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Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study

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Abstract

Introduction/Aims: NURTURE (NCT02386553) is an open-label study of nusinersen in children (two *SMN2* copies, $n = 15$; three *SMN2* copies, $n = 10$) who initiated treatment in the presymptomatic stage of spinal muscular atrophy (SMA). A prior analysis after ~3 y showed benefits on survival, respiratory outcomes, motor milestone achievement, and a favorable safety profile. An additional 2 y of follow-up (data cut: February 15, 2021) are reported.

Methods: The primary endpoint is time to death or respiratory intervention (≥6 h/day continuously for ≥7 days or tracheostomy). Secondary outcomes include overall survival, motor function, and safety.

Results: Median age of children was 4.9 (3.8–5.5) y at last visit. No children have discontinued the study or treatment. All were alive. No additional children utilized

Abbreviations: 6MWT, 6-Minute Walk Test; AE, adverse event; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; CSF, cerebrospinal fluid; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Hammersmith Infant Neurologic Examination, Section 2; PASA, Parent Assessment of Swallowing Ability; pNF-H, phosphorylated neurofilament-heavy chain; PT, physical therapist; SAE, serious adverse event; SMA, spinal muscular atrophy; SMN, survival motor neuron; *SMN1*, survival motor neuron 1; *SMN2*, survival motor neuron 2; WHO, World Health Organization.

Prior Presentation: Part of these data were previously presented at the 2022 Muscular Dystrophy Association—Clinical and Scientific Conference, Nashville, TN, USA, March 13–16, 2022; European Paediatric Neurology Society—14th Congress, Glasgow, UK, April 28–May 2, 2022; Cure SMA–2022 Annual Conference, Anaheim, CA, USA, June 15–17, 2022; SMA Europe–3rd International Scientific Congress on Spinal Muscular Atrophy, Barcelona, Spain, October 21–23, 2022; and 2023 Muscular Dystrophy Association—Clinical and Scientific Conference, Dallas, TX, USA, March 19–22, 2023.

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respiratory intervention (defined per primary endpoint) since the prior data cut. Children with three *SMN2* copies achieved all World Health Organization (WHO) motor milestones, with all but one milestone in one child within normal developmental timeframes. All 15 children with two *SMN2* copies achieved sitting without support, 14/15 walking with assistance, and 13/15 walking alone. Mean Hammersmith Functional Motor Scale Expanded total scores showed continued improvement. Subgroups with two *SMN2* copies, minimum baseline compound muscle action potential amplitude ≥2 mV, and no baseline areflexia had better motor and nonmotor outcomes versus all children with two *SMN2* copies.

Discussion: These results demonstrate the value of early treatment, durability of treatment effect, and favorable safety profile after ∼5 y of nusinersen treatment. Inclusion/exclusion criteria and baseline characteristics should be considered when interpreting presymptomatic SMA trial data.

KEYWORDS
motor function, NURTURE, nusinersen, safety, spinal muscular atrophy

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is a rare, progressive neuromuscular disease caused by a homozygous deletion or other pathogenic variants of the *survival motor neuron 1* (*SMN1*) gene.[1] A paralogous *SMN2* gene provides sufficient survival motor neuron (SMN) protein to sustain partial motor neuron development prenatally but cannot prevent later neurodegeneration, muscular atrophy, and weakness.[2–4] *SMN2* copy number correlates inversely with disease severity.[5,6]

Infants with two or three *SMN2* copies, who would likely develop SMA Type I or II without treatment, are often asymptomatic at birth; however, evidence suggests clinically silent but irreversible motor neuron degeneration precedes symptoms.[4,7–9] Consistent with these observations, emerging data indicate heterogeneity among presymptomatic patients, suggesting a spectrum ranging from clinically silent to prodromal disease.[10] The different inclusion/exclusion criteria used in presymptomatic trials of nusinersen, risdiplam, and onasemnogene abeparvovec reflect this heterogeneity.[11–14] Nevertheless, the importance of early, preferably presymptomatic, treatment to preserve motor neurons and maximize motor function development, is well established,[15,16] catalyzing implementation of newborn SMA screening in several countries, including the United States.[17,18]

Nusinersen is an antisense oligonucleotide that promotes expression of functional SMN protein by altering pre-messenger RNA splicing of *SMN2*.[19] Nusinersen has demonstrated significant and sustained, clinically meaningful efficacy on motor skills, respiratory function, survival, and other outcomes in infants, children, and adults,[20–29] with greatest effectiveness when initiated before or soon after symptom onset.[11,25]

NURTURE (NCT02386553) is an ongoing study evaluating safety and efficacy of nusinersen in infants likely to develop SMA Type I or II who initiated treatment before onset of overt clinical signs or symptoms of SMA.[11] We previously published an analysis, representing approximately 3 y of follow-up[11] and now present results after an additional 2 y of follow-up.

2 | METHODS

2.1 | Study design and participants

NURTURE is a Phase 2, open-label, single-arm, multinational study. The study was described previously[11] (details in Supplement). The study was approved by the local ethics committee at each site. Written informed consent was obtained from parents/legal guardians of all participants. No participants received onasemnogene abeparvovec. One initiated concomitant risdiplam 12 days before the current data cut without any visits or adverse events (AEs) reported in the 12-day interval. This interim analysis reports data from the February 15, 2021 data cut with data reflecting the last visit most proximal to this date.

2.2 | Interim analysis endpoints

The primary endpoint is time to death or respiratory intervention (invasive or noninvasive for ≥6 h/day continuously for ≥7 days or tracheostomy).[11] Secondary efficacy endpoints were evaluated by Hammersmith Infant Neurologic Examination, Section 2[30] (HINE-2; through Day 778) and the World Health Organization (WHO) motor milestone criteria.[31] Date of WHO motor milestone achievement was based on physical therapist (PT) or caregiver observation. The age at which a WHO motor milestone was achieved was determined by using the caregiver-reported date if confirmed at the subsequent study visit by the PT. Otherwise, the first instance the PT observed

the milestone was used. Permanent ventilation was defined as tracheostomy or ≥16 h ventilation/day continuously for >21 days in the absence of an acute reversible event. The Parent Assessment of Swallowing Ability (PASA)[32] questionnaire was used to assess dysphagia (exploratory endpoint). (See Supplement for additional endpoints.)

2.3 | Statistical and other methods

Efficacy and safety analyses were performed on the intention-to-treat population (all participants who received ≥1 nusinersen doses). The proportion of participants alive and the proportion achieving a maximum Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) score were estimated with the Kaplan–Meier method.

Descriptive statistics were used to summarize secondary and exploratory endpoints. Baseline HFMSE was defined as the first evaluable score (≤6 missing items) and excluded assessments at Day 700 (children had to be ≥2 y to be assessed). HFMSE scores from similarly aged participants (2–4 y at first assessment) with three *SMN2* copies from CHERISH[28] were included for comparison (CHERISH details in Supplement). This analysis was conducted using a linear mixed effects model with the intercept as a random effect; all available data for each participant were used and an average slope was obtained. Areflexia was defined as a "0" tendon reflex score on HINE, Section 1 and investigator-confirmed absent reflexes.

