of *SMN2*
- <6 months of age at dosing

### Primary outcomes

- Independent sitting ≥30 seconds at 18 months of age
- Event-free survival at 14 months

**No (0/25) patients had exclusionary antibody titers during screening**

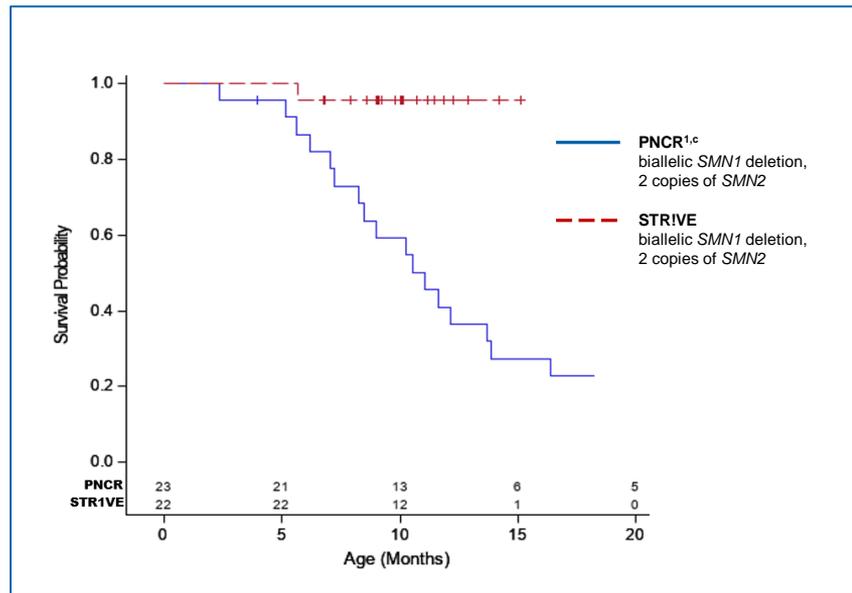
▶ New interim data continued to show Zolgensma® has the potential to provide prolonged event-free survival, increases in motor function and significant milestone achievement

▶ Safety comparable to START

▶ STR1VE continues to reinforce foundational role of Zolgensma® for SMA Type 1

"AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1: Phase 3 Study (STR1VE) Update," J. Day, et al. AAN, 2019.

# Event-free survival improved compared to natural history



Median age at datacut: **14.4 months**

Survival		
Age (months)	PNCR <sup>1</sup>	CL-303
10.5	50%	95% <sup>a</sup>
13.6	25%	87% <sup>b</sup>

At datacut (March 8, 2019):

<sup>a</sup>19 of 20 patients (95%) who had reached 10.5 months of age or discontinued the study prior to 10.5 months of age, survived without permanent ventilation<sup>c</sup>

<sup>b</sup>13 of 15 patients (87%) who had reached 13.6 months of age or discontinued the study prior to 13.6 months were surviving without permanent ventilation<sup>c,d</sup>

<sup>a</sup>Survival for PNCR<sup>1</sup> = 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*). March 8 2019 datacut. <sup>c</sup>One patient died at the age of 7.8 months due to causes unrelated to treatment. <sup>d</sup>One patient withdrew consent at 11.9 months of age. PNCR, Pediatric Neuromuscular Clinical Research; SMA1, spinal muscular atrophy type 1. 1. Finkel RS, et al. *Neurology*. 2014;83:810–7.

<sup>a</sup>AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1: Phase 3 Study (STR1VE) Update," J. Day, et al. AAN, 2019.

# Patients in STRIVE continue to gain motor function and motor milestones



11 infants (50%)  
sitting at a mean of  
8 months post-treatment,  
mean age of 11.9 months



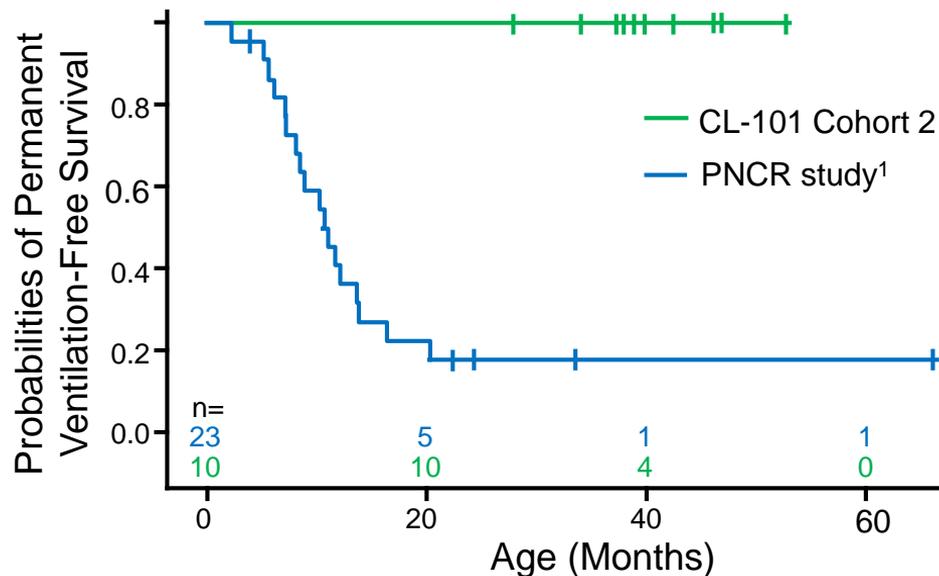
21/22 patients  
have achieved a  
CHOP-INTEND  
score ≥40

