

# Nusinersen Treatment in Adults With Spinal Muscular Atrophy

Tina Duong, PT, PhD, Connie Wolford, MSN, FNP-BC, Michael P. McDermott, PhD, Chelsea E. Macpherson, PT, DPT, NCS, Amy Pasternak, PT, DPT, PCS, Allan M. Glanzman, PT, DPT, PCS, William B. Martens, BA, Elizabeth Kichula, MD, BA, Basil T. Darras, MD, Darryl C. De Vivo, MD, Zarazuela Zolkipli-Cunningham, MBChB, MRCP, Richard S. Finkel, MD, Michael Zeineh, MD, PhD, Max Wintermark, MD, Jacinda Sampson, MD, PhD, Katharine A. Hagerman, PhD, Sally Dunaway Young, PT, DPT, and John W. Day, MD, PhD on behalf of the Stanford Neuromuscular Coordinating Center

**Correspondence**

Dr. Duong  
trduong@stanford.edu

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## Abstract

### Objective

To determine changes in motor and respiratory function after treatment with nusinersen in adults with spinal muscular atrophy (SMA) during the first two years of commercial availability in the USA.

### Methods

Data were collected prospectively on adult (age >17 years at treatment initiation) SMA participants in the Pediatric Neuromuscular Clinical Research (PNCR) Network. Baseline assessments of SMA outcomes including the Expanded Hammersmith Functional Rating Scale (EHFMRSE), Revised Upper Limb Module (RULM), and 6-Minute Walk Test (6MWT) occurred <5 months before treatment, and post-treatment assessments were made up to 24 months after nusinersen initiation.

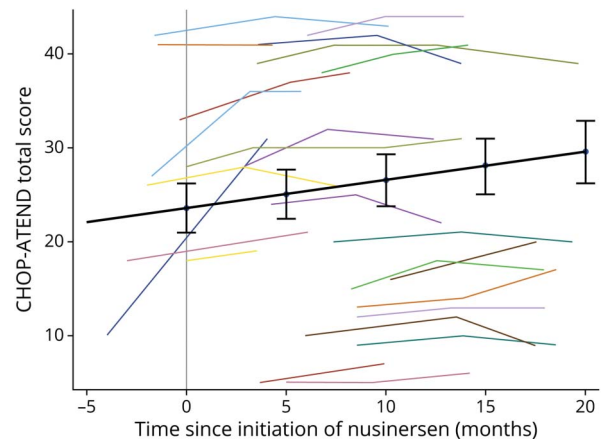
Patient-reported experiences, safety laboratory tests and adverse events were monitored. The mean annual rate of change over time was determined for outcome measures using linear mixed effects models.

### Results

Forty-two adult SMA participants (mean age: 34 years, range 17-66) receiving nusinersen for a mean of 12.5 months (range 3-24 months) were assessed. Several motor and respiratory measures showed improvement distinct from the progressive decline typically seen in untreated adults. Participants also reported qualitative improvements including muscle strength, stamina, breathing and bulbar related outcomes. All participants tolerated nusinersen with normal surveillance labs and no significant adverse events.

### Conclusions

Trends of improvement emerged in functional motor, patient-reported, and respiratory measures, suggesting nusinersen may be efficacious in adults with SMA. Larger well-controlled studies and additional outcome measures are needed to firmly establish the efficacy of nusinersen in adults with SMA.

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Criteria for rating therapeutic and diagnostic studies

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Departments of Neurology (TD, CW, SDY, KAH, JS, JWD), Rehabilitation (CEM), and Radiology (MZ, MW), Stanford University School of Medicine, Palo Alto, CA; Departments of Biostatistics and Computational Biology (MPM), and Neurology (MPM and WBM), University of Rochester Medical Center, NY; Department of Neurology (AP,BTD), Boston Children's Hospital, MA; Department of Neurology (DCD), Columbia University, New York; Department of Neurology (AMG EAK, ZZ) Children's Hospital of Philadelphia, PA; and Department of Pediatrics (RSF) Nemours Children's Hospital, Orlando, FL.

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Coinvestigators from the Stanford Neuromuscular Coordinating Center are listed in appendix 2 at the end of the article.

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## Classification of Evidence

This study provides Class IV evidence regarding nusinersen tolerability and efficacy based on reported side effects and pulmonary and physical therapy assessments in an adult SMA cohort.

Spinal muscular atrophy (SMA) is an autosomal recessive disorder affecting 1: 7,000–11,000 live births.<sup>1,2</sup> In SMA, survival motor neuron (SMN) protein deficiency leads to motor neuron dysfunction and degeneration, causing progressive muscle atrophy, weakness, and early mortality.<sup>3,4</sup> SMN protein is produced by *SMN1* and *SMN2* genes, with pathogenicity occurring only with no functional copies of *SMN1*. *SMN2* generates protein less efficiently, but increased *SMN2* gene copy number increases SMN protein and decreases disease severity.<sup>5,6</sup>

Nusinersen is an antisense oligonucleotide that modifies *SMN2* RNA splicing, increasing protein production.<sup>7,8</sup> Nusinersen was effective at improving motor function and survival in infantile- and childhood-onset SMA<sup>9–15</sup> leading to US Food and Drug Administration (FDA) approval in December 2016 for SMA in all ages. Notably, at the time of its approval, trials of nusinersen did not include adults.