3 | RESULTS

3.1 | NURTURE participants

Twenty-five infants enrolled in NURTURE: 15 with two *SMN2* copies; 10 with three *SMN2* copies. As of February 15, 2021, all remained in NURTURE without treatment discontinuation and with a median (range) time on study of 4.9 (3.9–5.7) y. The median (range) age was 4.9 (3.8–5.5) y as of last visit (Figure S1). See Tables S1 and S2 for individual demographics, baseline characteristics, and select outcomes.

3.2 | Event-free survival

All 25 infants are alive; none required permanent ventilation. No additional participants required respiratory intervention as defined per the primary endpoint since the prior data cut[11] when four were reported, all among children with two *SMN2* copies, with this endpoint being met at 14.9, 18.1, 19.1, and 20.7 mo of age (participants 3, 9, 12, 15; Table S1). At the time of the current data cut, one used twice daily cough assist for prophylactic respiratory support with no respiratory intervention required since age 3.3 y. Three received noninvasive ventilation for 9–10 h/day for prophylactic support ($n = 2$) or microaspiration treatment ($n = 1$). At baseline, all four had either complete areflexia ($n = 3$), ulnar CMAP amplitude <2 mV ($n = 3$), or peroneal CMAP <2 mV ($n = 1$). Additionally, weight-for-age was <50th WHO growth guidelines percentile ($n = 4$) and/or cerebrospinal fluid (CSF) phosphorylated neurofilament-heavy chain (pNF-H) levels were at or above the median (27,300 pg/mL) for the two *SMN2* copy children ($n = 3$). Only one had a baseline plasma pNF-H level above the median (33,300 pg/mL) for the children with two *SMN2* copies.

3.3 | Motor milestone achievement

All 25 children achieved and maintained the WHO motor milestone of sitting without support (Figure 1; Table S3). One additional child with two *SMN2* copies achieved crawling, walking with assistance, standing alone, and walking alone since the prior publication.[11] All children who achieved a WHO motor milestone retained this achievement at the last study visit. Overall, all children with three *SMN2* copies achieved all WHO motor milestones within normal developmental timeframes, apart from walking with assistance in one child. In children with two *SMN2* copies, all achieved sitting without support and standing with assistance, 14 achieved hands and knees crawling and walking with assistance, and 13 achieved standing alone and walking alone, with some attaining milestones within normal developmental timeframes (Figure 1A, C).

Seven children who previously developed protocol-defined SMA symptoms by 24 mo[11] (all with two *SMN2* copies; participants 2–4, 9, 10, 13, 15; Table S1) continued to grow and gain weight. The maximum milestones achieved were the ability to walk alone ($n = 5$), standing with assistance ($n = 1$), and walking with assistance ($n = 1$). Of these seven, four had baseline CMAP amplitudes <2 mV (peroneal: participant 9; ulnar: participants 2, 3, 9), and two were areflexic (participants 3, 15) (Figure S2).

3.4 | Changes in motor function

Since the prior publication,[11] two additional children with two *SMN2* copies achieved the maximum CHOP INTEND score (64) at age 3.8 (Study Day 1375) and 4.8 y (Study Day 1755). Overall, 22 (88%) children (12 [80%] with two *SMN2* copies; 10 [100%] with three *SMN2* copies) achieved the maximum CHOP INTEND score. Mean CHOP INTEND scores increased steadily from baseline before stabilizing around the maximum score (Figure S3). Mean CHOP INTEND scores were higher throughout the study and at the most recent assessment in NURTURE children with two or three *SMN2* copies than in the ENDEAR study of participants with symptomatic infantile-onset SMA, although scores increased in nusinersen-treated ENDEAR participants.

Beginning at age 2 y, initial HFSME assessments were obtained in 14/15 children with two *SMN2* copies (assessed at age: 2.1–3.2 y) and all 10 children with three *SMN2* copies (assessed at age: 2.1–3.8 y), with mean (SD; range) total scores of 33.1 (11.31; 11–48) and

