Interim Results From the Ongoing RESPOND Study of Nusinersen in Children With Spinal Muscular Atrophy Previously Treated With Onasemnogene Abeparvovec

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Disclosures

- **JFB:** consultant for Audentes, AveXis, Biogen, Cytokinetics, Genentech, Marathon, Momenta, NS Pharma, PTC Therapeutics, Sarepta, Scholar Rock, and WaVe; speaker for AveXis and Biogen; medical advisory council member for Cure SMA; site investigator for clinical trials with Alexion, AveXis, Biogen, Catabasis, CSL Behring, Cytokinetics, Fibrogen, Pfizer, PTC Therapeutics, Sarepta, Summit, and WaVe
- **RM:** Principal Investigator of SMA clinical trials sponsored by AveXis, Biogen, Novartis Gene Therapies, Roche, Sarepta, and Scholar Rock; received consultancy fees, speaker honoraria, and fees for educational events from Biogen, Novartis Gene Therapies, and Roche
- **CP:** advisory boards and consultant for AveXis, Biogen, and Sarepta; speaker for AveXis and Biogen; Principal Investigator of clinical studies for Astellas, AveXis, Biogen, Catabasis, CSL Behring, Pfizer, PTC, Sarepta, and Scholar Rock
- **JAP:** advisor and consultant for Biogen, Genentech, Novartis, and Pfizer; Principal Investigator for clinical studies for Biogen, Biohaven, Genentech, Novartis, PTC Therapeutics, and Scholar Rock
- **NLK:** advisory boards for Argenx, Astellas, Biogen, Biohaven, Catalyst, Entrada, Novartis, Sarepta and Scholar Rock; speaker for Sarepta; Site Principal Investigator for clinical research studies for Argenx, Astellas, Biogen, Biohaven, Catalyst, Novartis, Sarepta, and Scholar Rock
- **RSF:** advisory boards for AveXis, Novartis, and Roche; consultant for AveXis, Biogen, Neurogene, and Roche; honoraria from AveXis, Biogen, Elsevier, Excerpta Medica, Roche, and Voyager; grants from Biogen and Ionis during the CHERISH, ENDEAR, NURTURE, and SHINE studies, and from AveXis, Cytokinetics, Roche, and Scholar Rock; research funding from Biogen, Cure SMA, and National Institutes of Health; data safety monitoring board for the AveXis AVX-101 Phase 1 gene transfer study and Roche Moonfish Phase 1b study; advisory capacity for nonprofit organizations: Cure SMA, SMA Europe, SMA Foundation, and SMA Reach (UK); royalty payments from Children's Hospital of Philadelphia for licensing fees obtained for use of the CHOP INTEND motor function scale
- **RF, WL, SC, JS, BY, SF, ADP:** employees of and hold stock/stock options in Biogen
- **SR:** former employee of and holds stock/stock options in Biogen
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CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

RESPOND study rationale

- There have been reports of individuals with SMA receiving the AAV vector-based gene therapy OA followed by nusinersen in both clinical trials and postmarketing settings[1-3]
- However, there has been no systematic evaluation of clinical outcomes or safety of treatment with nusinersen following administration of OA
- Preclinical animal models and limited human postmortem studies suggest that the AAV9 vector transduces only a subpopulation of motor neurons[4-6]
- This raises the question of whether administration of nusinersen after OA may increase survival motor neuron protein in untransduced motor neurons, which may lead to additional clinical benefit for individuals with SMA

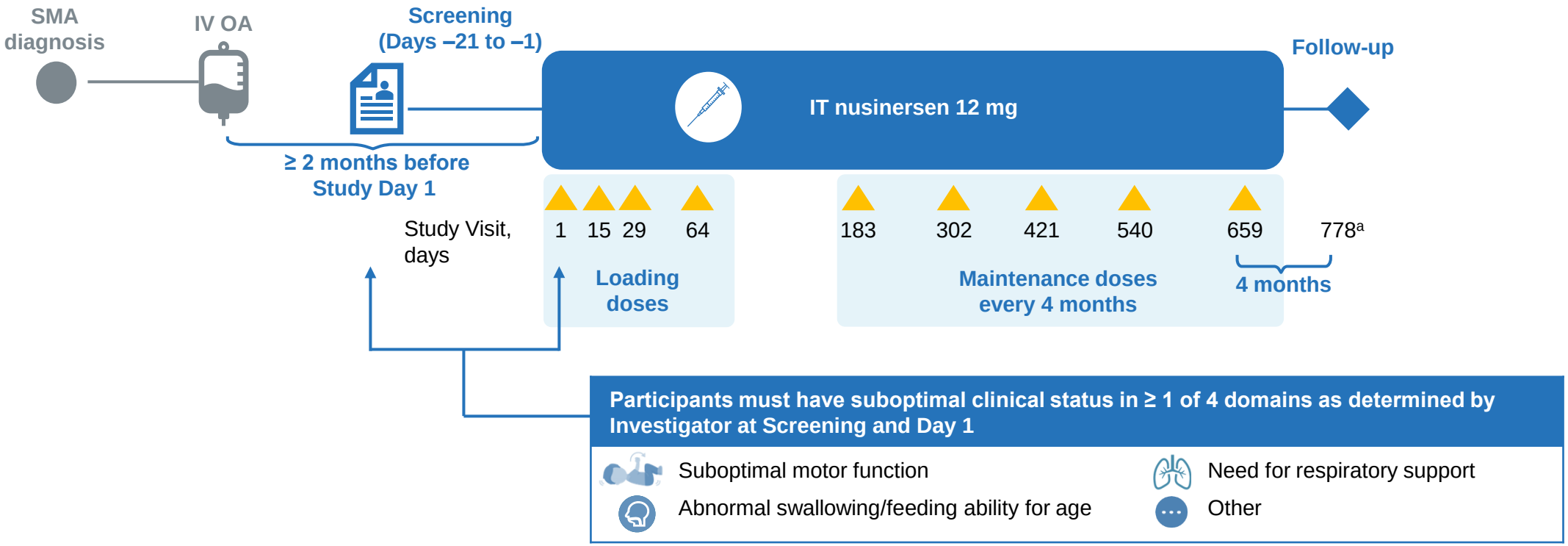
AAV9 = adeno-associated virus serotype 9; OA = onasemnogene abeparvovec; SMA = spinal muscular atrophy

