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Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

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ORIGINAL ARTICLE

Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

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ABSTRACT

BACKGROUND

Nusinersen is an antisense oligonucleotide drug that modulates pre–messenger RNA splicing of the survival motor neuron 2 (*SMN2*) gene. It has been developed for the treatment of spinal muscular atrophy (SMA).

METHODS

We conducted a multicenter, double-blind, sham-controlled, phase 3 trial of nusinersen in 126 children with SMA who had symptom onset after 6 months of age. The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The primary end point was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score at 15 months of treatment; HFMSE scores range from 0 to 66, with higher scores indicating better motor function. Secondary end points included the percentage of children with a clinically meaningful increase from baseline in the HFMSE score (≥3 points), an outcome that indicates improvement in at least two motor skills.

RESULTS

In the prespecified interim analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group (by 4.0 points) and a least-squares mean decrease in the control group (by –1.9 points), with a significant between-group difference favoring nusinersen (least-squares mean difference in change, 5.9 points; 95% confidence interval, 3.7 to 8.1; P<0.001). This result prompted early termination of the trial. Results of the final analysis were consistent with results of the interim analysis. In the final analysis, 57% of the children in the nusinersen group as compared with 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (P<0.001), and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively).

CONCLUSIONS

Among children with later-onset SMA, those who received nusinersen had significant and clinically meaningful improvement in motor function as compared with those in the control group. (Funded by Biogen and Ionis Pharmaceuticals; CHERISH ClinicalTrials.gov number, NCT02292537.)

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*A complete list of principal investigators in the CHERISH trial is provided in the Supplementary Appendix, available at NEJM.org.

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder that is characterized by atrophy and weakness of the skeletal muscles of the limbs and trunk and of the bulbar and respiratory muscles.[1,2] It is caused by homozygous deletions or loss-of-function mutations in the gene encoding survival motor neuron 1 (*SMN1*) at locus 5q13, which result in insufficient expression of the survival motor neuron (SMN) protein.[1,3-5] A paralogous gene, *SMN2*, also encodes the SMN protein, but the level of functional full-length SMN protein produced by *SMN2* is only 5 to 10% of the level produced by *SMN1*, because a splice-site variant in *SMN2* leads to exclusion of exon 7 from the mature RNA transcript and production of truncated, dysfunctional SMN protein.[5,6] Nusinersen is a modified antisense oligonucleotide drug that resists nucleases and binds to a specific sequence within the *SMN2* pre–messenger RNA, thereby modifying the splicing of the *SMN2* pre–messenger RNA to promote the expression of full-length SMN protein.[7-10]

The classification system for SMA is based on the age at symptom onset and the most advanced motor milestone attained during development.[5] Patients with a higher *SMN2* copy number and a higher level of SMN protein generally have a less severe phenotype.[11,12] SMA type 1 is characterized by symptom onset by 6 months of age and failure to sit without support, SMA type 2 by symptom onset between 6 and 18 months of age and failure to walk independently, and SMA type 3 by symptom onset after 18 months of age and an ability to walk independently at some point.[1,2,5,6,13,14] However, these motor milestones can be lost over time.[5,15,16] In this trial, we defined later-onset SMA as disease with symptom onset after 6 months of age (most likely to be classified as SMA type 2 or 3).[5] Two earlier open-label trials and their extensions showed that the administration of nusinersen did not raise safety concerns and had a benefit with respect to motor function in children with SMA type 2 or 3.[9,17] We therefore conducted the multicenter, randomized, double-blind, sham-controlled, phase 3 CHERISH trial to evaluate the efficacy and safety of nusinersen in children with later-onset SMA.

Methods

Trial Oversight

The CHERISH trial protocol (available with the full text of this article at NEJM.org) was approved by the independent review board or ethics committee at each participating site and was conducted according to the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The parents or legal guardians of eligible children provided written informed consent before participation; the children provided assent as appropriate, on the basis of institutional guidelines and the child's age. In collaboration with the sponsors (Biogen and Ionis Pharmaceuticals), an independent data and safety monitoring board reviewed safety data at quarterly intervals, including the results of the prespecified interim analysis.