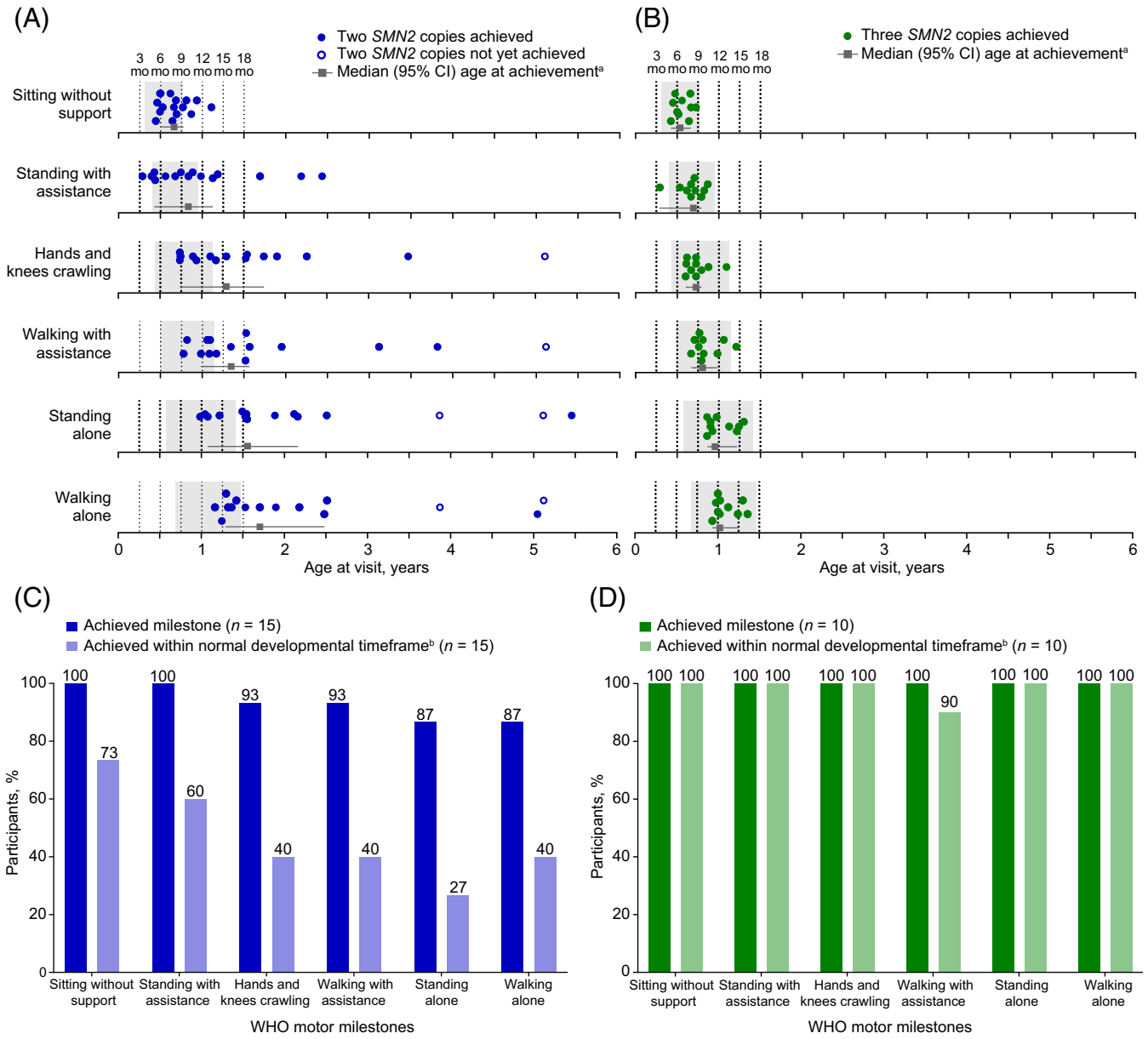

FIGURE 1 Achievement of WHO motor milestones by *SMN2* copy number. The age at first achievement of each of the WHO motor milestones is shown in children with two *SMN2* copies (A) and three *SMN2* copies (B). The percentage achieving each of the WHO motor milestones including within the normal developmental timeframe is shown in children with two *SMN2* copies (C) and three *SMN2* copies (D). Percentages shown are rounded. Gray shading indicates the WHO motor milestone first and 99th percentiles of age at achievement for healthy, typically developing children: sitting without support (3.8 and 9.2 mo, respectively), standing with assistance (4.8 and 11.4 mo, respectively), hands and knees crawling (5.2 and 13.5 mo, respectively), walking with assistance (5.9 and 13.7 mo, respectively), standing alone (6.9 and 16.9 mo, respectively), and walking alone (8.2 and 17.6 mo, respectively).[31] [a]Median age at achievement of milestone and 95% CI estimated from Kaplan–Meier curve. [b]Achieved by WHO motor milestone 99th percentile. mo, month; *SMN2*, survival motor neuron 2; WHO, World Health Organization.

46.4 (7.44; 36–60), respectively. HFMSE mean and individual total scores showed overall continued improvement in children with either two or three copies (Figure 2A, B). However, one child with two copies (participant 3; Table S1) had stable, low scores (11, 12) with baseline features suggestive of neurodegeneration at baseline (including low weight-for-age [6.7th percentile], areflexia, and ulnar CMAP amplitude [1.5 mV], peroneal not performed). In addition, one child with three copies had scores of 36 and 34 at Days 778 and 897. A lower score (28) was noted at Day 1135 (age 3.1 y); however, the PT noted poor patient cooperation and a score not reflective of the child's abilities.

The predicted mean (95% confidence interval [CI]) slopes in HFMSE total score over time (point change/year) were similar between two (+6.30 [4.70–7.90]; $n = 14$) and three (+6.99 [4.98–