## Patients continue to gain motor milestones

Milestone Reached, n (%) <sup>a</sup>	STRIVE (N=22)		
	Sep 27, 2018 Datacut	Dec 31, 2018 Datacut	March 8, 2019 Datacut
Head control <sup>b,c</sup>	11 (52.4) <sup>c</sup>	16 (76.2) <sup>c</sup>	16 (76.2) <sup>c</sup>
Rolls from back to sides <sup>d</sup>	3 (13.6)	7 (31.8)	9 (40.9)
Sits without support <sup>e</sup>	3 (13.6)	8 (36.4)	11 (50.0)
Stands with assistance <sup>f</sup>	0	1 (4.5)	1 (4.5)
Crawls <sup>g</sup>	0	0	1 (4.5)
Pulls to stand <sup>h</sup>	0	0	1 (4.5)
Median duration of follow-up at datacut	5.5 months	8.1 months	10.1 months
Median age at datacut	9.4 months	12.5 months	14.4 months
Patients ≥ 12 months, n (%) <sup>i</sup>	5 (22.7)	13 (59.1)	15 (68.2)

<sup>a</sup>Developmental milestones were confirmed by video. <sup>b</sup>Bayley-III, gross motor subtest item #4 (holds head erect ≥3 seconds without support). <sup>c</sup>One patient reached the milestone of head control at the first screening visit (prior to AVXS-101 dosing), therefore N=21 was used for this calculation. <sup>d</sup>Bayley-III, gross motor subtest item #20 (rolls from back to both right and left sides). <sup>e</sup>Bayley-III, gross motor subtest item #26 (sits unassisted for ≥30 seconds). <sup>f</sup>Bayley-III, gross motor subtest item #33 (supports own weight for ≥2 seconds). <sup>g</sup>Bayley-III, gross motor subtest item #34 (forward progress ≥5 feet by crawling on hands and knees). <sup>h</sup>Bayley-III, gross motor subtest item #35 (raises self to standing position using chair or other convenient object for support). <sup>i</sup>At last visit.  
March 8, 2019 datacut.

# All patients in Cohort 2 remain alive and free of permanent ventilation



Mean (range) **age** at last follow-up:  
**3.9 (3.4–4.8) years**

Mean (range) **time** since treatment:  
**3.7 (3.3–4.3) years**

- No patient was treated concomitantly with any other disease-modifying therapy during START
- 7 out of 10 patients in LTFU had received no other disease-modifying therapy aside from Zolgensma®\*

\*AVXS-101 Gene-Replacement Therapy in Spinal Muscular Atrophy Type 1: Long-Term Follow-Up From the Phase 1/2a Clinical Trial," J. Mendell, et al. AAN, 2019.

+ = censored. \*Per listings.

1. Finkel RS, et al. *Neurology*. 2014;83:810–7.

# No loss of milestones or waning of effect in long-term follow-up of START adds to evidence of long-term durability of Zolgensma<sup>®</sup>

The sustained clinical impact four years after dosing suggests that Zolgensma<sup>®</sup> has the potential to effectively halt motor neuron loss



- ▶ All enrolled Cohort 2 patients (n=10) maintained motor function and milestone achievements

---

- ▶ No patient experienced a worsening of nutritional or ventilatory requirements
  - 2 of 4 patients who used BiPAP at the start of the LTFU period no longer require it regularly

---

- ▶ No new treatment-related adverse events have emerged during the follow-up period

## Phase 1 study of intrathecal Zolgensma® in patients with SMA Type 2

- 3 copies of *SMN2*
- ≥6 to <60 months of age at dosing
- Ability to sit independently ≥10 seconds; cannot stand or walk independently

## Primary efficacy outcomes

- ≥6 to <24 months: standing without support (≥3 sec)
- ≥24 to <60 months: change in Hammersmith Functional Motor Scale-Expanded (HFMSE) from baseline