1. Harada Y, et al. *Muscle Nerve*. 2020;62(4):550-554. 2. Lee BH, et al. *Neurology*. 2019;93(14):640-641. 3. Mendell JR, et al. *JAMA Neurol*. 2021;78(7):834-841. 4. Foust KD, et al. *Nat Biotechnol*. 2009;27(1):59-65. 5. Thomsen G, et al. *Nat Med*. 2021;27(10):1701-1711. 6. Meyer K, et al. *Mol Ther*. 2015;23(3):477-487.

RESPOND study design

- RESPOND (NCT04488133) is a Phase 4, multicenter, single-arm, open-label study evaluating nusinersen in participants with SMA who have previously received OA and have suboptimal clinical status as determined by the Investigator

- **Analysis objective:** Provide baseline characteristics and interim clinical outcomes, neurofilament outcomes, and safety findings for participants enrolled in RESPOND



IT = intrathecal; IV = intravenous; OA = onasemnogene abeparvovec; SMA = spinal muscular atrophy
[a]Or 4 months from last dose.

Interim analyses

Interim Set (n = 29)

- Children who received ≥ 1 dose of nusinersen who had the opportunity to complete the Day 183 assessment as of the data cut[a]

Outcomes

- Total HINE-2 score (primary outcome)
- Plasma NfL

Analyses

- Analyses stratified by age at first nusinersen dose (≤ 9 mo, > 9 mo) and *SMN*2 copy number

Safety Set (N = 38)

- All children who received ≥ 1 dose of nusinersen as of the data cut

Outcomes

- Safety and tolerability

HINE-2 = Hammersmith Infant Neurological Examination – Section 2; NfL = neurofilament light chain; *SMN2* = survival motor neuron 2

[a]Cutoff date for clinical and safety data was 15 November 2022; cutoff date for NfL data was 26 June 2023, but analyses included only those in the Day 183 Interim Set as of the 15 November 2022 data cut. One participant with risdiplam use was excluded since there were no available post-baseline data on clinical endpoints when the participant was only treated with nusinersen.

Baseline demographics and SMA history (Interim Set)

- All participants were symptomatic at the time of OA dosing

	Age at First Nusinersen Dose Group		
	≤ 9 mo	> 9 mo	
Demographics and SMA History	**2 *SMN2* Copies n = 14**	**2 *SMN2* Copies n = 12**	**3 *SMN2* Copies n = 3**
Male/female, n (%)	9 (64.3) / 5 (35.7)	7 (58.3) / 5 (41.7)	3 (100) / 0
Age at SMA symptom onset, mo, median (range)	0.8 (0.0–3.0)	1.0 (0.0–5.0)[a,b]	6.0 (5.0–9.0)
Age at SMA diagnosis, mo, median (range)	0.9 (0.0–6.0)[c,d]	2.1 (0.9–6.0)[b]	15.0 (6.0–23.0)
Age at OA dosing, mo, median (range)	1.7 (0.7–5.1)	2.7 (0.8–6.9)	17.5 (13.6–24.3)
Age at first nusinersen dose, mo, median (range)	**7.7 (3.4–9.8)**	**16.3 (11.0–33.3)**	**30.8 (29.2–35.7)**
Time from OA dose to first nusinersen dose, mo, median (range)	**4.8 (2.6–7.7)**	**14.4 (6.3–31.3)**	**13.3 (4.9–22.2)**

OA = onasemnogene abeparvovec; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2

[a]One participant exhibited SMA symptoms on day of birth. The minimum age at SMA symptom onset was 0 days. [b]n = 11; age information was missing for 1 participant. [c]The minimum age at SMA diagnosis was 0 days. [d]n = 13; 1 participant with anomaly for diagnosis age was excluded.