Understanding of infantile- and childhood-onset SMA has progressed rapidly because of molecular confirmation of the diagnosis coupled with multicenter natural history studies that enabled stratification by age, functional ability, and rate of change.<sup>10,11,16–20</sup> Older, more chronically affected patients vary in functional ability and disease course, and tolerate fewer assessments without considerable fatigue, making research more difficult. An inverse relationship between motor function and disease progression for ages >15<sup>20</sup> and >20 years<sup>21</sup> have been described in treatment-naïve adults.

This is a case series of SMA adults in whom nusinersen was initiated. We report motor and respiratory changes before and after nusinersen treatment to better understand possible treatment effects.

## Methods

This study is part of a multisite longitudinal study of SMA. Data were collected based on initial functional status for all individuals in the study (figure 1). As part of the medical history, we also obtained information on surgical history, medications, SMA type (historically highest functional level achieved), age at diagnosis, disease duration, *SMN2* copy number, and current functional status.

### Standard Protocol Approvals, Registrations, and Patient Consents

Data were collected prospectively through an IRB-approved study conducted by the Pediatric Neuromuscular Clinical Research (PNCR) Network on all nusinersen-treated adults (age ≥17 years at the start of treatment) at participating centers with genetic confirmation and clinical symptoms of SMA. Forty-two participants provided informed consent before evaluations. Data

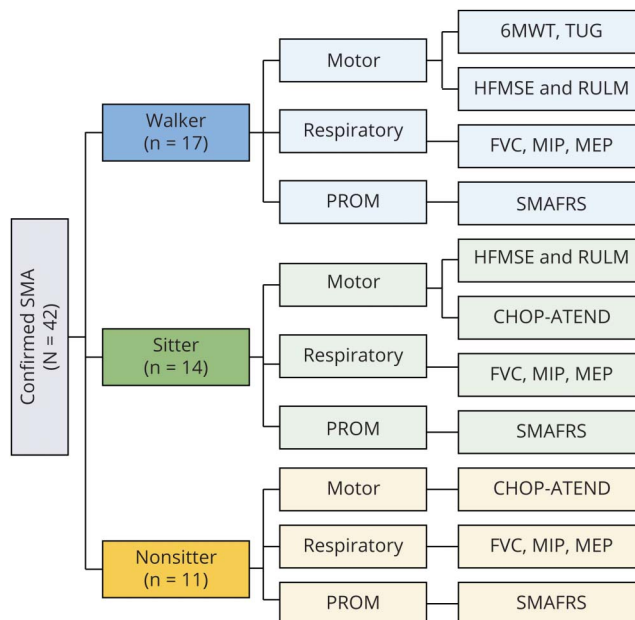
were collected from January 2017 to March 2019. The purpose was to evaluate changes in clinical outcome measures and to obtain safety information related to nusinersen treatment.

Clinical assessments were performed approximately every 4 months during clinic visits. Intrathecal loading doses of 12 mg of nusinersen were given based on the recommended schedule (baseline, day 14, day 28, day 58, and every 4 months thereafter). Safety laboratory tests performed before injection included platelet count, prothrombin time, partial thromboplastin time, and urine protein.

## Clinical Evaluations

Clinical outcomes were obtained during clinic visits using a minimal data set determined by the PNCR network based on participant functional status as well as insurance requirements (figure 1). Clinical evaluators were physical therapists with consistent training in the PNCR network and other clinical trials to administer the outcome measures. The same evaluator was used for most visits throughout the time frame of data collection. Clinical outcome measures were selected based on previous natural history studies in SMA and their

**Figure 1** Clinical Outcomes Based on Functional Groups



6MWT = 6-minute walk test; CHOP-ATEND = Children's Hospital of Philadelphia's Adult Test of Neuromuscular Disorders; FVC = forced vital capacity; HFMSE = Expanded Hammersmith Functional Motor Scale; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; PROM = patient-reported outcome measure; RULM = revised upper limb module; SMAFRS = Spinal Muscular Atrophy Functional Rating Scale; TUG = timed up and go.

sensitivity of assessment to detect change. Validated motor outcomes in SMA were selected for each participant based on the participant's baseline functional status: Walker (able to take 5 steps independently), sitter (able to sit independently for 3 seconds without support), and nonsitter (unable to sit independently) (figure 1).