## Zolgensma® appeared to be well-tolerated in STRONG with no dose-limiting toxicity

## 3/34 patients (8.8%) had exclusionary antibody titers during screening

## STRONG age and dose stratification

Age stratification	Age ≥6 to <24 months at dosing			Age ≥24 to <60 months at dosing
	Dose A (n=3)	Dose B (n=13)	Dose C (n=2)	Dose B (n=12)
Mean age (months) at enrollment	17.2	16.7	17.4	37.5
Mean age (months) at datacut	29	23	N/A	44
Median duration of follow-up (months)	12	6	N/A	7

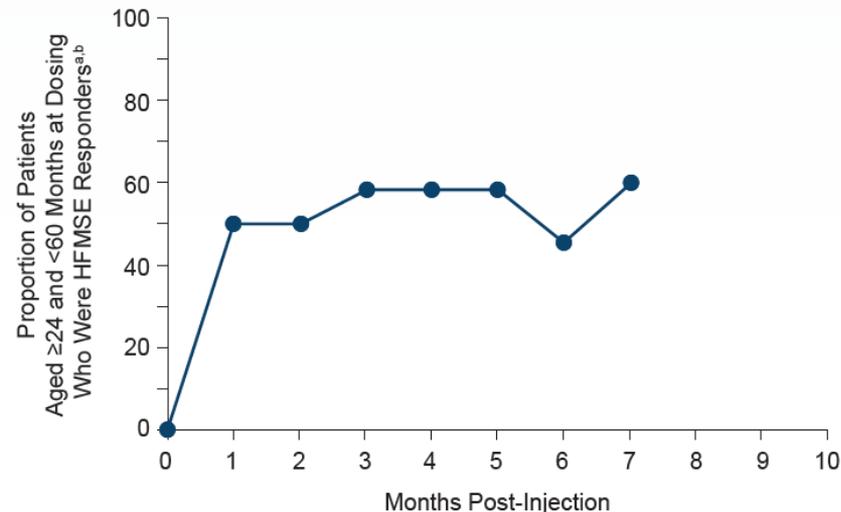
"Phase 1/2a Study of Intrathecal Administration of AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 2 (STRONG)," J. Mendell, et al. AAN, 2019.

# Patients with SMA Type 2 achieve rapid motor function improvement

Open label, data as of March 8, 2019  
Median 6.5 months of follow-up

**50%**  
responded  
by 1 month

Half of patients aged  $\geq 24$  months had  $\geq 3$ -point increase by 1 month post-treatment



n = 0 12 12 12 12 12 11 5

<sup>a</sup>Responders defined as patients with  $\geq 3$ -point increase relative to baseline. Proportion is the ratio of responders to total number of patients for whom HFMSE could be assessed at a given month post-infusion. <sup>b</sup>Only data from patients aged  $\geq 24$  and  $< 60$  months treated with Dose B ( $1.2 \times 10^{14}$  vg) are presented; data from patients treated with Dose C ( $2.4 \times 10^{14}$  vg) are not presented because enrollment is not complete.

March 8, 2019 datacut.

# Patients with SMA Type 2 achieve milestones early in study, including standing and walking

22 milestones in 10 patients achieved after a median 6.5 months of follow-up

≥6 months to <60 months at dosing (n=16)



3 patients  
**crawl**



2 patients  
**stand independently**



1 patient who could stand went on to  
**walk alone**

≥24 to <60 months at dosing (n=12)



1 patient  
**walks with assistance**

"Phase 1/2a Study of Intrathecal Administration of AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 2 (STRONG)," J. Mendell, et al. AAN, 2019.

# Preliminary data support Zolgensma<sup>®</sup> as promising therapy for SMA Type 2



Open label, data as of March 8, 2019  
Median 6.5 months of follow-up

- ✓ Intrathecal data reported for the first time show rapid motor function gains and promising milestone achievements in SMA Type 2
- ✓ Low rates of exclusionary AAV9 antibody titers were observed in patients 6-60 months of age
- ✓ Study closeout anticipated September 2020
- ✓ Plan to initiate discussions with regulators to define the path to registration for intrathecal administration of Zolgensma<sup>®</sup>

"Phase 1/2a Study of Intrathecal Administration of AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 2 (STRONG)," J. Mendell, et al. AAN, 2019.

# Robust data show clinically transformative impact of Zolgensma<sup>®</sup> in broad spectrum of SMA

- ✓ Data indicate Zolgensma<sup>®</sup> provides rapid improvement in motor function, transformative milestones and durable milestone achievement
- ✓ Zolgensma<sup>®</sup> potentially appropriate as foundational therapy for SMA
- ✓ Expansive program with >150 patients treated & <5% of patients excluded due to elevated anti-AAV9 antibodies
- ✓ Prepared to launch IV Zolgensma<sup>®</sup> in U.S. with FDA approval expected this month