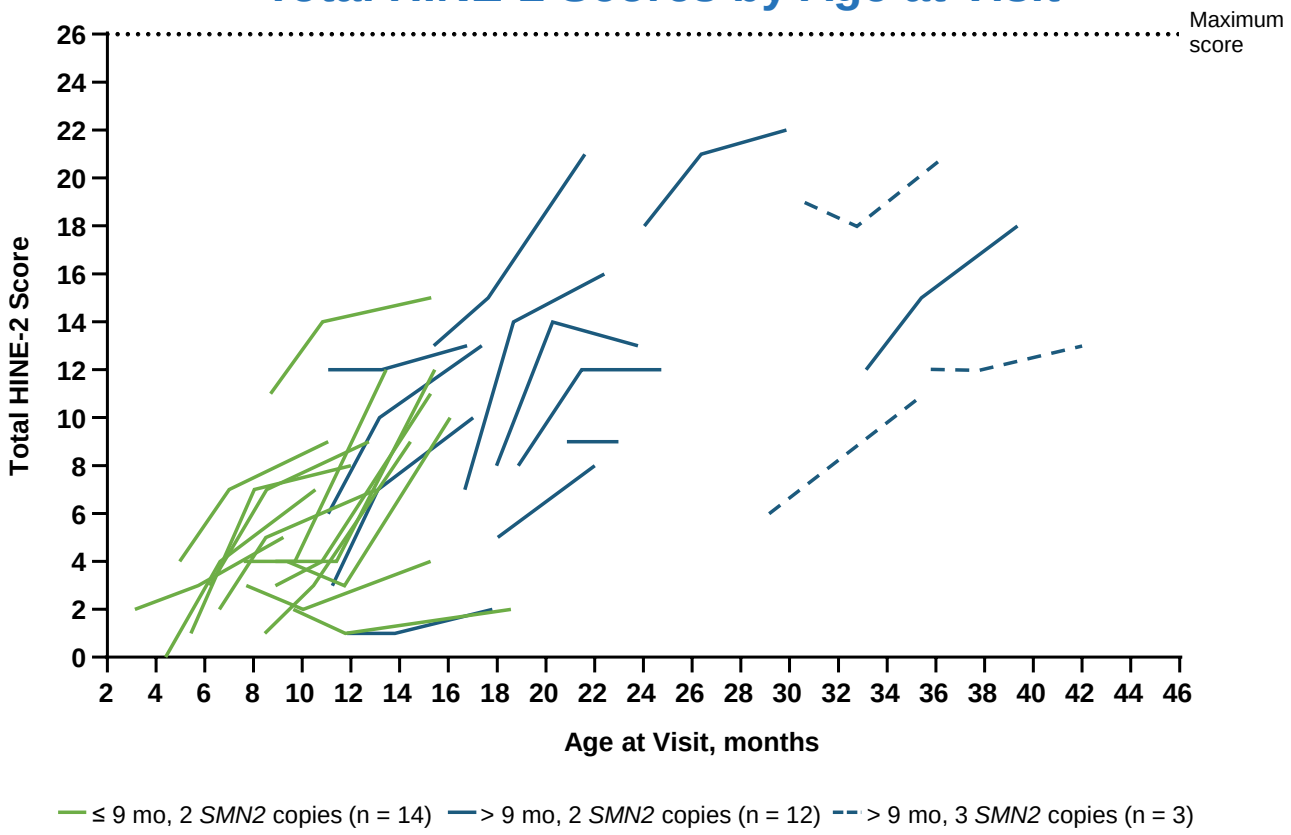
Baseline disease characteristics (Interim Set)

	Age at First Nusinersen Dose Group		
	≤ 9 mo	> 9 mo	
Disease Characteristics	**2 *SMN2* Copies n = 14**	**2 *SMN2* Copies n = 12**	**3 *SMN2* Copies n = 3**
Suboptimal clinical status at Baseline per Investigator, n (%)			
Motor function	13 (93)	11 (92)	3 (100)
Swallowing or feeding ability for age	9 (64)	5 (42)	1 (33)
Respiratory function	10 (71)	9 (75)	0
Other	2 (14)	1 (8)	0
Sitting without support at Screening, n (%)	0	7 (58)	1 (33)
HINE-2 total score, median (range)	3.0 (0–11)	8.0 (1–18)[a]	12 (6–19)
CMAP ulnar amplitude (mV),[b] median (range)	**0.75 (0.19–2.10)**	**0.66 (0.20–2.70)**	**0.90 (0.70–5.60)**
≤ 1 mV, n (%)	**11 (79)**	**9 (75)**	**2 (67)**

CMAP = compound muscle action potential; HINE-2 = Hammersmith Infant Neurological Examination – Section 2; *SMN2* = survival motor neuron 2
[a]n = 11. [b]Ulnar nerve innervation of abductor digiti minimi.

Mean total HINE-2 scores increased from Baseline to Day 183

Total HINE-2 Scores by Age at Visit

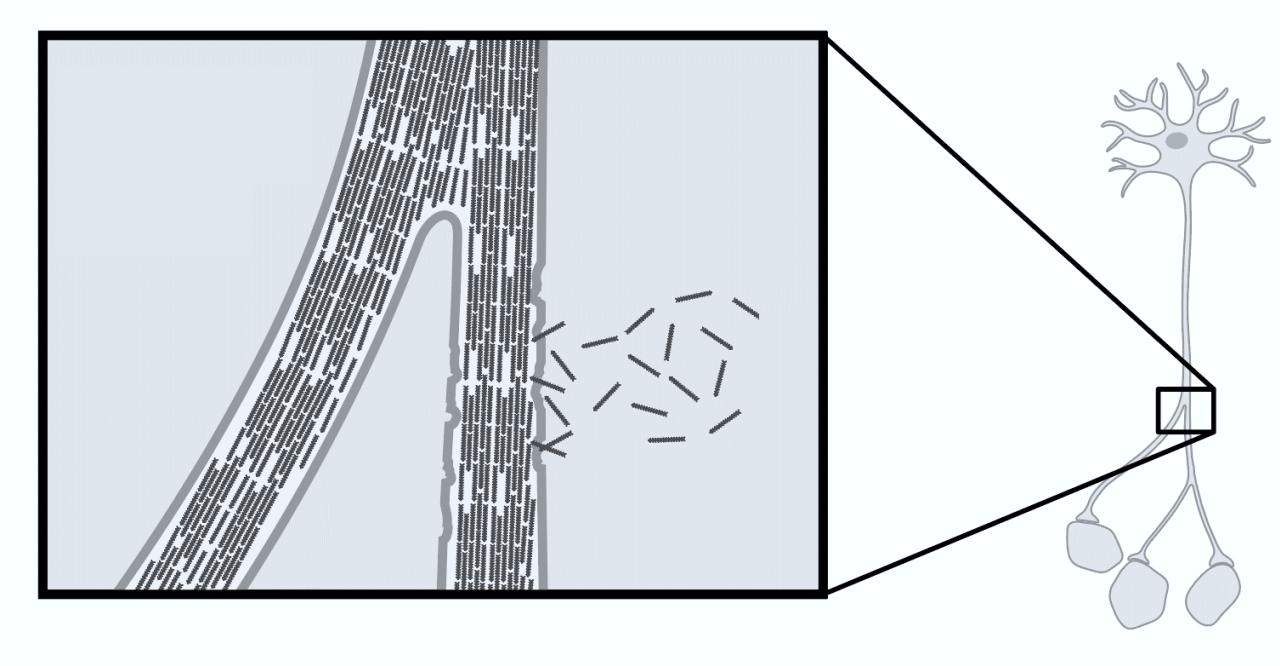


Age at First Nusinersen Dose Group	n	Actual Mean (SD) HINE-2 Scores Baseline	n	Day 183	n	Mean (SD) Change from Baseline to Day 183
≤ 9 mo, 2 *SMN2* copies	14	3.1 (2.60)	14	8.6 (3.46)	14	5.4 (2.62)
> 9 mo, 2 *SMN2* copies	11	8.8 (4.79)	11	13.5 (5.77)	10	5.2 (2.74)

Mean changes not shown for participants with 3 *SMN2* copies due to small sample size.