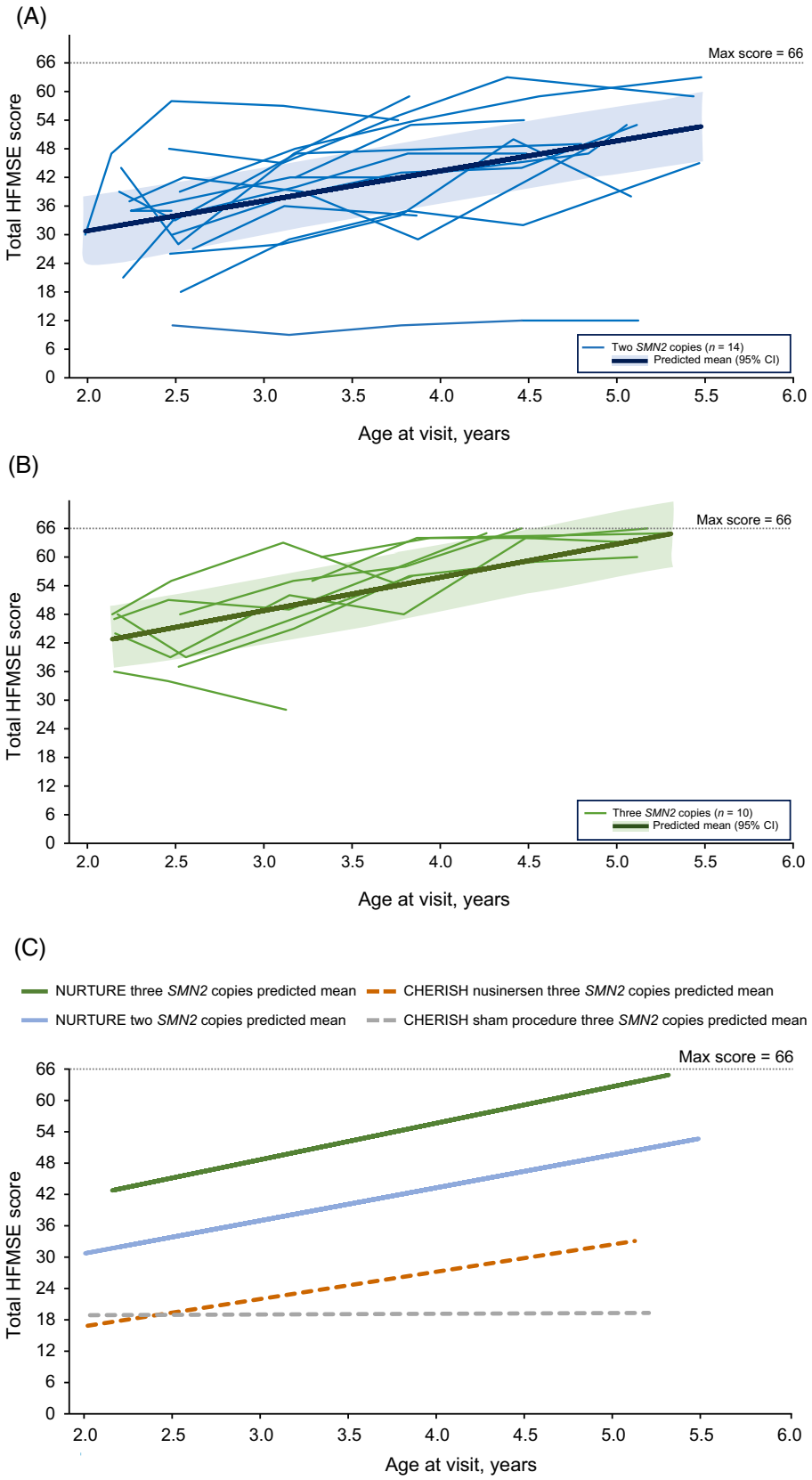

FIGURE 2 HFMSE total scores improved over time in children with two or three *SMN2* copies. Individual trajectories of HFMSE total scores over time are shown for children in the NURTURE study with two *SMN2* copies ($n = 14$) (A) or three *SMN2* copies ($n = 10$) (B); see Section 3.3 for details about the two participants with outlying results. Only evaluable assessments (with ≤6 items missing) were included. HFMSE assessments at Day 700 were excluded (children had to be ≥2 y to be assessed). (C) The predicted mean slopes (with 95% CI) by *SMN2* copy number graphed alongside the predicted mean slopes of HFMSE total scores in children with symptomatic later-onset SMA and three *SMN2* copies in the CHERISH study[28] who received nusinersen or sham procedure control and were non-ambulatory and 2–4 y old at the time of the first HFMSE assessment. This indirect analysis included a random slope and random intercept model to create the fitted lines. In this model, all available data for each participant were used and an average slope was obtained. A limitation of this model is that younger participants on sham who had a decline in function are not as apparent since this analysis is based on age. HFMSE, Hammersmith Functional Motor Scale–Expanded; max, maximum; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2.

9.00]; $n = 10$) *SMN2* copy children (Figure 2C). Predicted mean total score and slopes of improvement over time were higher in NURTURE children with two or three *SMN2* copies than in CHERISH participants with symptomatic later-onset SMA who were treated with nusinersen (+5.22 [4.51–5.94]; $n = 34$) or sham procedure (+0.138 [−0.79, 1.06]; $n = 24$; Figure 2C).

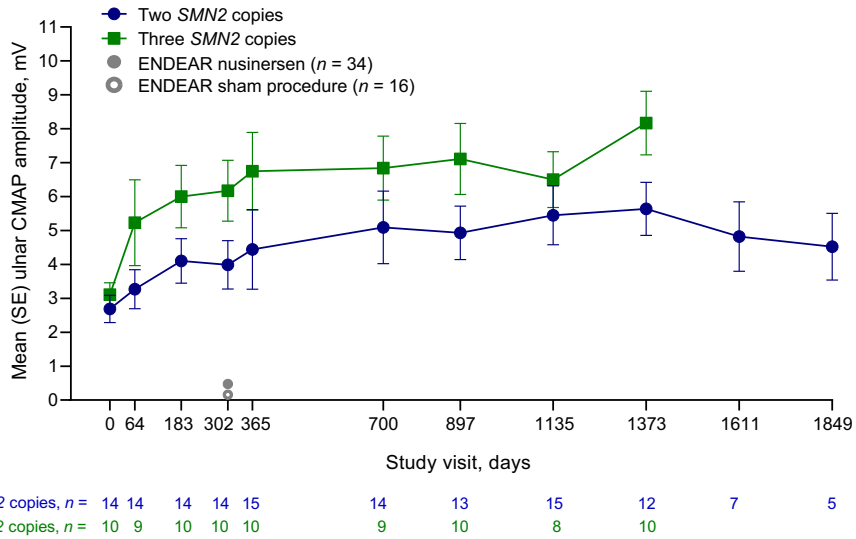

FIGURE 3 Mean ulnar CMAP amplitude improved over time in children with either two or three *SMN2* copies and was higher in those with three *SMN2* copies. Mean ulnar CMAP amplitude improved over time, as would be expected in growing healthy infants.[36] At the Day 302 visit in the ENDEAR study,[25] the mean ulnar CMAP amplitude in symptomatic infants with two *SMN2* copies was 0.48 mV in the nusinersen-treated group and 0.16 mV in the sham procedure control group. Change from baseline at Day 302 was +1.29 mV in NURTURE participants with two *SMN2* copies, +3.06 in NURTURE participants with three *SMN2* copies, +0.267 mV in ENDEAR nusinersen-treated participants, and −0.125 mV in ENDEAR sham control infants. See the Supplement for a description of ENDEAR. CMAP, compound muscle action potential; *SMN2*, survival motor neuron 2.

Eleven children, five with two and six with three *SMN2* copies, had at least one valid 6-Minute Walk Test (6MWT) assessment with total distances of 150–325 m and 238–444 m, respectively, indicating capability of sustained independent walking.

3.5 | Additional endpoints

Baseline mean (SD) ulnar CMAP amplitude was higher in those with three versus two *SMN2* copies (3.11 [1.12] vs. 2.69 [1.52] mV) and increased during the first treatment year with stabilization over time (Figure 3). At Day 1849 ($n = 5$), mean amplitude was 4.52 (2.20) mV in children with two copies (mean change from baseline: 2.32 [1.93] mV). At Day 1373 ($n = 10$), the mean was 8.17 (2.96) mV in children with three copies (mean change from baseline: 5.06 [3.13] mV). Similar results were observed for peroneal CMAP amplitude (not shown).

All children continued to grow and gain weight (Figure 4). Mean weight-for-age stabilized over time, and half (12/25 [48%]) were between the 25th and 75th percentiles of weight-for-age at last visit while 7/25 (28%) were in the <25th percentile and 6/25 (24%) were in the >75th percentile. This contrasts with the lower mean weight-for-age in ENDEAR-SHINE participants treated with nusinersen post-symptom onset (Figure S4). At the last visit when length was measured (age: 3.2–5.1 y), 10/25 (40%) were between the 25th and 75th percentiles for length-for-age, 11/25 (44%) were in the <25th percentile, and 4/25 (16%) were in the >75th percentile.

Since the prior publication,[11] two additional children had percutaneous gastrostomy tube placement, giving a current total of five with gastrostomy tubes, all with two *SMN2* copies (Figure 4A, B). Gastrostomy tube placement occurred at ages 5.9, 19.4, 22.5, 41.9, and 50.1 mo. The reason for tube placement was dysphagia ($n = 3$; 1 used as needed), and low weight ($n = 2$). Of these five (participants 3, 9, 12, 13, 15, Table S1): at baseline, one had low peroneal CMAP amplitude (participant 9; 1.1 mV), three had low ulnar CMAP amplitude (participants 3, 9, 12; 1–1.5 mV); three were areflexic (participants 3, 12, 15), and four were in the <50th percentile for weight-for-age (participants 3, 9, 12, 15). Three of five had plasma and 3/5 had CSF pNF-H levels at or above the median for participants with two *SMN2* copies. During the study, 4/5 required respiratory intervention. All five continued to achieve motor milestones after tube placement, three attained independent walking, and two reached the CHOP INTEND maximum score.