The trial was designed by employees of the sponsors in collaboration with clinicians who had experience in the treatment of SMA. Investigators collected the data, which were held and analyzed by Biogen. The authors had access to the complete data set after unblinding, participated in data analysis and interpretation and in manuscript development, and vouch for the accuracy and completeness of the data. The principal investigators vouch for the fidelity of the study to the protocol and protocol amendments. The first draft of the manuscript was written by the first author and the senior industry author from Biogen; medical-writing assistance was paid for by Biogen. The sponsors reviewed the manuscript and provided feedback to the authors, who had full editorial control and approved the final manuscript for submission.

Patients

Key eligibility criteria were genetic documentation of 5q SMA (a homozygous deletion, mutation, or compound heterozygote in *SMN1*) with symptom onset after 6 months of age, as well as the presence of the following features at screening: an age of 2 to 12 years, the ability to sit independently, no history of the ability to walk independently (defined as the ability to walk ≥15 ft unaided), and a Hammersmith Functional Motor Scale–Expanded (HFMSE) score of 10 to 54.

HFMSE scores range from 0 to 66, with higher scores indicating better motor function.[18,19] Children were not eligible for inclusion in the trial if they had a severe contracture (i.e., any contracture that could interfere with assessment of the HFMSE score, according to the investigator), evidence of severe scoliosis on radiography (i.e., spine curvature with a Cobb angle of >40 degrees), respiratory insufficiency (i.e., receipt of invasive or noninvasive ventilation for >6 hours during a 24-hour period), or a gastric tube placed to provide adequate nutrition (see the Supplementary Appendix, available at NEJM.org).

TRIAL DESIGN AND TREATMENT

The trial was conducted at 24 sites in 10 countries and was designed to have a screening period of 4 weeks, a treatment period of 9 months, and a follow-up period of 6 months. To ensure balance across the trial groups, the children were stratified according to age at screening (<6 years vs. ≥6 years) and then were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group). Randomization was performed with the use of an interactive Web response system. Nusinersen was administered or the sham procedure was performed by dedicated personnel who were aware of the group assignments; the child's parents and key trial personnel who performed assessments were unaware of the group assignments until trial completion and were not present for the procedure. Participants were sedated to avoid any awareness of the procedure. Treatments that were considered to be necessary to manage adverse events or provide supportive care were permitted, in accordance with standard-of-care guidelines.[20]

TRIAL PROCEDURES AND END POINTS

Nusinersen was administered intrathecally on days 1, 29, and 85, and a maintenance dose was administered on day 274. The sham procedure was performed on the same days; it consisted of a small needle prick to the lower back, which was covered with a bandage to simulate the appearance of a lumbar puncture. Children were observed at the trial site for at least 24 hours after the first procedure was performed and for at least 6 hours after each procedure thereafter.

The primary end point was the least-squares mean change from baseline in the total HFMSE score at month 15. Trained clinical evaluators[21] assessed the HFMSE score twice during the screening period and at 3, 6, 9, 12, and 15 months. The HFMSE is a 33-item measure of motor function that is specifically validated for use in patients with SMA to assess activities related to daily living.[2,18,19,21,22] Each of the 33 activities is scored on a scale ranging from 0 (no response) to 2 (full response), and total HFMSE scores range from 0 to 66 points, with an increase in total score indicating an improvement in motor function.[19] A change in the HFMSE score of at least 3 points is considered to be clinically meaningful.[23]