The Children's Hospital of Philadelphia Adult Test of Neuromuscular Disorders (CHOP-ATEND) used in this study was a new scale modified from the original Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and excluded items that cannot be performed with adults (items 11, 15, and 16).<sup>24</sup> Because the CHOP-INTEND was a scale designed to assess infants with SMA type 1,<sup>25</sup> there were minimal considerations in the manual for the impact of contractures on scoring. With adults, contractures have greater influence on test administration and evaluation of results; therefore, criteria for start positions, contracture considerations, and grading methodology were clarified while keeping the construct of the items intact. The Spinal Muscular Atrophy Functional Rating Scale (SMAFRS),<sup>26</sup> a patient-reported outcome measure, and pulmonary function tests of forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) were performed in all functional groups. The Hammersmith Functional Motor Scale Expanded (HFMSSE),<sup>27</sup> Revised Upper Limb Module (RULM),<sup>28</sup> 6-minute walk test (6MWT), and timed up and go (TUG)<sup>29</sup> were performed using standardized reliable methods established by the PNCN Network.<sup>16,17</sup>

### Statistical Analysis

Five participants did not have clinical evaluations coincident with nusinersen initiation; therefore, the most recent evaluations before starting nusinersen, all within 5 months of the first dose, were used as the pretreatment value in the analyses. All data collected after nusinersen initiation were also included. Linear mixed-effects models were used to estimate the mean annual rate of change (slope) for each outcome. This was done for the cohort of all participants as well as by subgroups defined by SMA type (2 and 3), SMN2 copy number (3 and 4), functional status (nonsitter, sitter, and walker), and history of spinal surgery. The model for estimating the overall mean slope included time after nusinersen initiation (continuous, expressed in years) with random intercept and slope coefficients. To estimate mean slopes in subgroups, the above model was expanded to include the appropriate main effect and interaction terms (e.g., SMA type and the interaction between SMA type and year).

### Data Availability

Deidentified data may be shared with any qualified investigator on request. Data can be requested by all interested stakeholders for clinical research and trial planning. Data requests are reviewed by the PNCN Steering Committee, which can be contacted via the corresponding author.

## Results

The 42 nusinersen-treated participants were adults with SMA type 2 or type 3 (table 1) who were treated for a range of 3–24 months (mean treatment duration 12.5 months). The mean age at treatment initiation was 33.7 years (range 17.7–66.1 years), 57% were male, and 62% had 3 copies of the SMN2 gene. The distribution of functional status was nonsitter (n = 17), sitter (n = 14), and walker (n = 11) (table 1). A broad spectrum of function was represented at baseline, with a median HFMSSE score of 19.0 (range 0–60) and a mean RULM score of 18.2 (range 0–37) (table 1).

A total of 306 injections were performed. Procedure approaches were all through lumbar access with 155 traditional blind lumbar punctures (LPs), 136 fluoroscopy guided LPs, and 15 LPs requiring CT guidance. An interlaminar lumbar approach took place in all but 2.3% that required a transforaminal approach. Four patients discontinued treatment: 1 for personal reasons despite continued successful injections, 2 for a combination of insurance limitations and lack of perceived ongoing effectiveness, and 1 due to bony overgrowth at the only thecal access site. Of these patients who discontinued treatment, 3 had treatment for 18 months and 1 for 10 months.

Overall, nusinersen was well tolerated with 2 reported cases of mild thrombocytopenia (platelet counts between 100,000 and 150,000) that resolved spontaneously and 3 cases of transient limb pain not directly related to the injection procedure that resolved within a few months. Adverse events were rare, mild, and transient and did not warrant discontinuation of therapy. The most common adverse event post-LP was transient headache that in all cases resolved spontaneously. This occurred following 16 of 234 injections (6.8%) and affected 6 patients (14.3%), an incidence comparable to that in other studies using atraumatic needles to reduce post-LP headaches.<sup>30,31</sup> Other infrequently reported adverse events included injection site pain, nausea/vomiting, lightheadedness, and anxiety. No cases of hydrocephalus, bleeding/bruising, or renal compromise were identified. All adverse events resolved quickly without intervention.

Table 2 shows the mean annual rates of change (slopes) with corresponding 95% confidence intervals (CIs) for all participants. Notably, all mean slopes were in a positive direction, although some were accompanied by wide CIs. For the motor measures, the most prominent improvement was seen with the CHOP-ATEND (mean slope = 3.59 points/year, 95% CI 0.67–6.51, figure 2) and the SMAFRS (mean slope = 1.44 points/year, 95% CI 0.04–2.83,  $p = 0.04$ ). Improvements in the CHOP-ATEND were most noticeable in those with more severe phenotypes (SMA type 2, nonsitters, and those with 3 SMN2 copies; table 3). In the small subset of participants who performed the TUG test (n = 8), the mean slope on the log scale was –0.10 (95% CI –0.21 to 0.01) with a negative value indicating improvement in the time to complete this task. To interpret this on a time scale (seconds), exponentiating these values reveals that, on average, the time to