3.6 | Potential impact of baseline low CMAP amplitude and areflexia

As described earlier, eight children, all with two *SMN2* copies, required respiratory intervention, had gastrostomy tube placement, or developed SMA symptoms by age 24 mo (Tables 1, S4). All had at least one of the following baseline characteristics: relatively low (<2 mV) peroneal ($n = 1$) or ulnar ($n = 4$) CMAP amplitudes, areflexia ($n = 3$), and elevated plasma or CSF pNF-H (at or above the median for children with two *SMN2* copies; $n = 5$). To assess the potential impact of these factors on overall outcomes, we analyzed the subset of participants with two *SMN2* copies who at baseline were not areflexic and had peroneal CMAP ≥2 mV, criteria also used in the SPR1NT trial of onasemnogene abeparvovec in presymptomatic children.[12] Eight children

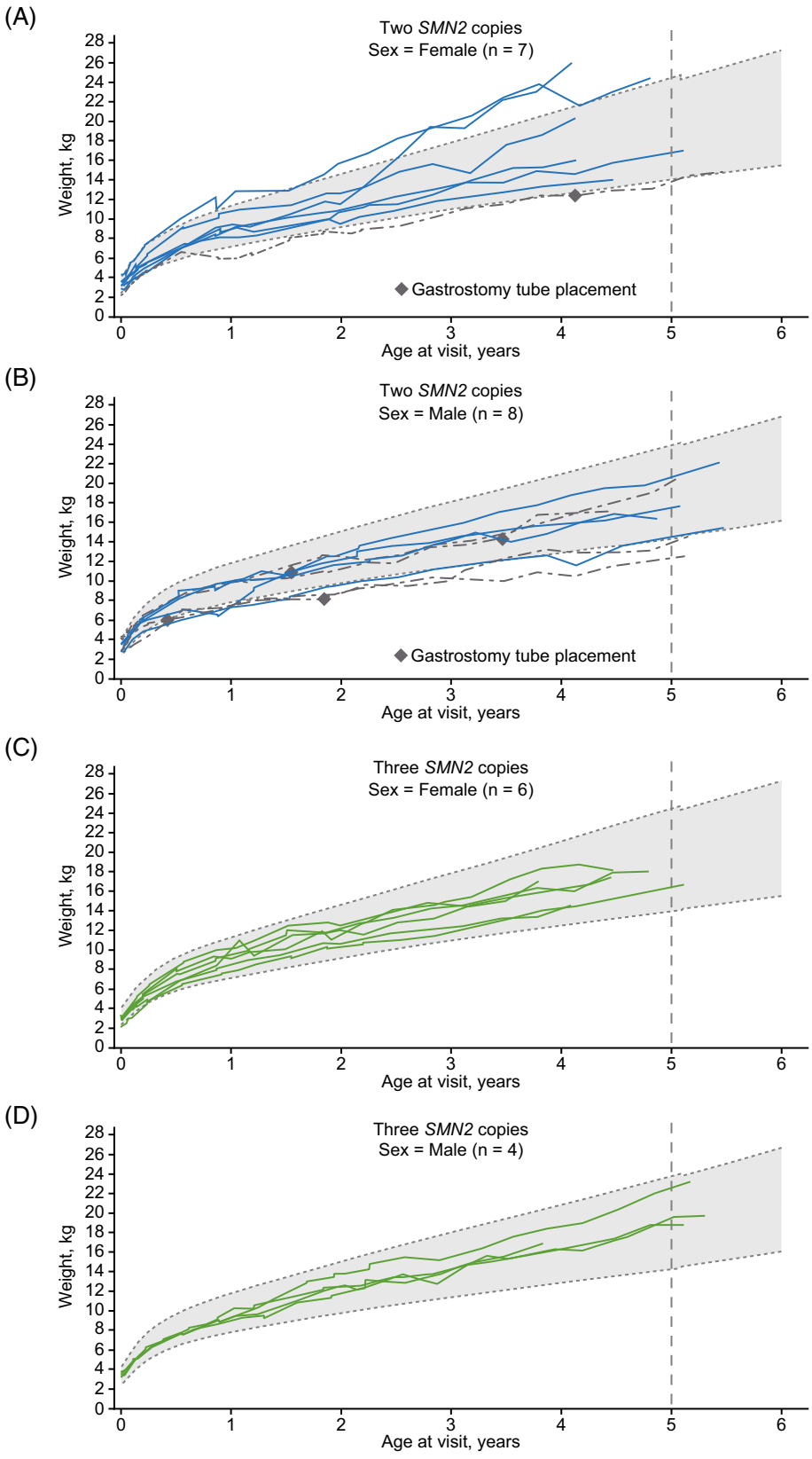

FIGURE 4 Most children with two *SMN2* copies (A, B) and all children with three *SMN2* copies (C, D) maintain body weight over time within the WHO third and 97th growth percentiles for healthy children (shown in gray). The gray dotted lines denote participants who received gastrostomy tube and diamonds denote age of participant at insertion of gastrostomy tube. *SMN2*, survival motor neuron 2; WHO, World Health Organization.

met these criteria (referred to here as "subgroup 1"; participants 1, 5–8, 10, 11, 14). These children were of similar age at first nusinersen dose, had similar baseline HINE-2 scores, and their baseline CHOP INTEND scores were higher versus all children in NURTURE with two *SMN2* copies (Table 2). No child in subgroup 1 received respiratory intervention or gastrostomy tube placement versus four and five children, respectively, among all NURTURE children with two *SMN2* copies. One child (1/8, 13%; participant 10) in this subgroup met the

TABLE 1 Association of baseline characteristics with outcomes of respiratory intervention, gastrostomy tube placement, or development of symptoms of SMA in eight children in NURTURE with two *SMN2* copies[a]

Outcome	*n*	Details at baseline	Participant ID (peroneal CMAP value)
Respiratory intervention[b]	4	• 3 Areflexia • 1 Peroneal CMAP amplitude <2 mV	• 3, 12, 15 • 9 (1.1 mV)
Gastrostomy tube placement[c]	5	• 3 Areflexia • 1 Peroneal CMAP amplitude <2 mV	• 3, 12, 15 • 9 (1.1 mV)
SMA symptoms by 24 mo	7	• 2 Areflexia • 1 Peroneal CMAP amplitude <2 mV	• 3, 15 • 9 (1.1 mV)

Abbreviations: CMAP, compound muscle action potential; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2.
[a]Median (range) age of treatment initiation for the eight children with two *SMN2* copies who required respiratory intervention, had gastrostomy tube placement, or developed symptoms of SMA by age 24 mo was 15 (8–41) days versus 21 (12–29) days in the other seven children with two *SMN2* copies. See Table S4 for additional data shown by each participant.
[b]Endpoint in NURTURE defined as invasive or noninvasive ventilation for ≥6 h/day continuously for ≥7 days or tracheostomy.
[c]Gastrostromy term in the procedures page was used.
[d]Defined by any of the following conditions: (1) age-adjusted weight <fifth percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) compared with baseline, or a percutaneous gastrostomy tube placement for nutritional support by 24 mo of age; (2) failure to achieve sitting without support, standing with assistance, and hands and knees crawling at age 24 mo; or (3) failure to achieve the milestones defined at age 13 mo and failure to achieve walking with assistance, standing alone, and walking alone at age 24 mo.

protocol-specified criteria for SMA symptoms versus 8/15 (53%) among all NURTURE children with two *SMN2* copies. A higher proportion in subgroup 1 achieved WHO motor milestones within normal developmental timeframes versus the overall NURTURE group with two *SMN2* copies (Figure 5).