The trial had six secondary end points, including the percentage of children who had an increase from baseline to month 15 in the HFMSE score of at least 3 points, the percentage of children who achieved at least one new World Health Organization (WHO) motor milestone (out of a total of six milestones),[24] and the change from baseline in the Revised Upper Limb Module (RULM) score (which ranges from 0 to 37, with higher scores indicating better function).[25] Safety was evaluated throughout the trial (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We estimated that a sample size of 117 children would give the trial at least 90% power to detect a mean (±SD) difference of 3±4.4 points between trial groups in the change from baseline in the HFMSE score, at a two-sided alpha level of 0.05. To control the overall type I error rate at 0.05 across the interim and final analyses for the primary and secondary end points, a hierarchical strategy with independent alpha spending functions for primary and secondary end points was applied[26] (see the Supplementary Appendix). Because the P value for the primary end point was significant in the interim analysis, this end point was not formally tested for significance in the final analysis. All secondary efficacy end points were assessed in the final analysis.

The prespecified interim analysis of the primary end point was performed in the intention-

to-treat population, which included patients who were randomly assigned to a group and underwent at least one assigned procedure (Fig. S1 in the Supplementary Appendix); this analysis was conducted when all the children had been enrolled for at least 6 months and at least 39 children had completed their 15-month assessment. Because some children would not have completed the 15-month assessment by the time of the interim analysis, the analysis was performed with the use of a multiple-imputation method to account for missing data on HFMSE scores obtained after baseline. Least-squares mean values are reported. In the final analysis, the least-squares mean changes in the total HFMSE score, the number of WHO motor milestones achieved per child, and the RULM score and least-squares mean differences in change between groups were based on an analysis of covariance, with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline.

RESULTS

PATIENTS

A total of 179 children were screened; 126 were enrolled in the trial, were randomly assigned to a group, and underwent the assigned procedure (84 in the nusinersen group, and 42 in the control group) (Fig. S2 in the Supplementary Appendix). The first child underwent the first assigned procedure on November 24, 2014, and the last child's last visit occurred on February 20, 2017. At the data cutoff date for the prespecified interim analysis (August 31, 2016), 54 children (43%) had completed the 15-month assessment and all the children had an HFMSE score that had been obtained at 6 months or later. In the prespecified interim analysis, nusinersen showed efficacy superior to that of the sham procedure; at the recommendation of the data and safety monitoring board, we stopped the trial early. All the children who had not had a 15-month assessment were invited to attend a visit that represented the end of the double-blind period; at this visit, all assessments that had been scheduled for the 15-month assessment were performed. Children who completed the CHERISH trial were invited to enroll in the open-label extension study (ClinicalTrials.gov number, NCT02594124), in which all children were to receive nusinersen.

At the time of the final analysis, no child had been withdrawn from the trial. A total of 66 children (79%) in the nusinersen group and 34 (81%) in the control group had completed the 15-month assessment; 26 children were enrolled in the open-label extension study early. At the 15-month assessment or the visit that represented the end of the double-blind period, all the children had undergone the four assigned procedures, except for 1 child who had received only three doses of nusinersen before the trial ended (Fig. S2 in the Supplementary Appendix). The demographic characteristics of the children at baseline were similar in the two trial groups; there were slight differences in age, sex, race, disease duration, and motor milestones achieved, but no formal statistical testing was performed. The stratum that included children younger than 6 years of age was larger than the stratum that included children 6 years of age or older. A higher percentage of children in the control group than in the nusinersen group had achieved weight-bearing motor milestones, including the ability to stand alone or walk with support (Table 1, and Table S1 in the Supplementary Appendix).

EFFICACY

Primary End Point

In the prespecified interim analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group and a least-squares mean decrease in the control group, resulting in a significant between-group difference favoring nusinersen (least-squares mean difference in change, 5.9 points; 95% confidence interval [CI], 3.7 to 8.1; P<0.001) (Table 2). In the final analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group and a least-squares mean decrease in the control group (least-squares mean difference in change, 4.9 points; 95% CI, 3.1 to 6.7) (Table 2 and Fig. 1A). Similar results favoring nusinersen were observed in all sensitivity analyses for the primary end point and across subgroups defined according to *SMN2* copy number (Tables S2 and S3 in the Supplementary Appendix).