**Table 1** Clinical Characteristics

Variable	
<b>Age (y); mean (SD), range</b>	33.7 (12.6), 17.7 to 66.1
<b>Age at onset (mo); median, range</b>	18.0, 3.0 to 180.0
<b>Disease duration (y); mean (SD), range</b>	30.9 (12.3), 12.1 to 60.6
<b>Sex; N (%)</b>	
Male	24 (57.1)
Female	18 (42.9)
<b>SMN2 copy number; N (%)<sup>a</sup></b>	
2	1 (2.8)
3	26 (72.2)
4	9 (25.0)
<b>SMA type<sup>22</sup>; N (%)<sup>b</sup></b>	
2A	8 (19.1)
2B	10 (23.8)
3A	12 (28.6)
3B	12 (28.6)
<b>Functional status at baseline; N (%)</b>	
Nonsitter	17 (40.5)
Sitter	14 (33.3)
Walker	11 (26.2)
<b>Spinal fusion; N (%)</b>	
Yes	16 (38.1)
No	26 (61.9)
<b>HFMSE: median, range (n = 39)</b>	19, 0 to 60
<b>RULM: mean (SD), range (n = 41)</b>	18.2 (14.0), 0 to 37
<b>CHOP-ATEND: mean (SD), range (n = 26)</b>	23.4 (12.1), 5 to 42
<b>6MWT distance (m): mean (SD), range (n = 10)</b>	300.2 (123.8), 69 to 466
<b>TUG (s): median, range (n = 8)</b>	10.0, 8.4 to 44.7
<b>SMAFRS: median, range (n = 33)</b>	15.0, 0 to 49
<b>FVC (%): mean (SD), range (n = 31)</b>	61.5 (33.0), 9 to 112
<b>MEP (cm H<sub>2</sub>O): mean (SD), range (n = 29)</b>	50.6 (26.8), 11 to 97
<b>MIP (cm H<sub>2</sub>O): mean (SD), range (n = 29)</b>	-79.8 (44.0), -174 to -8

Abbreviations: 6MWT = 6-minute walk test; CHOP = Children's Hospital of Philadelphia; CHOP-ATEND = Children's Hospital of Philadelphia Adult Test for Neuromuscular Disorders; CI = confidence interval; FVC = forced vital capacity; HFMSE = Hammersmith Functional Motor Scale Expanded; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; RULM = revised upper limb module; SMA = spinal muscular atrophy; SMAFRS = Spinal Muscular Atrophy Functional Rating Scale; SMN2 = survival motor neuron 2; TUG = timed up and go.

<sup>a</sup> SMN2 copy number was missing in 6 subjects.

<sup>b</sup> 2A = able to sit unsupported and no ability to stand or walk with help; 2B = able to sit unsupported and able to stand or walk with help; 3A = able to walk independently and symptom onset ≤36 mo of age; 3B = able to walk independently and symptom onset >36 mo of age.

perform the TUG test at 1 year was 0.90 (or 90%) of that at baseline (95% CI 0.81–1.01).

There was a wide range of ventilatory function among participants (table 1). Overall, respiratory measures exhibited a mean rate of change indicating potential improvement after nusinersen treatment (table 2), most prominently with respiratory muscles of MEP (mean slope = 6.38 cm H<sub>2</sub>O/year, 95% CI 2.52–10.25) and to a lesser extent MIP (mean slope = -5.50 cm H<sub>2</sub>O per year, 95% CI -11.47 to 0.47).

Subcohort analyses were also performed to better understand the influence of SMN2 copy numbers (table 3). In our study, 9 individuals had 4 copies of SMN2, 2 of whom were female. We found broad heterogeneity in this cohort with 2 nonsitters, 2 sitters, and 5 ambulatory participants with age ranging from 26.7 to 65.5 years. All were diagnosed as SMA type 3 except 1 being SMA type 2, and disease duration ranged from 12 months to 15 years. This range in phenotypes and small sample size explains the variation in rates of change seen in the outcome measures.

## Discussion

This study is a prospective observational study of adults with SMA treated with nusinersen in the real-world setting. Results indicate that nusinersen is safe and tolerable in a heterogeneous group of adults with SMA types 2 and 3 ranging from ages 17 to 66 years. Participants of this study were not included in the 2 pivotal clinical trials of nusinersen and began treatment after FDA approval of nusinersen.

Participants in this study have reported common subjective improvements that are consistent with those of recent reports<sup>31–33</sup> including greater active range of motion in the fingers and hands; louder voice; and improved jaw movement and speech, which differ from reported natural history of progressive bulbar dysfunction and decreased mouth opening associated with fatty degeneration of the lateral pterygoid muscles.<sup>34</sup> These gains are consistent with a previous study of older individuals with SMA in which 8 of 12 individuals had similar improvements in upper limb and head movement.<sup>33</sup>

Although limited natural history data in SMA are available for the TUG,<sup>29</sup> SMAFRS,<sup>26</sup> and the respiratory measures including MIP and MEP,<sup>35</sup> our data in adults treated with nusinersen diverge from the expected progressive course of the disease.<sup>16,35</sup> Further data collection and validation will be helpful to determine the utility of these measures in monitoring response to treatment.