HINE-2 = Hammersmith Infant Neurological Examination – Section 2; *SMN2* = survival motor neuron 2
All data from Baseline to Day 183 are shown in the figure for participants with post-Baseline scores.

Neurofilaments



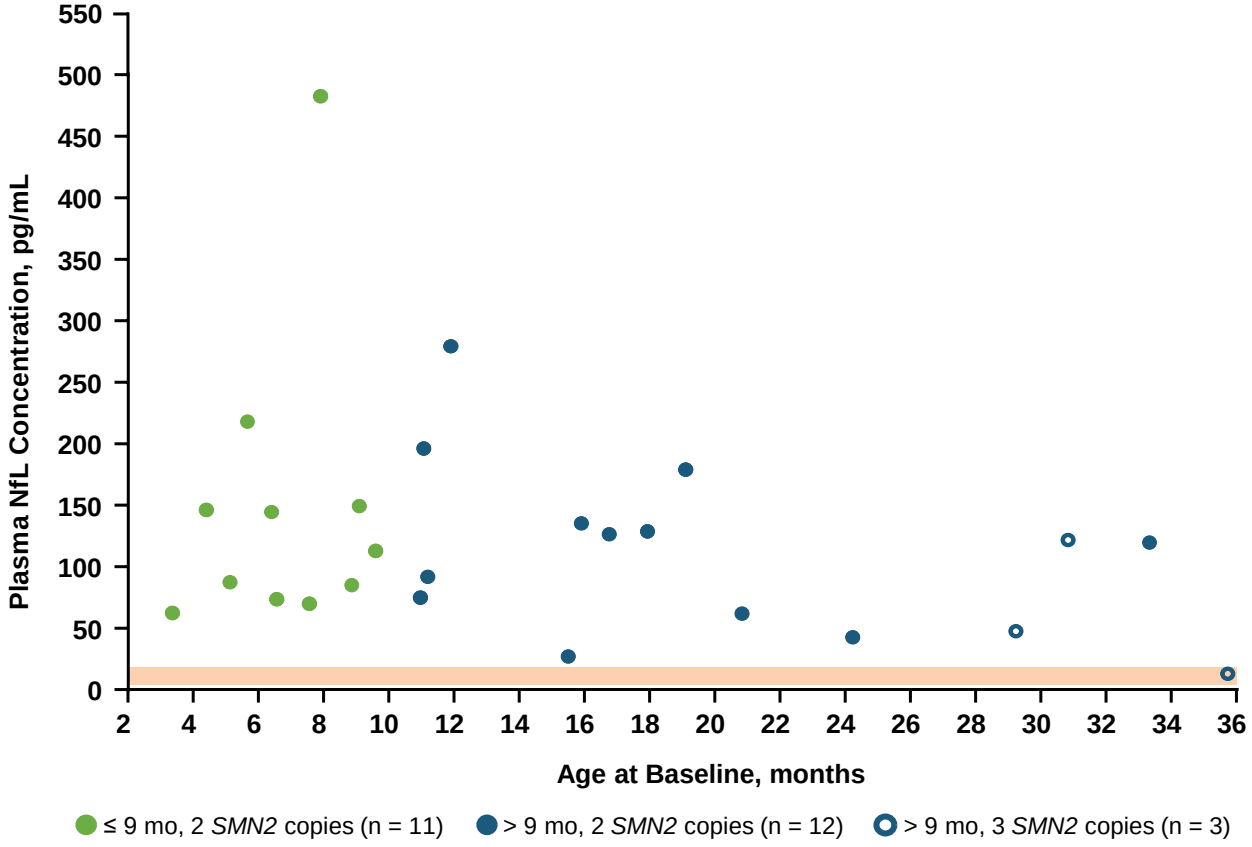
- Neurofilaments are structural proteins that are released into interstitial fluid (CSF and blood) following axonal damage or neuronal degeneration[1,2]
- In infants and younger children with SMA, neurofilament levels, including NfL, have been shown to be:
  - Elevated, reflecting neuroaxonal damage that is central to the disease
  - Prognostic for disease severity and responsive to treatment[3-6]

CSF = cerebrospinal fluid; NfL= neurofilament light chain; SMA = spinal muscular atrophy

1. Xu Z, et al. *PLoS One.* 2016;11(10):e0164625. 2. Petzold A. *J Neurol Sci*. 2005;233(1-2):183-198. 3. Darras BT, et al. *Ann Clin Transl Neurol*. 2019;6(5):932-944. 4. De Vivo DC, et al. *Neuromuscul Disord*. 2019;29(11):842-856. 5. Pino MG, et al. *Biomark Insights.* 2021;16:11772719211035643. 6. Nitz E, et al. *Ann Clin Transl Neurol*. 2021;8(10):2013-2024.
Figure concept from Yuan A, et al. *Cold Spring Harb Perspect Biol*. 2017;9(4):a018309.