Greater improvements in total HFMSE score were observed in the nusinersen group than in the control group at time points starting after month 6 (Fig. 1A). At month 15, the greatest

increases from baseline in the HFMSE score had occurred in the nusinersen group, and the greatest decreases had occurred in the control group, with generally similar results observed at months 9 and 12 (Fig. S3 in the Supplementary Appendix).

Secondary End Points

A higher percentage of children in the nusinersen group than in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (57% vs. 26%, P<0.001) (Table 2, and Fig. S4 in the Supplementary Appendix). The percentage of children who achieved at least one new WHO motor milestone did not differ significantly between the nusinersen group and the control group (20% and 6%, respectively) (Table 2). Because the P value for the second secondary end point was not significant, all subsequent analyses of end points in the hierarchical testing strategy were considered to be exploratory and are not reported. At month 15, there was a least-squares mean increase from baseline in the number of new WHO motor milestones achieved per child in the nusinersen group (by 0.2) and a least-squares mean decrease in the control group (by −0.2). There was a least-squares mean increase from baseline in the RULM score in the nusinersen group and in the control group (by 4.2 points and 0.5 points, respectively) (Table 2 and Fig. 1B). The greatest increases in the RULM score were observed in the nusinersen group (Fig. S5 in the Supplementary Appendix). The proportion of children who had achieved the ability to stand alone or walk with assistance did not differ significantly between groups (Table 2). Analyses of the change from baseline to month 15 in the HFMSE score according to age and disease duration revealed greater improvements in younger children and in those who received treatment earlier in their disease course, respectively (Fig. 2). Results of analyses according to geographic region were generally consistent with the overall results (Table S4 in the Supplementary Appendix).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nusinersen (N=84)	Control (N=42)
Female sex — no. (%)	46 (55)	21 (50)
Age at screening — yr		
Median	4.0	3.0
Range	2–9	2–7
Age at symptom onset — mo		
Median	10.0	11.0
Range	6–20	6–20
Age at diagnosis of SMA — mo		
Median	18.0	18.0
Range	0–48	0–46
Disease duration — mo†		
Median	39.3	30.2
Range	8–94	10–80
SMN2 copy number — no. (%)		
2	6 (7)	4 (10)
3	74 (88)	37 (88)
4	2 (2)	1 (2)
Unknown	2 (2)	0
Motor milestones ever achieved — no. (%)‡		
Ability to sit without support	84 (100)	42 (100)
Ability to walk with support	20 (24)	14 (33)
Ability to walk independently, ≥15 ft	0	0
HFMSE score§	22.4±8.3	19.9±7.2
WHO motor milestones achieved¶	1.4±1.0	1.5±1.0
RULM score‖	19.4±6.2	18.4±5.7

* Plus–minus values are means ±SD. No formal statistical testing was performed to assess differences between trial groups in baseline characteristics. Percentages may not total 100 because of rounding. SMA denotes spinal muscular atrophy.
† Disease duration is a child's age at screening minus the age at symptom onset.
‡ These data do not reflect the maximal milestone achieved.
§ Hammersmith Functional Motor Scale–Expanded (HFMSE) scores range from 0 to 66, with higher scores indicating better motor function.[19]
¶ The six World Health Organization (WHO) motor milestones are sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone, and walking alone.[24]
‖ Revised Upper Limb Module (RULM) scores range from 0 to 37, with higher scores indicating better function.[25]

SAFETY

The overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively), as was the incidence of moderate or severe adverse events (Table 3). Serious adverse events were reported in 17% of the children in the nusinersen group and in 29% in the control group. Some of the events that were reported as adverse events could plausibly be linked to SMA and may not reflect adverse drug effects (Table 3). No child discontinued treatment or was withdrawn from the trial because of an adverse event. The incidences of pyrexia, headache, vomiting, back pain, and