Subgroup 1 did not include data from seven children with two *SMN2* copies: three were areflexic, one had peroneal CMAP <2 mV, and three had missing tendon reflex ($n = 2$) or peroneal CMAP ($n = 1$) data. To evaluate the potential impact of missing data on these analyses, we conducted a sensitivity analysis and included the children with missing data (participants 2, 4, 13) in a new subgroup (referred to as "subgroup 2"). Subgroup 2 had similar mean age at the first dose and baseline HINE-2 score as all children with two *SMN2* copies in NURTURE and subgroup 1, with CHOP INTEND baseline values of subgroup 2 between these two groups. The proportion achieving WHO motor milestones in subgroup 2 within normal timeframes was generally higher than all NURTURE children with two *SMN2* copies and lower than subgroup 1 (Figure 5).

3.7 | PASA

For most PASA items, participants were consistently rated, on average, as never to rarely experiencing difficulty swallowing over a mean of 2.6 y (assessments began >1 y after treatment initiation; Figures S5–S8). This pattern was observed regardless of *SMN2* copy number, although those with three copies typically had higher mean scores on swallowing-related items. As of their last assessment, 92% (23/25) maintained the ability to swallow. Parents/caregivers did not have concerns about swallowing independent of *SMN2* copy number. At the participant's last PASA assessment, 76% (19/25) of parents/caregivers "disagreed" or "strongly disagreed" with being concerned about their child choking, and 80% (20/25) "disagreed" or "strongly disagreed" with being concerned about their child aspirating on food while eating. All assessed children (10/10) with three *SMN2* copies and the majority (67% [10/15]) with two copies were identified by PASA as not being tube-fed as of the last assessment. Of the five with two *SMN2* copies ever identified by PASA as being tube-fed, two were "always" tube-fed, and three were "often" tube-fed in the 7 days preceding the last assessment.

3.8 | Safety

No new safety concerns were identified with 2 additional years of follow-up. No AE was considered by investigators to be study-drug related (Table S5). Ten (40%) participants had an AE considered possibly related to study drug; all resolved despite continued treatment, except for proteinuria in one child and clonus in another. Twelve (48%) had one or more serious adverse events (SAEs); none were considered by investigators to be study-drug related. When analyzed in approximately yearly intervals, the incidence of SAEs was lower over time with six SAEs in Year 1, five in Year 2, and three in Years 3 and 4 in participants with two *SMN2* copies (Table 3). SAEs were less frequent in children with three *SMN2* copies, with only one to two SAEs in Years 1–3 and zero SAEs in Year 4. No participant discontinued treatment or withdrew because of an AE. The lumbar puncture procedure, which required sedation for some participants, was generally well tolerated. No meningitis, hydrocephalus, or renal/liver failure cases were reported. No clinically relevant trends related to nusinersen in hematology, blood chemistry, urinalysis, coagulation, vital signs, or electrocardiograms were observed.

TABLE 2 Summary of baseline characteristics and select outcomes for children with two *SMN2* copies in NURTURE and SPR1NT[12]

	NURTURE participants with two *SMN2* copies			SPR1NT participants with two *SMN2* copies ($n = 14$)[c]
	All children ($n = 15$)	Subgroup 1 ($n = 8$)[a]	Subgroup 2 ($n = 11$)[b]	
Baseline characteristics, median (range)				
Age at first dose (nusinersen) or dosing (OA), days	19.0 (8–41)	18.5 (8–41)	22.0 (8–41)	21.0 (8–34)
CHOP INTEND	45.0 (25–60)	54.5 (35–60)	50.0 (35–60)	48.5 (28–57)
HINE-2	3.0 (0–5)	3.5 (1–5)	3.0 (0–5)	NR
Ulnar CMAP amplitude, mV	2.30 (1.0–6.7)[d]	3.2 (1.5–6.7)[e]	3.1 (1.5–6.7)[f]	NR
Peroneal CMAP amplitude, mV	3.2 (1.1–9.7)[g]	3.6 (2.5–9.7)	3.3 (2.0–9.7)[f]	3.9 (2.1–6.1)
Outcomes, *n* (%)				
Respiratory intervention[h]	4 (27)	0 (0)	0 (0)	0 (0)
Gastrostomy tube placement	5 (33)[ij]	0 (0)[i]	1 (9)[ik]	0 (0)[i]
SMA symptoms by 24 mo	7 (47)[l]	1 (13)[l]	4 (36)[l]	NR
Time on study, median (range), months	60.4 (48.9–68.6)	58.3 (48.9–68.6)	59.1 (48.9–68.6)	17.1–18.1[m]

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neurological Examination Section 2; OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2.

[a]With peroneal CMAP amplitude ≥2 mV and without areflexia ($n = 8$).

[b]With peroneal CMAP amplitude ≥2 mV and without areflexia ($n = 8$); also includes children with two *SMN2 copies* with missing data who could have met criteria of peroneal CMAP ≥2 mV and no areflexia ($n = 3$).

[c]Data from children with two *SMN2* copies from the SPR1NT trial of onasemnogene abeparvovec[12] included for reference only, not for direct comparison to NURTURE (see Section 4).

[d]Data available in $n = 14$.

[e]Data available in $n = 7$.

[f]Data available in $n = 10$.

[g]Data available in $n = 12$.

[h]Endpoint in NURTURE defined as invasive or noninvasive ventilation for ≥6 h/day continuously for ≥7 days or tracheostomy. Endpoint in SPR1NT defined as mechanical respiratory support (e.g., cough-assist, bilevel positive airway pressure, or invasive ventilatory support) of any kind throughout the duration of the trial.[12]

[i]Gastrostomy term in the procedures page was used in NURTURE. All 14 children in SPR1NT did not receive nutrition through mechanical support (i.e., feeding tube).[12]

[j]Gastrostomy tube placement occurred at ages 5.9, 19.4, 22.5, 41.9, and 50.1 mo.

[k]Gastrostomy tube placement occurred at age 5.9 mo.

[l]Defined by any of the following conditions: (1) age-adjusted weight <fifth percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) compared with baseline, or a percutaneous gastrostomy tube placement for nutritional support by 24 mo of age; (2) failure to achieve sitting without support, standing with assistance, and hands and knees crawling at age 24 mo; or (3) failure to achieve the milestones defined at age 13 mo and failure to achieve walking with assistance, standing alone, and walking alone at age 24 mo.