Baseline NfL levels were elevated compared with healthy children of similar ages[1]

Baseline Plasma NfL Concentrations by Age



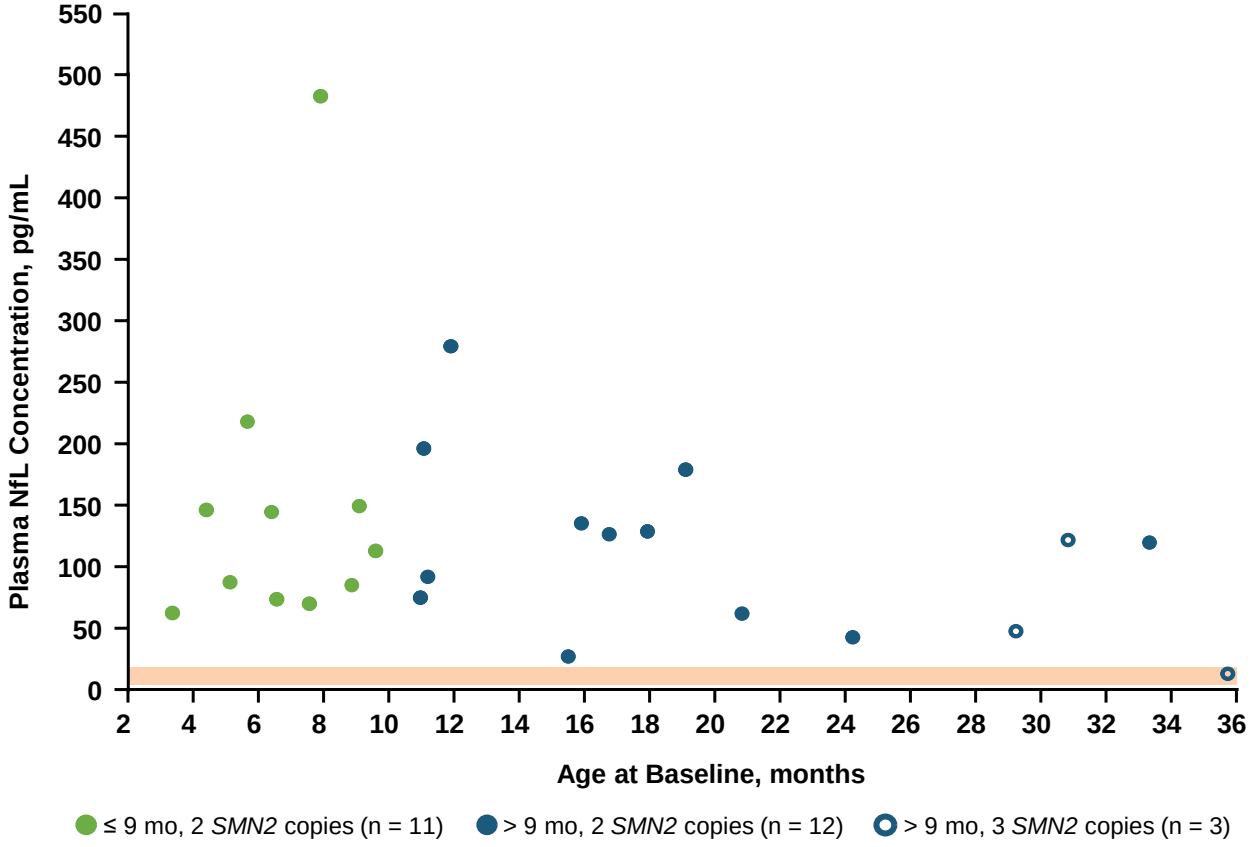
Shading indicates 5th through 95th percentile serum NfL concentrations for healthy children[1]

	Age at First Nusinersen Dose Group		
	≤ 9 mo	> 9 mo	
Baseline Plasma NfL, pg/mL	**2 *SMN2* Copies n = 11**	**2 *SMN2* Copies n = 12**	**3 *SMN2* Copies n = 3**
Mean (SD)	148.3 (120.34)	121.8 (71.22)	60.6 (55.63)
Median (range)	112.9 (62–483)	122.9 (27–279)	47.5 (13–122)

NfL = neurofilament light chain; *SMN2* = survival motor neuron 2
Plasma samples may have approximately 10% lower NfL levels than serum samples.
1. Bayoumy S, et al. *Clin Chem Lab Med*. 2024. published online January 15, 2024, doi:10.1515/cclm-2023-1311, is licensed under CC BY 4.0.

Baseline NfL levels were elevated compared with healthy children of similar ages[1]

Baseline Plasma NfL Concentrations by Age



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Age at First Nusinersen Dose Group

Baseline Plasma NfL, pg/mL	≤ 9 mo	> 9 mo	
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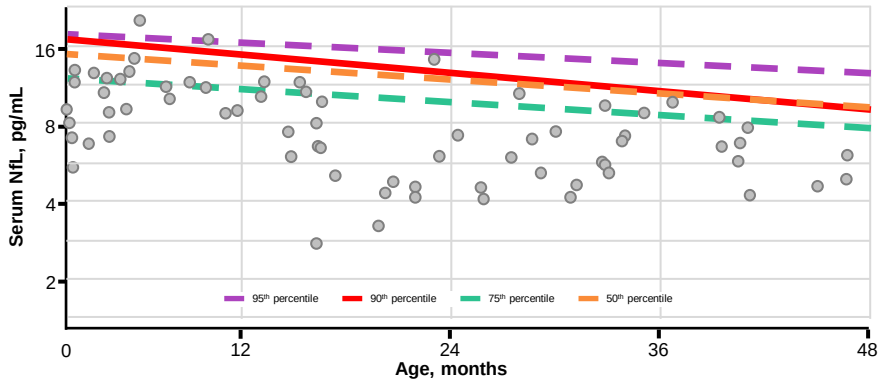
NfL levels in healthy children steadily decline from birth
Adapted from Bayoumy S, et al[1]