Table 2. Primary and Secondary End Points Assessed at Month 15.*

End Point	Nusinersen (N=84)	Control (N=42)	Difference	P Value
Interim analysis†				
Primary end point: change from baseline in HFMSE score — least-squares mean (95% CI)‡	4.0 (2.9 to 5.1)	−1.9 (−3.8 to 0)	5.9 (3.7 to 8.1)	<0.001
Final analysis§				
Primary end point: change from baseline in HFMSE score — least-squares mean (95% CI)‡	3.9 (3.0 to 4.9)	−1.0 (−2.5 to 0.5)	4.9 (3.1 to 6.7)	—
Secondary end points				
Children with change in HFMSE score of ≥3 points				
% (95% CI)¶	57 (46 to 68)	26 (12 to 40)	30.5 (12.7 to 48.3)	
Odds ratio (95% CI)	—	—	6 (2 to 15)‖	<0.001
Children who achieved ≥1 new WHO motor milestone				
No.	13	2	—	—
% (95% CI)**	20 (11 to 31)	6 (1 to 20)	14 (−7 to 34)	0.08
Change from baseline in number of WHO motor milestones achieved — least-squares mean (95% CI)‡	0.2 (0.1 to 0.3)	−0.2 (−0.4 to 0)	0.4 (0.2 to 0.7)	—
Change from baseline in RULM score — least-squares mean (95% CI)‡	4.2 (3.4 to 5.0)	0.5 (−0.6 to 1.6)	3.7 (2.3 to 5.0)	—
Children who achieved ability to stand alone				
No.	1	1	—	—
% (95% CI)**	2 (0 to 8)	3 (0 to 15)	−1 (−22 to 19)	—
Children who achieved ability to walk with assistance				
No.	1	0	—	—
% (95% CI)**	2 (0 to 8)	0 (0 to 10)	2 (−19 to 22)	—

* To control the overall type I error rate at 0.05 across the interim and final analyses for the testing of primary and secondary end points, a hierarchical strategy was used, in which significance of the primary end point was required before inferential conclusions could be drawn about the secondary end points. If an end point failed to reach significance, subsequent end points were not tested within the hierarchical analysis. Secondary end points are listed in hierarchical order. Because the P value for the second secondary end point was not significant, all subsequent end points analyzed in the hierarchical testing strategy were considered to be exploratory. (Details are provided in the Supplementary Appendix.)

† The interim analysis of the primary end point was conducted when all the children had been enrolled for at least 6 months and at least 39 children had completed the 15-month assessment. The analysis was performed with the use of a multiple-imputation method. The number of children with observed data for the 15-month assessment was 35 in the nusinersen group and 19 in the control group, and the number of children with imputed data was 49 in the nusinersen group and 23 in the control group.

‡ The least-squares mean change and least-squares mean difference in change between groups were based on an analysis of covariance, with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline.

§ In the final analysis, the following end points were analyzed with the use of a multiple-imputation method: change from baseline in the HFMSE score, percentage of children with a change in HFMSE score of at least 3 points, and change from baseline in the RULM score. Only children with observed data were included in the other analyses. The number of children with observed data for the 15-month assessment was 66 in the nusinersen group and 34 in the control group, and the number of children with imputed data was 18 in the nusinersen group and 8 in the control group.

¶ The percentages and difference (in percentage points) were based on binomial proportions.

‖ This value is an odds ratio instead of a difference. The odds ratio for nusinersen versus control was based on logistic regression, with group assignment as a fixed effect and with adjustment for each child's age at screening and the HFMSE score at baseline.

** The percentages were based on an exact confidence interval, and the differences (in percentage points) on an exact unconditional confidence interval.

epistaxis were at least 5 percentage points higher in the nusinersen group than in the control group (Table 3). No cases of epistaxis occurred in the context of abnormal platelet counts, and there were alternative causes that could explain these events. The incidences of back pain, headache, and vomiting — known complications of lumbar puncture[27-29] — were at least 5 percentage points higher in the nusinersen group than in the control group within 72 hours after the assigned procedure (Table S5 in the Supplementary Appendix). The overall rate of events associated with lumbar puncture (i.e., back pain, cerebrospinal fluid leakage, headache, nausea, the post–lumbar puncture syndrome, procedural pain, procedural nausea, procedural headache, and vomiting) within 24, 72, 120, and 168 hours after the assigned procedure was 9%, 14%, 15%, and 15%, respectively, in the nusinersen group and 3% for each time period in the control group (Table S6 in the Supplementary Appendix). There were no clinically relevant changes related to nusinersen in clinical laboratory test results (see the Supplementary Appendix).

