ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

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ABSTRACT

BACKGROUND

Spinal muscular atrophy is an autosomal recessive neuromuscular disorder that is caused by an insufficient level of survival motor neuron (SMN) protein. Nusinersen is an antisense oligonucleotide drug that modifies pre–messenger RNA splicing of the *SMN2* gene and thus promotes increased production of full-length SMN protein.

METHODS

We conducted a randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial of nusinersen in infants with spinal muscular atrophy. The primary end points were a motor-milestone response (defined according to results on the Hammersmith Infant Neurological Examination) and event-free survival (time to death or the use of permanent assisted ventilation). Secondary end points included overall survival and subgroup analyses of event-free survival according to disease duration at screening. Only the first primary end point was tested in a prespecified interim analysis. To control the overall type I error rate at 0.05, a hierarchical testing strategy was used for the second primary end point and the secondary end points in the final analysis.

RESULTS

In the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], P<0.001), and this result prompted early termination of the trial. In the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; P=0.005). The likelihood of overall survival was higher in the nusinersen group than in the control group (hazard ratio for death, 0.37; P=0.004), and infants with a shorter disease duration at screening were more likely than those with a longer disease duration to benefit from nusinersen. The incidence and severity of adverse events were similar in the two groups.

CONCLUSIONS

Among infants with spinal muscular atrophy, those who received nusinersen were more likely to be alive and have improvements in motor function than those in the control group. Early treatment may be necessary to maximize the benefit of the drug. (Funded by Biogen and Ionis Pharmaceuticals; ENDEAR ClinicalTrials.gov number, NCT02193074.)

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

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Spinal muscular atrophy is an autosomal recessive neuromuscular disorder that is characterized by progressive muscle atrophy and weakness, with an estimated incidence of 1 in 11,000 live births.[1,2] Approximately 60% of infants who are born with spinal muscular atrophy have type 1 disease,[3] which is characterized by onset of symptoms at 6 months of age or younger and a median life expectancy of less than 2 years without respiratory support.[3-5] New developmental motor milestones are rarely achieved after diagnosis.[6]

Spinal muscular atrophy is caused by a homozygous deletion or mutation in the survival motor neuron 1 (*SMN1*) gene, which results in decreased expression of the survival motor neuron (SMN) protein and degeneration of motor neurons in the spinal cord and brain stem.[7,8] A paralogous gene, survival motor neuron 2 (*SMN2*), also encodes the SMN protein; however, 90 to 95% of the translated protein is truncated and nonfunctional as a result of aberrant splicing.[9,10] Infants with a higher copy number of *SMN2* generally have a milder phenotype.[8] Therefore, modulation of pre–messenger RNA (pre-mRNA) splicing of *SMN2* to promote increased production of SMN protein could be an effective treatment strategy across the disease spectrum of spinal muscular atrophy.

Nusinersen is an antisense oligonucleotide drug that modifies pre-mRNA splicing of *SMN2* to promote increased production of full-length SMN protein.[11] In a phase 2, open-label, dose-escalation study of nusinersen in infantile-onset spinal muscular atrophy, infants who received nusinersen had progressive improvements in motor function and prolonged survival, relative to data from a published natural-history case series.[12] We report the final results of the ENDEAR trial, a 13-month, international, randomized, multicenter, sham-controlled, phase 3 trial that assessed the clinical efficacy and safety of nusinersen in infants who had received a genetic diagnosis of spinal muscular atrophy, had two copies of *SMN2* (which is subject to copy-number variation), and had had onset of symptoms at 6 months of age or younger.[7]

METHODS

TRIAL OVERSIGHT

The sponsors, Biogen and Ionis Pharmaceuticals, designed the trial in collaboration with clinicians who had experience in the treatment of spinal muscular atrophy. An independent data and safety monitoring board provided trial oversight in collaboration with the sponsors. Investigators collected the data, which was analyzed by the sponsors. All the authors contributed to data interpretation and manuscript development, approved the manuscript for submission, and vouch for the accuracy and completeness of the reported data. All the principal investigators agreed to follow the protocol and protocol amendments (available with the full text of this article at NEJM.org). The first draft of the manuscript was written by the first author and the senior industry author (penultimate author); medical-writing assistance was paid for by Biogen. The sponsors reviewed the manuscript and provided feedback to the authors, who had full editorial control.