Clinical evaluations performed were based on baseline functional status of the participants (figure 1). For this reason, all 42 participants did not receive the same evaluations. The HFMSE was performed on some nonsitters showing a floor effect of

**Table 2** Average Rates of Change per Year in Outcome Measures

Outcome	N	Slope <sup>a</sup>	95% CI
HFMSE	31	0.86	(-0.52 to 2.24)
RULM	39	0.11	(-0.45 to 0.67)
CHOP-ATEND	24	3.59	(0.67 to 6.51)
6MWT distance (m)	10	3.29	(-28.04 to 34.62)
Log [TUG (s)]	8	-0.10 <sup>b</sup>	(-0.21 to 0.01)
SMAFRS	31	1.44	(0.04 to 2.83)
FVC (%)	27	0.75	(-1.87 to 3.38)
MEP (cm H <sub>2</sub> O)	25	6.38	(2.52 to 10.25)
MIP (cm H <sub>2</sub> O)	26	-5.50 <sup>b</sup>	(-11.47 to 0.47)

Abbreviations: 6MWT = 6-minute walk test; CHOP-ATEND = Children's Hospital of Philadelphia Adult Test for Neuromuscular Disorders; CI = confidence interval; FVC = forced vital capacity; HFMSE = Hammersmith Functional Motor Scale Expanded; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; RULM = revised upper limb module; SMAFRS = Spinal Muscular Atrophy Functional Rating Scale; TUG = timed up and go.

<sup>a</sup> Slope is expressed as the unit change in outcome per year.

<sup>b</sup> The negative slopes for TUG and MIP are consistent with functional improvements in those measures.

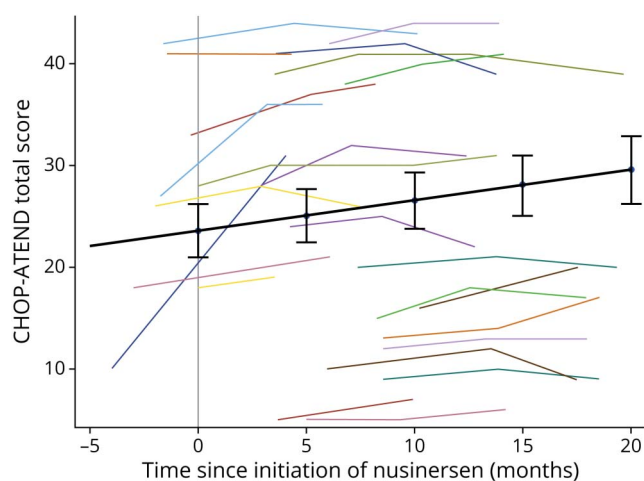
only being able to complete 2 items (hip and knee flexion when supine). For those who had a CHOP-ATEND assessment alongside the RULM or HFMSE assessment, 90.9% (10/11) individuals had a floor effect (score of 0) on the HFMSE and 54.5% (6/11) had a floor effect (score of 0) on the RULM. We were able to capture a broader range of motor abilities in those who were weaker with the CHOP-ATEND score, which ranged from 5 to 28.

The mean HFMSE rate of change did not differ substantially among the functional groupings in a natural history study and was fairly consistent with estimated decline between 0.5 and 1 points

per year.<sup>35</sup> Unlike the recent publication performed by 10 clinical sites in Germany, none of the subgroups or functional cohorts we analyzed had a significant 3 point improvement on the HFMSE.<sup>36</sup> This may be due to our small sample size and the heterogeneity of our cohort (range of 0–60 points on the HFMSE, figure 3). Patients with SMA with long-standing spinal fusions have greater truncal stability, ventilatory ability, and upper limb function with fewer compensatory mechanisms; despite a wide CI, our observation of improved respiratory function and RULM responses with nusinersen in adults with spinal fusions were consistent with the German study.<sup>36</sup>

Insurance approvals for nusinersen treatment may be varied for individuals with 4 copies of *SMN2*. Our study highlights a heterogeneous group of 9 adults with 4 copies of *SMN2* including 4 participants with SMA type 2/3 classified as nonsitters and 5 participants with SMA type 3 classified as ambulatory. Despite inherent flaws in accurately ascertaining symptom onset in the adult population, disease duration should be monitored as a phenotypic feature that may clarify prognosis and response to treatment for adults with 4 *SMN2* copies.

Initial reports regarding tolerability in adults assessed motor function scores before and after loading doses of nusinersen in 28 adults with SMA. They found that nusinersen administration was safe and tolerable, yet unsurprisingly found no significant improvements in the 2-month follow-up period.<sup>31</sup> Initial real-world studies reported on a cohort of 19 adults treated for up to 10 months and found improvements in the 6MWT and RULM, but no significant changes in other measures.<sup>37</sup> Compared with our study, their patient cohort was functionally stronger with 63% being ambulatory compared with only 26% in our study. Similar to our findings, there were no significant changes in FVC; however, they found significant improvements in peak cough, which

**Figure 2** Average Annual Rate of Change in CHOP-ATEND

Children's Hospital of Philadelphia Adult Test for Neuromuscular Disorders (CHOP-ATEND) results for the entire population studied (n = 24). Individual subject trajectories are shown. The dark line (with standard error bars) depicts the average trajectory, as estimated from a linear mixed-effects model.