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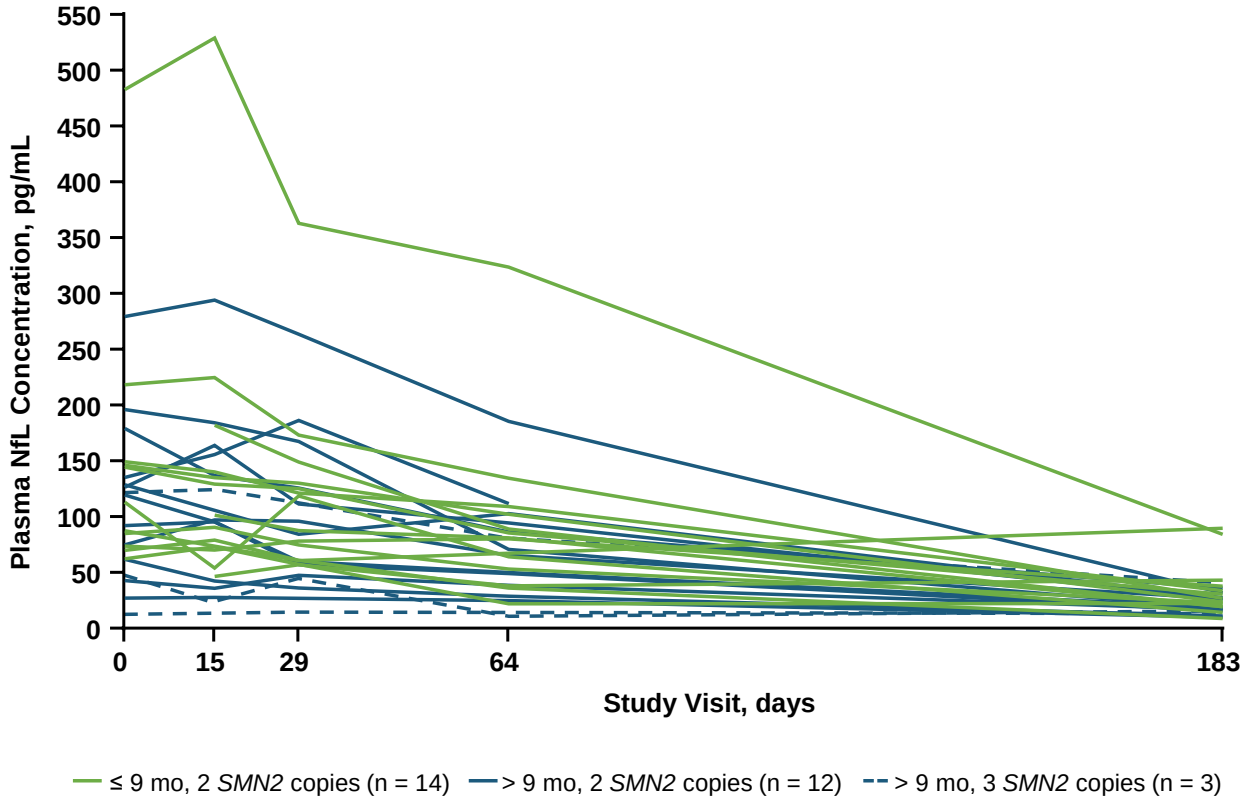
Mean NfL levels were reduced from Baseline to Day 183

Plasma NfL Concentrations by Study Visit



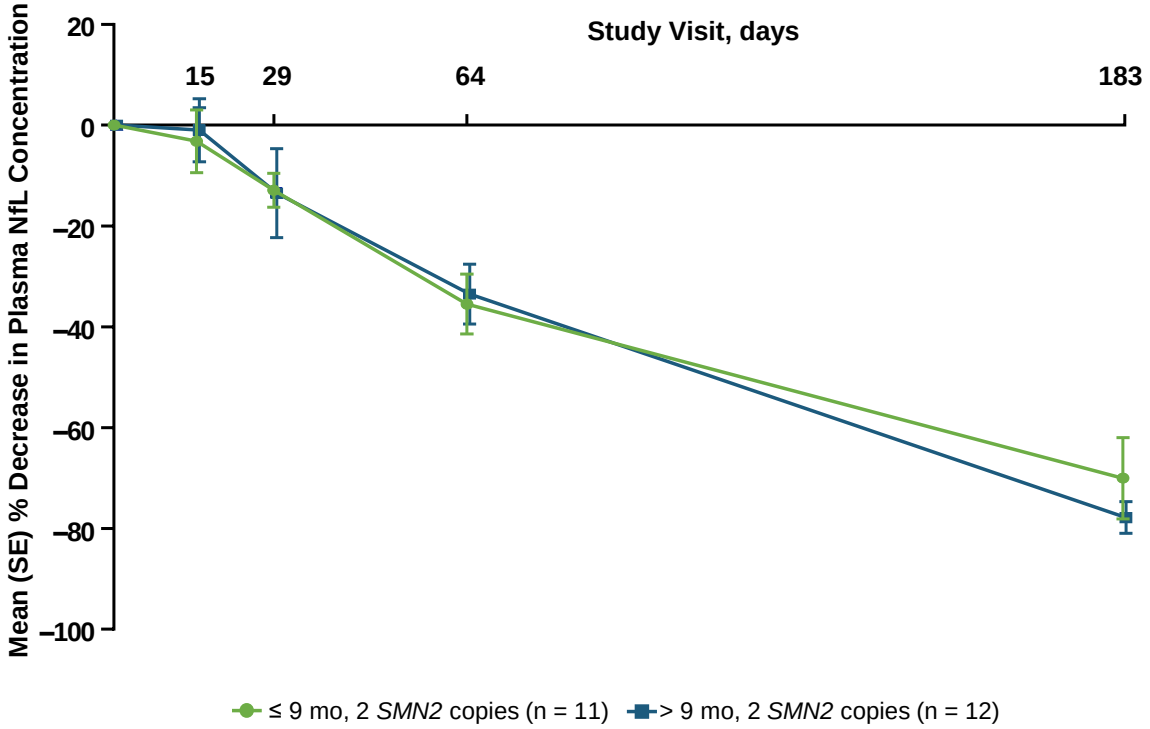
Age at First Nusinersen Dose Group	Actual Mean (SD) Plasma NfL Concentrations, pg/mL n	Baseline	n	Day 183	n	Mean (SD) Change from Baseline to Day 183
≤ 9 mo, 2 *SMN2* copies	11	148.3 (120.34)	14	33.9 (24.15)	11	–112.5 (108.53)
> 9 mo, 2 *SMN2* copies	12	121.8 (71.22)	11	21.6 (8.50)	11	–99.0 (69.21)

Mean changes not shown for participants with 3 *SMN2* copies due to small sample size.