PATIENTS

Infants at 31 centers were enrolled in the trial. Eligible infants had genetic documentation of a homozygous deletion or mutation in the *SMN1* gene. They also had two copies of the *SMN2* gene, had had onset of clinical symptoms that were consistent with spinal muscular atrophy at 6 months of age or younger, were 7 months of age or younger at screening, did not have low peripheral oxygen saturation, and met all additional eligibility criteria (see the Supplementary Appendix, available at NEJM.org). A health care proxy for each patient provided written informed consent. The trial was approved by an ethics committee at each institution and was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and with the World Medical Association Declaration of Helsinki.

TRIAL DESIGN AND TREATMENT

After a screening period of up to 21 days, eligible infants were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen (nusinersen group) or a sham procedure (control group). The nusinersen dose was adjusted according to the estimated volume of cerebrospinal fluid for the infant's age on the day of dosing, such that the infant received a dose that was equivalent to a 12-mg dose in a person 2 years of age or older; thus, younger infants were injected with smaller volumes that contained lower doses of the drug. To maintain blinding, nusinersen was administered or the sham procedure was performed by dedicated trial personnel who were

aware of the group assignments, whereas the infant's parents and key trial personnel who were responsible for assessments were unaware of the group assignments and were not present for the procedure. The sham procedure consisted of a small needle prick to the skin over the lumbar spine, which was covered with a bandage to simulate the appearance of a lumbar-puncture injection. Randomization was stratified according to disease duration at screening, which was the age at screening minus the age at symptom onset (≤12 weeks or >12 weeks).

TRIAL PROCEDURES AND OUTCOMES

In the nusinersen group, doses were administered on days 1, 15, 29, and 64 and maintenance doses on days 183 and 302. In the control group, sham procedures were performed on the same days. Efficacy end points were assessed on days 64, 183, 302, and 394 (±7 days for each visit). Safety-monitoring visits occurred on days 16, 30, 65, 184, and 303. Follow-up after the procedure consisted of weekly assessments by telephone and a visit to the study center on day 394 (±7 days). A prespecified interim analysis was performed by the sponsor and the data and safety monitoring board when approximately 80 infants had been enrolled for at least 6 months (Fig. S1 in the Supplementary Appendix). The analysis showed a benefit–risk assessment in favor of nusinersen. This result prompted early termination of the trial. At that time, infants were invited to complete an end-of-trial visit at least 2 weeks after they had received their most recent dose of nusinersen or undergone their most recent sham procedure. The assessments that were scheduled to be performed on day 394 were performed at the end-of-trial visit. Infants who completed the ENDEAR trial were invited to enroll in the open-label extension study SHINE (ClinicalTrials.gov number, NCT02594124).

The trial had two primary efficacy end points. The first was a motor-milestone response, which was defined according to results on the Hammersmith Infant Neurological Examination (HINE). The HINE is a three-section, 37-item, quantifiable assessment of overall neurologic function in infants.[13] Section 2 of the HINE (HINE-2) assesses the development of motor function through the achievement of motor milestones; scores on the HINE-2 range from 0 to 26, with higher scores indicating better motor function.[13,14] The HINE-2 involves evaluation in eight motor-milestone categories: voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking. For this primary end point, infants who had been enrolled for at least 6 months were evaluated in seven of the eight categories (excluding voluntary grasp) at screening, before the procedure on days 183 and 302, and on day 394. The infants were considered to have a motor-milestone response if they met the following two criteria: improvement in at least one category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point, an increase in the score for kicking of ≥2 points, or achievement of the maximal score for kicking) and more categories with improvement than categories with worsening (i.e., a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point or a decrease in the score for kicking of ≥2 points). Infants who died or were withdrawn from the trial were considered to have had no response, regardless of whether they attended the visit on day 183.

The second primary efficacy end point was event-free survival, which was defined as the time to death or the use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event). The use of permanent assisted ventilation as of days 91, 182, 273, 364, and 394 was determined on the basis of patient data from parental diaries and hospital records obtained at those visits. All events of permanent assisted ventilation were adjudicated by an independent end-point adjudication committee whose members were unaware of the group assignments.