**Table 3** Average Rates of Change per Year in Outcome Measures in Participant Subgroups

Outcome	N	Slope <sup>a</sup>	95% CI
<b>HFMSE</b>			
Type 2	11	0.66	-1.63 to 2.95
Type 3	20	0.99	-0.77 to 2.74
3 SMN2 copies	18	0.55	-0.97 to 2.06
4 SMN2 copies	7	-0.15	-2.41 to 2.10
Nonsitter	9	-0.24	-3.57 to 3.09
Sitter	11	1.13	-1.11 to 3.36
Walker	11	1.09	-1.26 to 3.44
No spinal fusion	21	1.24	-0.53 to 3.01
Spinal fusion	10	0.13	-2.21 to 2.47
<b>RULM</b>			
Type 2	16	0.43	-0.44 to 1.31
Type 3	23	-0.12	-0.81 to 0.57
3 SMN2 copies	24	0.22	-0.41 to 0.85
4 SMN2 copies	8	-0.23	-1.11 to 0.66
Nonsitter	16	-0.17	-1.09 to 0.74
Sitter	12	0.74	-0.32 to 1.80
Walker	11	-0.01	-1.02 to 0.99
No spinal fusion	25	-0.22	-0.77 to 0.33
Spinal fusion	14	1.01	0.03 to 1.98
<b>SMAFRS</b>			
Type 2	12	0.74	-1.57 to 3.06
Type 3	19	1.89	0.21 to 3.58
3 SMN2 copies	19	1.32	-0.37 to 3.02
4 SMN2 copies	8	0.43	-1.81 to 2.66
Nonsitter	13	0.69	-1.67 to 3.04
Sitter	9	2.88	0.56 to 5.19
Walker	9	0.51	-1.98 to 3.00
No spinal fusion	23	1.28	-0.35 to 2.91
Spinal fusion	8	1.85	-1.06 to 4.77
<b>CHOP-ATEND</b>			
Type 2	14	3.75	-0.16 to 7.66
Type 3	10	3.26	-1.34 to 7.86
3 SMN2 copies	18	3.62	-0.10 to 7.35
4 SMN2 copies	3	3.05	-5.96 to 12.05
Nonsitter	15	6.44	2.25 to 10.62
Sitter	9	-0.29	-5.07 to 4.50
No spinal fusion	14	3.12	-0.77 to 7.01

Continued

**Table 3** Average Rates of Change per Year in Outcome Measures in Participant Subgroups (*continued*)

Outcome	N	Slope <sup>a</sup>	95% CI
<b>Spinal fusion</b>	10	4.41	-0.25 to 9.07
<b>FVC (%)</b>			
<b>Type 2</b>	11	2.61	-1.66 to 6.89
<b>Type 3</b>	16	-0.31	-3.65 to 3.04
<b>3 SMN2 copies</b>	18	1.81	-2.06 to 5.68
<b>4 SMN2 copies</b>	7	-2.13	-7.50 to 3.25
<b>Nonsitter</b>	11	1.36	-2.31 to 5.03
<b>Sitter</b>	11	2.25	-2.33 to 6.83
<b>Walker</b>	5	-1.97	-7.78 to 3.85
<b>No spinal fusion</b>	16	-1.03	-4.14 to 2.09
<b>Spinal fusion</b>	11	5.31	0.36 to 10.25
<b>MEP (cm H<sub>2</sub>O)</b>			
<b>Nonsitter</b>	10	1.95	-4.84 to 8.74
<b>Sitter</b>	10	3.92	-4.54 to 12.38
<b>Walker</b>	5	18.25	6.86 to 29.64
<b>No spinal fusion</b>	16	7.68	2.23 to 13.12
<b>Spinal fusion</b>	9	3.61	-4.38 to 11.59
<b>MIP (cm H<sub>2</sub>O)</b>			
<b>Type 2</b>	11	-4.34	-13.68 to 4.99
<b>Type 3</b>	15	-6.27	-13.82 to 1.28
<b>3 SMN2 copies</b>	18	-1.88	-8.73 to 4.97
<b>4 SMN2 copies</b>	6	-8.67	-17.91 to 0.58
<b>Nonsitter</b>	11	-7.63	-16.83 to 1.58
<b>Sitter</b>	10	-1.12	-12.04 to 9.81
<b>Walker</b>	5	-7.79	-22.42 to 6.83
<b>No spinal fusion</b>	16	-4.51	-11.81 to 2.78
<b>Spinal fusion</b>	10	-6.74	-18.12 to 4.64