[m]Minimum and maximum values were determined from Table S4 in the supplementary information for Strauss et al.[12]

4 | DISCUSSION

Two additional years of follow-up in NURTURE, to a median of approximately 5 y, demonstrate durability of benefit with continued improvement associated with nusinersen treatment before the onset of overt clinical signs and symptoms. Unlike untreated SMA Type I patients for whom median time to death or requirement for ventilation support was 13.5 mo,[33] all 25 participants are alive, and none require permanent respiratory ventilation. This cohort is generally manifesting features of normal motor development and improvements in motor skills, even if delayed for some, which contrasts sharply with the progressive decline documented in natural history studies of SMA "Type I or II" phenotypes.[34]

All NURTURE children compare favorably with CHERISH[28] children with symptomatic SMA and three *SMN2* copies who first received nusinersen at age 2–4 y (Figure 2). The additional time for development now available permits further differentiation of the phenotypes associated with early treatment of those inheriting two versus three *SMN2* copy genotypes. In children with two copies, evidence suggests neurodegeneration precedes the onset of symptomatic weakness, whereas neurodegeneration is nascent or less established at this early time in those with three copies.[35] NURTURE thus demonstrates the pathway of more normal developmental maturation is restored by nusinersen-induced amelioration of SMA-associated degeneration: the earlier this begins, the better the outcome. Furthermore, this process appears durable over approximately 5 y of treatment.

Mean ulnar CMAP amplitude increased initially in NURTURE infants before stabilizing. The values were also within the range of those in healthy children aged 0 days–12 mo (3.2–14.8 mV) at study

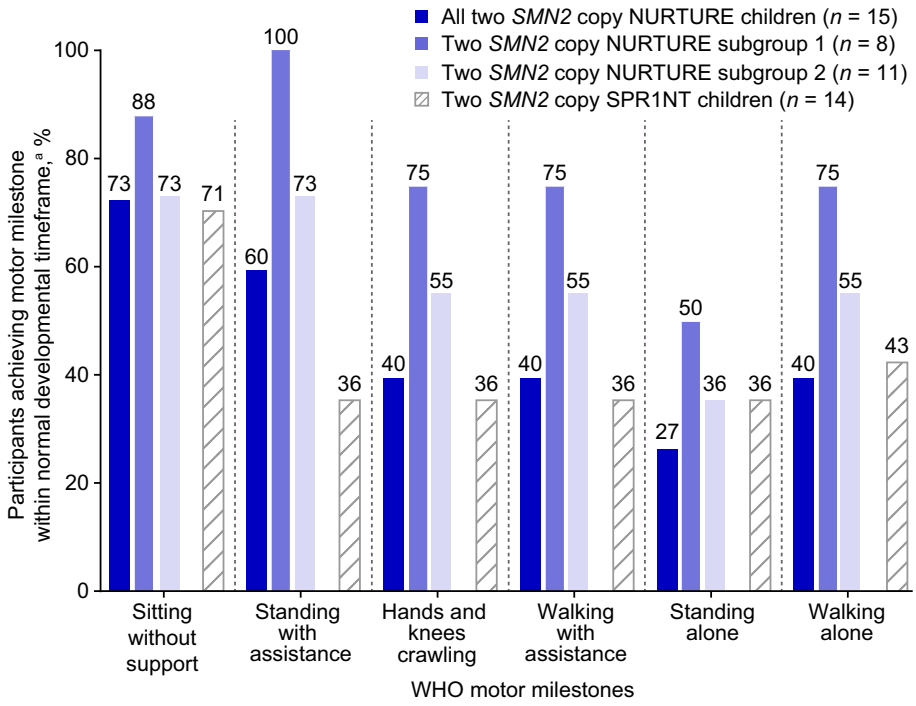

FIGURE 5 Higher proportions of NURTURE children without areflexia and with CMAP amplitude ≥2 mV achieve WHO milestones within normal development timeframe compared with all NURTURE children with two *SMN2* copies. Subgroup 1 includes all NURTURE children with two *SMN2 copies* who have peroneal CMAP amplitude ≥2 mV and who are not areflexic at baseline. Subgroup 2 includes all children in subgroup 1 and three children with two *SMN2 copies* with missing data on reflexes or peroneal CMAP amplitude (i.e., some of whom could have met criteria of peroneal CMAP amplitude ≥2 mV and no areflexia, if data were available). Data from children with two *SMN2* copies from the SPR1NT trial of onasemnogene abeparvovec[12] included for reference only, not for direct comparison to NURTURE (see Section 4). [a]Achieved by WHO motor milestone 99th percentile. CMAP, compound muscle action potential; *SMN2*, survival motor neuron 2; WHO, World Health Organization.

TABLE 3 Incidence of serious adverse events by 360-day interval

	Interval			
	Days 0 to 360	**Days > 360 to 720**	**Days > 720 to 1080**	**Days > 1080 to 1140**
Two *SMN2* copies				
n	15	15	15	15
Any serious AE, *n* (%)	6 (40)	5 (33)	3 (20)	3 (20)
Three *SMN2* copies				
n	10	10	10	10
Any serious AE, *n* (%)	1 (10)	2 (20)	1 (10)	0

Note: Participants are counted only once within each interval.
Note: Year 1 = Days 0–360; Year 2 = Days >360 to 720; Year 3 = Days >720–1080; Year 4 = Days >1080–1140.
Abbreviations: AE, adverse event; *SMN2*, survival of motor neuron 2.

visits of comparable age (Days 183–365).[36,37] This contrasts with ulnar CMAP amplitude deterioration in natural history studies, where maximum ulnar amplitude in infants aged ≥6 mo with two *SMN2* copies was 0.6 mV and rapidly decreased over 24 mo, often to undetectable levels.[34] NURTURE participants with two *SMN*2 copies had greater gains in mean ulnar CMAP amplitude compared with ENDEAR[25] children with symptomatic infantile-onset SMA and two *SMN2* copies, further supporting the importance of early nusinersen initiation.

The magnitude of occult motor neurodegeneration before definitive SMA symptom manifestations may be an important determinant of clinical outcomes.[10] Of eight children (all with two *SMN2* copies) who required respiratory intervention, had gastrostomy tube placement, or developed SMA symptoms by age 24 mo, all had ≥1 of the following baseline characteristics, suggesting greater than average occult neurodegeneration for the *SMN2* copy group: low CMAP amplitude, areflexia, or elevated pNF-H. This raises the question of whether these eight children would meet the definition of

presymptomatic today, for example, as prodromal,[10] or would be classified as early symptomatic patients.