NfL= neurofilament light chain; *SMN2* = survival motor neuron 2
All data from Baseline to Day 183 are shown in the figure for participants with post-Baseline scores. Individual participant trajectories may overlap.

Continued reductions in NfL levels were observed among participants with 2 *SMN2* copies

Mean % Decrease in Plasma NfL by Study Visit



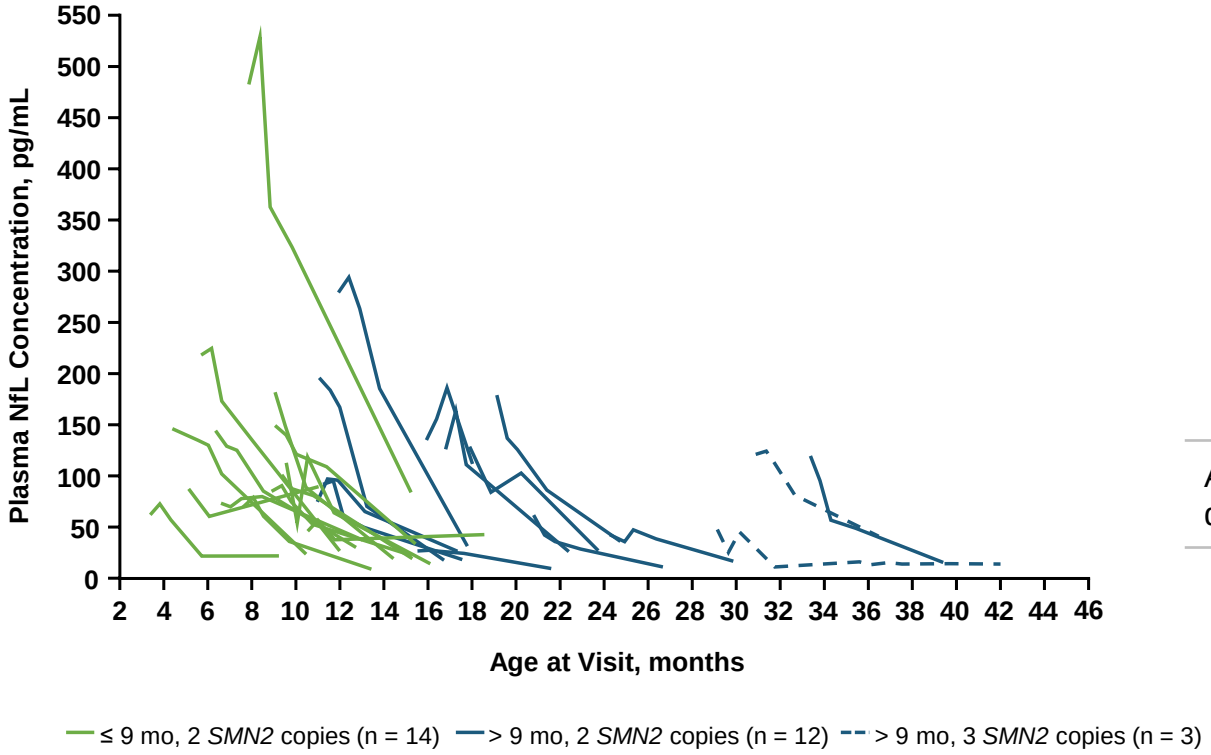
Age at First Nusinersen Dose Group	n	Mean (SD) % Change from Baseline to Day 183
≤ 9 mo, 2 *SMN2* copies	11	−70.0% (26.72)
> 9 mo, 2 *SMN2* copies	11	−77.8% (10.38)

Mean % change not shown for participants with 3 *SMN2* copies due to small sample size.

NfL = neurofilament light chain; *SMN2* = survival motor neuron 2
All data from Baseline to Day 183 are shown in the figure for participants with post-Baseline scores.