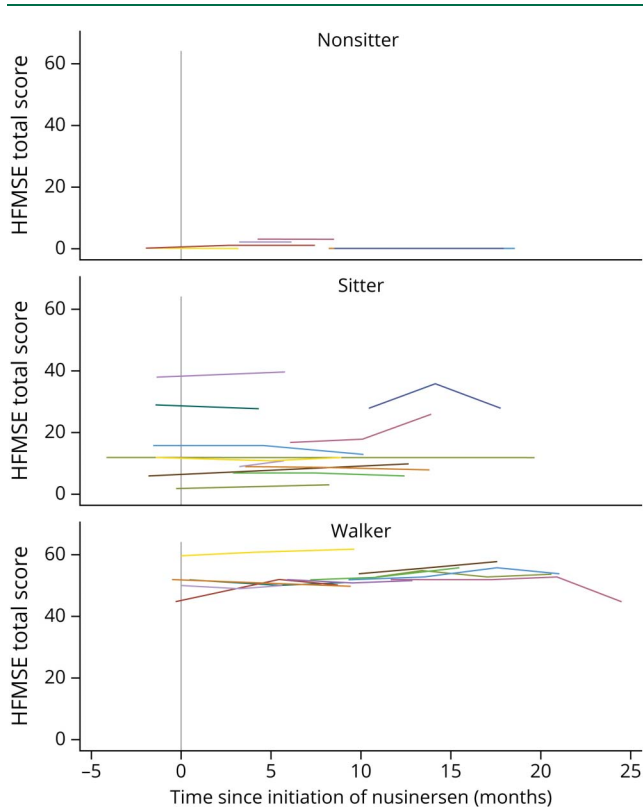
Abbreviations: 6MWT = 6-minute walk test; CHOP-ATEND = Children's Hospital of Philadelphia Adult Test for Neuromuscular Disorders; CI = confidence interval; FVC = forced vital capacity; HFMSE = Hammersmith Functional Motor Scale Expanded; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; RULM = Revised Upper Limb Module; SMAFRS = SMA Functional Rating Scale; TUG = timed up and go.

<sup>a</sup> Slope is expressed as the unit change in outcome per year.

parallels the improved MEP that was found to be a sensitive indicator of change in our study. Studies have shown that peak cough is correlated with MIP and MEP<sup>38</sup> and that MEP plays an important role in peak cough ability.<sup>39</sup> More recently, a larger German cohort reported on 139 participants indicating efficacy in treatment using HFMSE, RULM, and 6MWT.<sup>36</sup> Comparing our patient cohorts, individuals in our study had a more varied and severe phenotype with 38% spinal fusion compared with 25%, and 14% more individuals who were nonambulatory.

The primary limitation of this study is the lack of a concurrent control group as all patients in our clinics were treated with nusinersen. Selection bias may be present because patients unable to tolerate intrathecal treatments are also most likely to be severely affected with scoliosis. The lack of blinding is an especially noteworthy limitation to this study, but because the FDA approved nusinersen for individuals of all ages affected by SMA, a randomized placebo-controlled trial is no longer feasible for any population of patients with SMA in the United States. It is possible that the observed improvements in our study could be ascribed, at least in

**Figure 3** HFMSE Total Score Trajectories Based on Functional Status



Hammersmith Functional Motor Scale Expanded (HFMSE) results for entire population studied (n = 31) grouped by functional status at baseline: nonsitters (n = 9), sitters (n = 11), and walkers (n = 11).

part, to placebo effects or a learning curve of the assessments. Longer follow-up will be valuable to assess durability of the response, which is more likely for biological than placebo effects of treatment. Furthermore, subgroup analyses were limited by the relatively small number of patients and the broad range of their functional abilities, which can only be addressed by longitudinal assessments of more adult patients on nusinersen, or other SMN restoring treatments.

Other limitations resulted from variable timing of and circumstances surrounding evaluations. Forty-three percent of participants had evaluations on the same day of injections, and only 1 participant had a 1-week delay in dosing. For these reasons, the real-world data obtained in this study are inherently more variable than the published data of nusinersen's effects on infantile- and juvenile-onset patients in more structured randomized controlled trials.

This study attempts to fill some of the knowledge gaps identified in nusinersen treatment of SMA,<sup>40</sup> which included more severely weak individuals than is true of currently published studies of nusinersen in adults with SMA. The high cost of treatment associated with nusinersen is a consideration that must be addressed particularly in a value to health care-based system. Typical motor outcome measures used in clinical trials may not

show improvements in this older more heterogeneous population. Given the range of subjective improvements reported by participants in this study, future directions should focus on development and validation of novel outcome measures that may better assess treatment responses, such as patient-reported outcome measures; measures of endurance and fatigability; measures of bulbar function including voice, speech, swallow, jaw, or tongue movement; and measures of trunk and neck movements. Quantification of these features in the severely and chronically weak adults may be more responsive to the effects of interventions. Careful clinical guidance should be considered in the management of expectation for older individuals as efficacy may be affected by other clinical factors such as disease duration, contractures, spinal fusions, and adherence to standards of care.

Although improved motor function is always a goal of treatment, stabilization of the otherwise progressively declining disease course of SMA would itself be of tremendous benefit to individuals affected by this chronic degenerative disorder. Stabilization and improvement of respiratory function is also of value to this population for whom respiratory infection is a considerable cause of morbidity and mortality. Ongoing studies of nusinersen, and development of biomarkers and novel outcome measures that can more completely ascertain response to treatment, will be important to confirm and extend the results of this initial study and to provide greater understanding of the changing natural history of adults with SMA in this new era of genetic treatments. These measures will also help determine when the cellular pathophysiology of SMA has been controlled and will help define unmet needs in the adult SMA population that can be addressed with approaches complementary to SMN protein restoration.