A NURTURE inclusion criterion was ulnar CMAP amplitude ≥1 mV. Subsequent trials of other agents, however, used higher CMAP amplitude values: ≥1.5 mV CMAP amplitude for the primary analysis group[14] in a presymptomatic study with risdiplam (RAINBOWFISH) and ≥2 mV peroneal CMAP amplitude in a presymptomatic trial with onasemnogene abeparvovec (SPR1NT) and also excluding areflexia (SPR1NT).[12] This raises the possibility that these trials may have included different types of presymptomatic populations.

Application of these criteria by post hoc exclusion of NURTURE participants who did not have peroneal CMAP amplitude ≥2 mV or had areflexia yielded a subgroup with outcomes better than those of the broader NURTURE group with increased proportions achieving motor milestone within normal developmental timeframes and either no or fewer children with respiratory intervention, gastrostomy tube placement, and SMA symptoms within 24 mo. This post hoc analysis "rectifies" some of the key inclusion/exclusion criteria between different treatment trials of two *SMN2* copy patients. Overall, these data suggest that even relatively small differences in inclusion/exclusion criteria and baseline characteristics impact clinical outcomes observed during long follow-up and are important to consider when comparing clinical treatment trials.

When assessing the percentage of children with two *SMN2* copies reaching motor milestones within normal developmental windows in NURTURE and SPR1NT, similar outcomes were observed. While the length of follow-up in SPR1NT to age 18 mo[12] for children with two *SMN2* copies was shorter than in NURTURE, this is sufficient to assess milestones within normal developmental windows, given the walking-alone normal developmental window is ≤17.6 mo.[31] With application of inclusion/exclusion criteria for CMAP amplitude and areflexia used in SPR1NT, a greater percentage in these NURTURE subgroups attained motor milestones within normal developmental timeframes (Figure 5). However, no conclusions can be drawn about the comparative efficacy of these two agents based on these analyses due to inherent limitations, for example, small sample size and trial design and baseline characteristic differences. The important differences in trial design include shorter follow-up in SPR1NT versus NURTURE. While four children met the endpoint for respiratory intervention and five had gastrostomy tube placed in NURTURE, most of these events in NURTURE (two of four and four of five) occurred after the "18-month" visit in SPR1NT, underscoring challenges of data interpretation across different trials.

It is particularly important to highlight the differences in baseline characteristics in the NURTURE subgroups and SPR1NT (Table 2), as this is one of the key reasons that outcomes in this and other trials cannot be compared. For example, while baseline CHOP INTEND values were higher in NURTURE subgroups 1 and 2 versus all NURTURE children with two *SMN2* copies, SPR1NT baseline CHOP INTEND values were intermediate between these groups. Similarly, CMAP amplitude baseline values in SPR1NT children with two *SMN2* copies were higher than those in any NURTURE groups. Thus, while our analyses highlight the importance of the different baseline characteristics for trial outcomes, they do not inform on comparative efficacy of these two agents.

Although tempting to draw conclusions about the frequency of gastrostomy tube use among nusinersen patients treated presymptomatically, the above analyses highlight important considerations of baseline characteristics. Furthermore, gastrostomy tube use is not necessarily an indicator of impaired bulbar function as clinicians use different criteria as a threshold for placement. All five participants with gastrostomy tube placement continue to demonstrate motor function improvements and three achieved independent walking. This illustrates the benefit of nusinersen in a broad population and is consistent with prior studies in older nusinersen-treated infants and children.[38–41]

This study has limitations. Participant cooperation and ability to adhere to test instructions are crucial for achieving motor function scores that reflect the participant's true ability. Thus, HMFSE and 6MWT are likely more reliable in older children. In addition, COVID-19 pandemic-related constraints resulted in treatment delays of up to 2 mo, though rapid restoration of nusinersen CSF levels would be expected following administration of subsequent doses at regularly scheduled visits.[42]

The data support the favorable safety profile of nusinersen over longer treatment durations. The safety profile of nusinersen is consistent with previous clinical studies in infantile-onset SMA.[20,23–25,43]

Treatment following onset of early neurodegeneration before definitive symptoms creates an opportunity to examine previously obscured features. The experience suggests new assessment opportunities (e.g., assessing two *SMN2* copy children with HFMSE and 6MWT) and previously unknown limitations. CHOP INTEND was developed for SMA Type I infants but with survival beyond 2 y, some infant-specific items can no longer be reliably tested in older children. Progressive deficits in older children are also less well-assessed by infantile metrics due to confounding factors, for example, obesity, scoliosis, contractures. Ordinal scales developed in the pretreatment era may thus be insensitive to treatment effects and limitations. Subtle features (e.g., fasciculations, tremor, muscle tone) and improvements missed by existing assessments might be detected by patient-reported assessments[44] or physical exam.

In contrast with natural history patients, NURTURE children were alive, did not require permanent respiratory support, and continued to progress without evidence of motor function regression. Most achieved motor milestones in normal developmental timeframes. Nusinersen has demonstrated a favorable safety profile with no new safety concerns identified. These results demonstrate long-term treatment effect across approximately 5 y and emphasize the value of early diagnosis, inclusion of SMA in recommended national uniform newborn screening panels, and early nusinersen initiation in the presymptomatic stage.

AUTHOR CONTRIBUTIONS

Thomas Crawford: Investigation; writing – review and editing. **Kathryn J Swoboda:** Investigation; writing – review and editing. **Darryl C. De Vivo:** Investigation; writing – review and editing. **Enrico Bertini:** Investigation;

writing – review and editing. **Wuh-Liang Hwu:** Investigation; writing – review and editing. **Richard Finkel:** Investigation; writing – review and editing. **Janbernd Kirschner:** Investigation; writing – review and editing. **Nancy Kuntz:** Investigation; writing – review and editing. **Aledie Navas Nazario:** Investigation; writing – review and editing. **Julie A Parsons:** Investigation; writing – review and editing. **Astrid Pechmann:** Investigation; writing – review and editing. **Monique Ryan:** Investigation; writing – review and editing. **Russell Butterfield:** Investigation; writing – review and editing. **Haluk Topaloğlu:** Investigation; writing – review and editing. **Tawfeg Ben-Omran:** Investigation; writing – review and editing. **Valeria Ada Sansone:** Investigation; writing – review and editing. **Yuh-Jyh Jong:** Investigation; writing – review and editing. **Francy Shu:** Investigation; writing – review and editing. **Cong Zhu:** Formal analysis; writing – review and editing. **Stephanie Raynaud:** Formal analysis; writing – review and editing. **Tiffany R Lago:** Formal analysis; writing – review and editing. **Angela Paradis:** Formal analysis; writing – review and editing. **Richard Foster:** Conceptualization; formal analysis; writing – review and editing. **Russell Chin:** Conceptualization; formal analysis; writing – review and editing. **Zdenek Berger:** Conceptualization; formal analysis; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Requests for the materials and data supporting this manuscript should be submitted to https://vivli.org/.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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