DISCUSSION

In the CHERISH trial, among children with later-onset SMA, significant improvement in motor function was observed with nusinersen treatment as compared with a sham procedure. Persons with later-onset SMA and their caregivers indicated that stabilization of their current state would meet their therapeutic expectations and represent a clinically meaningful response.[22,30] In this trial, as in the ENDEAR trial for infantile-onset SMA (most likely to be classified as SMA type 1),[31] we found that nusinersen had the capacity to produce meaningful changes in the clinical course of SMA. In this trial, more than half the children in the nusinersen group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (i.e., a clinically meaningful improvement),[23] which is uncommon among children with later-onset SMA.[32,33] The final results were consistent with the interim results. The greatest improvements in the HFMSE score over the 15-month period were observed in younger children and in those who received treatment soon after symptom onset.

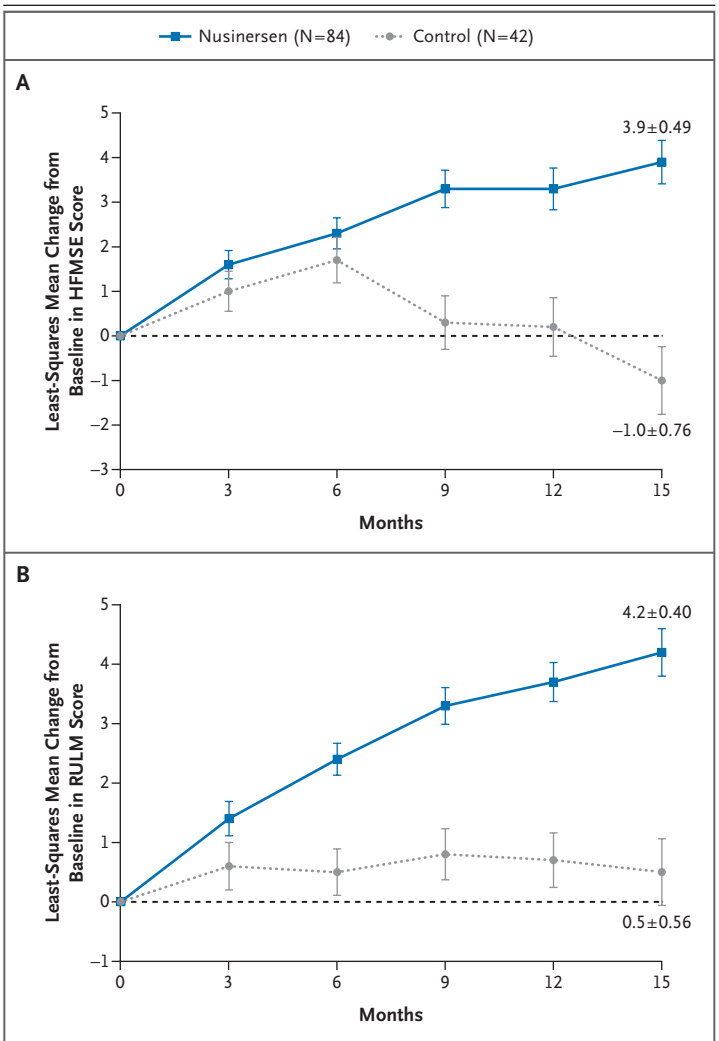

Figure 1. Change Over Time in the Hammersmith Functional Motor Scale–Expanded Score and the Revised Upper Limb Module Score (Final Analysis).