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### Disclosure

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## TAKE-HOME POINTS

- This natural history study of nusinersen in adults identifies different responses to treatment in the real-world setting.
- Nusinersen is safe, feasible, and well tolerated in adults with SMA.
- Initial results show an emerging positive trend in both motor and respiratory function in a heterogeneous cohort, including severely weak adults, contrary to the natural history.
- Future studies must address unmet needs pertaining to patient-reported outcomes, endurance, bulbar function, and motor assessments for those who are very weak and contracted to better understand the impact of changes with nusinersen and complementary approaches to SMN protein restoration.

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## Publication History

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## Appendix 1 Authors

Name	Location	Contribution
<b>Tina Duong, PT, PhD</b>	Stanford University, Palo Alto, CA	Designed and conceptualized the study; major role in acquisition of data; analyzed and interpreted data; and drafted and revised the manuscript for intellectual content
<b>Connie Wolford, MSN, FNP-BC</b>	Stanford University, Palo Alto, CA	Designed and conceptualized the study; major role in acquisition of data; analyzed and interpreted data; and revised the manuscript for intellectual content

Continued

## Appendix 1 (continued)

Name	Location	Contribution
<b>Michael P. McDermott, PhD</b>	University of Rochester, New York	Performed biostatistical analysis of results; interpreted the data; and revised the manuscript for intellectual content
<b>Chelsea E. Macpherson, PT, DPT, NCS</b>	Stanford University, Palo Alto, CA	Major role in the acquisition of data and revised the manuscript for intellectual content
<b>Amy Pasternak, PT, DPT, PCS</b>	Boston Children's Hospital, MA	Designed and conceptualized the study; major role in acquisition of data; analyzed and interpreted data; and revised the manuscript for intellectual content
<b>Allan M. Glanzman, PT, DPT, PCS</b>	Children's Hospital of Philadelphia, PA	Designed and conceptualized the study; major role in acquisition of data; analyzed and interpreted data; and revised the manuscript for intellectual content
<b>William B. Martens, BA</b>	University of Rochester, New York	Performed biostatistical review of results; interpreted the data; and revised the manuscript for intellectual content
<b>Elizabeth A. Kichula, MD, BA</b>	Children's Hospital of Philadelphia, PA	Designed and conceptualized the study and revised the manuscript for intellectual content
<b>Basil Darras, MD</b>	Boston Children's Hospital, MA	Designed and conceptualized the study and revised the manuscript for intellectual content
<b>Darryl C. De Vivo, MD</b>	Columbia University Medical Center, New York	Designed and conceptualized the study and revised the manuscript for intellectual content
<b>Zarazuela Zolkipli-Cunningham, MBChB, MRCP</b>	Children's Hospital of Philadelphia, PA	Designed and conceptualized the study and revised the manuscript for intellectual content
<b>Richard Finkel, MD</b>	Nemours, Orlando, FL	Designed and conceptualized the study and revised the manuscript for intellectual content
<b>Michael Zeineh, MD, PhD</b>	Stanford University, Palo Alto, CA	Major role in the acquisition of data and revised the manuscript for intellectual content
<b>Max Wintermark, MD</b>	Stanford University, Palo Alto, CA	Major role in the acquisition of data and revised the manuscript for intellectual content

## Appendix 1 (continued)

Name	Location	Contribution
<b>Katharine A. Hagerman, PhD</b>	Stanford University, Palo Alto, CA	Major role in acquisition of data; analyzed and interpreted data; and revised the manuscript for intellectual content
<b>Jacinda Sampson, MD, PhD</b>	Stanford University, Palo Alto, CA	Designed and conceptualized the study and revised the manuscript for intellectual content
<b>Sally Dunaway Young, PT, DPT</b>	Stanford University, Palo Alto, CA	Designed and conceptualized the study; major role in acquisition of data; analyzed and interpreted data; and drafted and revised the manuscript for intellectual content
<b>John W. Day, MD, PhD</b>	Stanford University, Palo Alto, CA	Designed and conceptualized the study; analyzed and interpreted data; and drafted and revised the manuscript for intellectual content

## Appendix 2 Coinvestigators

Coinvestigators from the Stanford Neuromuscular Coordinating Center are listed below.

Name	Location	Role	Contribution
<b>Shirley Paulose</b>	Stanford University, Palo Alto, CA	Coinvestigator	Led and coordinated communication among the study
<b>Lesly Welsh</b>	Stanford University, Palo Alto, CA	Coinvestigator	Coordinated study visits
<b>Whitney Tang</b>	Stanford University, Palo Alto, CA	Coinvestigator	Data entry and management
<b>Rachel Salazar</b>	Columbia University, New York	Coinvestigator	Performed Clinical evaluations

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