Consistent pattern of decline in NfL levels was observed by age

Plasma NfL Concentrations by Age at Visit



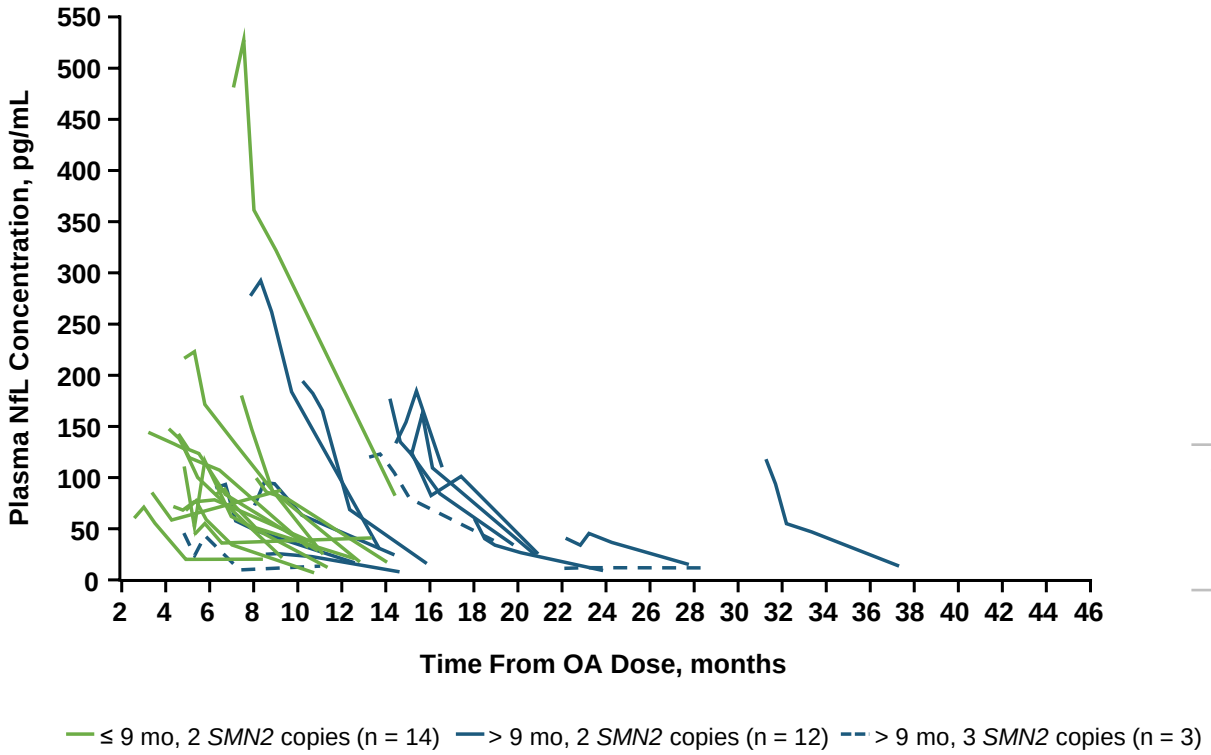
Age at First Nusinersen Dose Group

	≤ 9 mo	> 9 mo	
	2 *SMN2* Copies n = 14	**2 *SMN2* Copies n = 12**	**3 *SMN2* Copies n = 3**
Age at first nusinersen dose, mo, median (range)	7.7 (3.4–9.8)	16.3 (11.0–33.3)	30.8 (29.2–35.7)

NfL = neurofilament light chain; *SMN2* = survival motor neuron 2
All data from Baseline to Day 183 are shown in the figure for participants with post-Baseline scores. Individual participant trajectories may overlap.

Consistent pattern of decline in NfL levels was observed by time from OA dose

Plasma NfL Concentrations by Time from OA Dose



	Age at First Nusinersen Dose Group		
	≤ 9 mo	> 9 mo	
	2 *SMN2* Copies n = 14	2 *SMN2* Copies n = 12	3 *SMN2* Copies n = 3
Time from OA dose to first nusinersen dose, mo, median (range)	4.8 (2.6–7.7)	14.4 (6.3–31.3)	13.3 (4.9–22.2)

NfL = neurofilament light chain; OA = onasemnogene abeparvovec; *SMN2* = survival motor neuron 2
All data from Baseline to Day 183 are shown in the figure for participants with post-Baseline scores. Individual participant trajectories may overlap.

AEs reported after a median of ~230 days on study (Safety Set)

Safety Parameters, n (%)	Overall Population N = 38
Participants dosed	38 (100)
Time on study, days, median (range)	230.5 (28.0–677.0)
Participants with any AE	31 (81.6)
AE considered related to study drug by investigator	
Mild	2 (5.3)[a]
Moderate	0
Severe	0
Serious AE	13 (34.2)[b]
AE leading to study or drug withdrawal	0[c]
Death	0

Most Common AEs by System Organ Class, n (%)	Overall Population N = 38
Infections and infestations	24 (63.2)
Respiratory, thoracic, and mediastinal disorders	10 (26.3)
Gastrointestinal disorders	5 (13.2)
General disorders and administration site conditions	5 (13.2)
Skin and subcutaneous tissue disorders	5 (13.2)

Proportion of Participants With Any AEs and Severity, n (%)	Overall Population N = 38
No AEs	7 (18.4)
Mild AEs	16 (42.1)
Moderate AEs	8 (21.1)
Severe AEs[d]	7 (18.4)

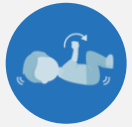
- **No serious AEs were considered related to nusinersen by the investigator**
- **No clinically significant trends related to nusinersen in hematology, blood chemistry, urinalysis, coagulation, vital signs, ECGs, or liver function tests were observed**

AE = adverse event; ECG = electrocardiogram

[a]Mild AEs of proteinuria in 2 participants were considered related to the study drug by the Investigator. A nephrology consultation was not required. The events resolved and the participants continued to receive nusinersen treatment. [b]None of the serious AEs were considered related to study drug, and all events were resolved. All participants continued treatment with nusinersen. [c]One participant (2.6%) discontinued after first dose of nusinersen due to parent/guardian decision. [d]Severe AEs: acute respiratory failure, chronic respiratory failure, COVID-19, enterovirus infection, feeding intolerance, metapneumovirus pneumonia, Moraxella infection, pneumonia viral, pyrexia, respiratory failure, respiratory syncytial virus infection, and viral upper respiratory infections.

Summary and Conclusions

Available data support the potential benefit and safety of nusinersen treatment in infants and children with suboptimal clinical response to OA



- At Day 183, mean total HINE-2 scores increased across age groups

- At Baseline, plasma NfL levels were elevated compared with healthy children

- Reductions in NfL levels occurred after nusinersen initiation, suggestive of a slowing of axonal injury and neurodegeneration
- Mean reductions in NfL levels were not dependent on age or time from OA dose

- No emerging safety concerns have been identified at the time of the data cut in enrolled participants who received nusinersen after OA

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HINE-2 = Hammersmith Infant Neurological Examination – Section 2; NfL = neurofilament light chain; OA = onasemnogene abeparvovec

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