Shown is the least-squares mean change from baseline to the time of each trial assessment in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score (Panel A) and in the Revised Upper Limb Module (RULM) score (Panel B) in the final analysis. HFMSE scores range from 0 to 66, with higher scores indicating better motor function[19]; a change in the HFMSE score of at least 3 points is considered to be clinically meaningful.[23] RULM scores range from 0 to 37, with higher scores indicating better function.[25] I bars indicate standard errors.

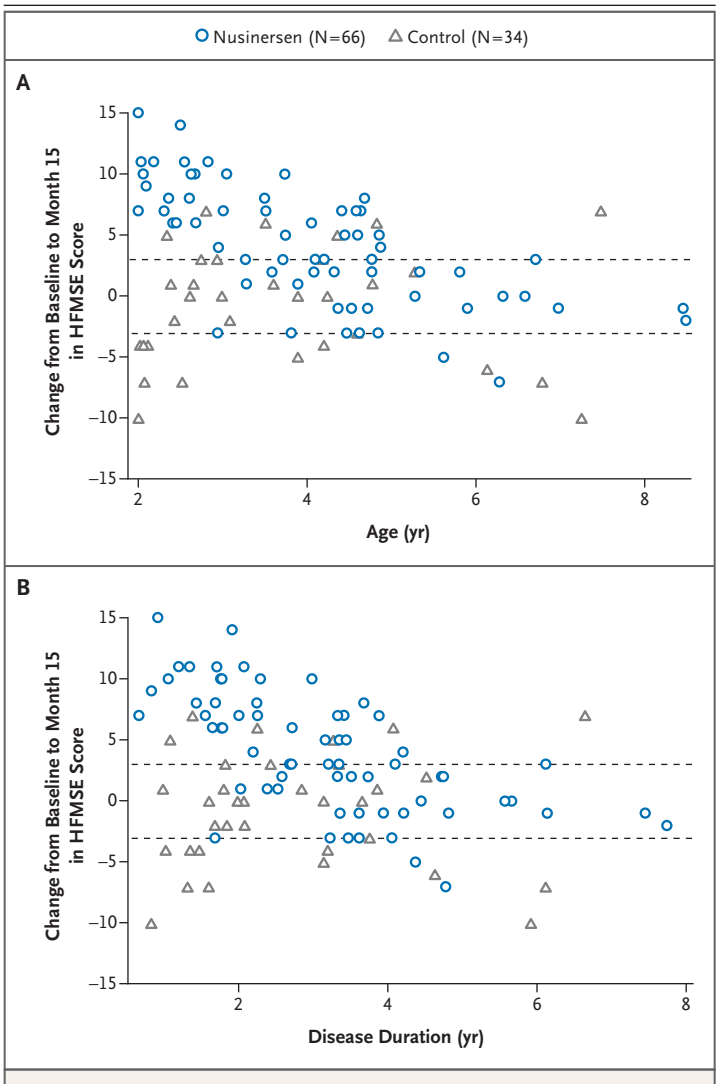

Figure 2. Change from Baseline to Month 15 in Individual HFMSE Scores According to Age and Disease Duration at Screening (Final Analysis).

Shown is the change from baseline to month 15 in each child's HFMSE score according to age (Panel A) and disease duration (Panel B) at screening in the final analysis. Disease duration is a child's age at screening minus the age at symptom onset. The analyses included children in the intention-to-treat population who did not have missing data for the 15-month assessment (66 in the nusinersen group, and 34 in the control group). The dotted lines indicate a 3-point change in the HFMSE score, which is considered to be clinically meaningful.[23]

The ENDEAR trial also showed greater improvements in infants who received treatment with nusinersen earlier in their disease course than in those who received later treatment.[31]

In the control group, there was improvement in the least-squares mean HFMSE score until month 6, after which the difference in change between the nusinersen group and the control group became more apparent. Least-squares mean changes in the HFMSE score in the control group were largely confined to a ±2-point range over the 15-month period, a finding similar to observations in a nonambulant natural-history cohort over a 12-month period.[32] The short-lived improvements observed in the control group during the first months of the treatment period probably resulted from a combination of the placebo effect, the learning curve for the assessment of the HFMSE and RULM scores, and initial developmental gains, particularly in younger children.[32] Some children in the control group had a decrease in the HFMSE score of up to 10 points, a finding that is consistent with results in a recent retrospective study,[32] but those treated with nusinersen had a more stable course.

No new safety concerns were identified.[9,10,31] Back pain and headache are common after lumbar puncture, occurring in up to one third of children who undergo the procedure,[27,34] a rate that is consistent with the incidences of these adverse events within 72 hours after lumbar puncture in the nusinersen group in this trial. The overall rate of adverse events associated with lumbar puncture observed in the nusinersen group in this trial (9 to 15% within 24 to 168 hours after lumbar puncture) was similar to rates reported in the literature (8 to 25%).[35-38]

This trial had some limitations. For example, the strict eligibility criteria (i.e., no severe contractures or scoliosis, outlying HFMSE scores, respiratory insufficiency, or reliance on a gastric tube) meant that the enrolled population was more homogeneous and younger than the population that is encountered in the clinical-practice setting. In the trial, 16% of the enrolled children were 6 years of age or older.

The results we report here are consistent with the results of previous open-label studies that enrolled children up to 15 years of age. The studies showed that nusinersen had positive effects in populations of children with SMA type 2 or 3 that were broader and more hetero-

Table 3. Summary of Adverse Events.*

Event	Nusinersen (N=84)	Control (N=42)
	no. of patients (%)	
Any adverse event	78 (93)	42 (100)
Any moderate or severe adverse event	39 (46)	23 (55)
Any severe adverse event	4 (5)	3 (7)
Any serious adverse event	14 (17)	12 (29)
Any adverse event leading to treatment discontinuation	0	0
Any adverse event leading to withdrawal from the trial	0	0
Adverse events with the highest incidence†		
Pyrexia	36 (43)	15 (36)
Upper respiratory tract infection‡	25 (30)	19 (45)
Headache	24 (29)	3 (7)
Vomiting	24 (29)	5 (12)
Back pain	21 (25)	0
Cough‡	21 (25)	9 (21)
Nasopharyngitis‡	20 (24)	15 (36)
Serious adverse events with the highest incidence§		
Pneumonia‡	2 (2)	6 (14)
Influenza‡	0	2 (5)
Respiratory distress‡	2 (2)	2 (5)
Fecaloma	0	2 (5)
Dehydration	0	2 (5)
Adverse events with an incidence ≥5 percentage points higher in the nusinersen group than in the control group¶		
Pyrexia	36 (43)	15 (36)
Headache	24 (29)	3 (7)
Vomiting	24 (29)	5 (12)
Back pain	21 (25)	0
Epistaxis	6 (7)	0

* Investigators rated the severity of each adverse event (mild, moderate, or severe). Moderate adverse events were defined as events that caused discomfort and interrupted the child's usual daily activities. Severe adverse events were defined as events that caused severe discomfort or incapacitation or had a substantial effect on daily life. Investigators reported an adverse event as a serious adverse event if it met the following criterion: any untoward medical occurrence that resulted in death or a risk of death, hospitalization or prolonged hospitalization, persistent or substantial disability or incapacitation, or a congenital anomaly or birth defect. Reporting of serious adverse events and rating of the severity of each adverse event were conducted separately, on the basis of the criteria for each type of adverse event. For participants who reported more than one adverse event, only one event of the highest severity was counted in the total incidence.

† The events, classified according to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, occurred in at least 20% of children in either trial group.

‡ The events could plausibly be linked to spinal muscular atrophy.

§ The events, classified according to MedDRA preferred terms, occurred in at least 5% of children in either trial group.

¶ The events were classified according to MedDRA preferred terms. A child was counted only once within each category.

geneous than the population enrolled in this trial.[9,17]

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APPENDIX

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