Descriptions of the six secondary end points are provided in the Supplementary Appendix. Scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) range from 0 to 64, with higher scores indicating better motor function; a CHOP INTEND response was defined as an increase of at least 4 points from baseline in the CHOP INTEND score at the end-of-trial visit (day 183, 302, or 394).[15,16] A compound muscle action potential (CMAP) response was defined as an increase in the peroneal CMAP amplitude to at least 1 mV (or maintenance of an amplitude of ≥1 mV) at the end-of-trial visit (day 183, 302, or 394). Adverse events included all untoward events that occurred during the trial period, including those that were expected to occur in a population of infants with

spinal muscular atrophy; details are provided in the Supplementary Appendix. Other safety assessments included vital-sign measurements, laboratory tests, and neurologic examinations.

STATISTICAL ANALYSIS

In accordance with the statistical analysis plan, only the first primary efficacy end point was statistically assessed in the interim analysis. Because the P value for the first primary end point was significant in the interim analysis, this end point was not tested for significance in the final analysis. The second primary efficacy end point and all secondary efficacy end points were assessed in the final analysis. A hierarchical testing strategy was used to control the overall type I error rate at 0.05; in the final analysis, end points were ranked and tested for statistical significance in a hierarchical order (see the Supplementary Appendix).[17]

The difference between the nusinersen group and the control group in the proportion of infants who had a motor-milestone response was analyzed with the use of Fisher's exact test. Event-free survival and overall survival were assessed with the use of a log-rank test that was stratified according to disease duration at screening (≤12 weeks or >12 weeks). The median time to death or the use of permanent assisted ventilation in each group and associated 95% confidence intervals were estimated with the use of the Kaplan–Meier product-limit method; probability of survival was estimated with the use of the Kaplan–Meier method. A hazard ratio for death or the use of permanent assisted ventilation and a hazard ratio for death were calculated with the use of a Cox proportional-hazards model that was adjusted for disease duration at screening in each infant. A hazard ratio of less than 1.00 indicated a lower risk of an event in the nusinersen group than in the control group. For details about patients included in the final analysis, see Figure S1 in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 149 infants were screened, and 122 underwent randomization (81 were assigned to the nusinersen group, and 41 to the control group). One infant in the nusinersen group was withdrawn from the trial before treatment; 121 infants underwent the assigned procedure. The first infant was treated on August 21, 2014, and the last infant's last visit was on November 21, 2016. Baseline characteristics were generally balanced between the two groups, except for age at the time of diagnosis of spinal muscular atrophy, use of ventilatory support, and the presence of symptoms specific to spinal muscular atrophy; the infants in the nusinersen group had earlier onset of symptoms and greater burden of disease than the infants in the control group (although formal statistical testing was not performed) (Table 1). At baseline, all the infants were symptomatic, hypotonic, and weak; these features are consistent with a phenotype that is most likely to be classified as spinal muscular atrophy type 1. The median duration of disease at screening was 13.1 weeks. (For details, see Table S1 and Fig. S2 in the Supplementary Appendix.)

EFFICACY

Primary End Points

For the prespecified interim analysis, the clinical cutoff date was June 15, 2016. In the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (41% vs. 0%, P<0.001) (Table 2). These results prompted early termination of the trial, and infants were evaluated at end-of-trial visits.

For the final analysis, the 121 infants (80 in the nusinersen group and 41 in the control group) who had undergone randomization and the assigned procedure at least one time were included in time-to-event analyses, and the 110 infants (73 in the nusinersen group and 37 in the control group) who had been enrolled at least 6 months before the last infant's last visit were included in all other analyses. In the final analysis, 51% of the infants in the nusinersen group and no infants in the control group had a motor-milestone response (Table 2 and Fig. 1). In the nusinersen group, 22% of the infants achieved full head control, 10% were able to roll over, 8% were able to sit independently, and 1% were able to stand; in the control group, no infants achieved these milestones. (For details, see Figs. S1 and S4 in the Supplementary Appendix.)

The likelihood of event-free survival was significantly higher in the nusinersen group than in the control group, most notably among infants who had a disease duration at screening that

was no longer than the median duration of 13.1 weeks (Table 2 and Fig. 2A, and Fig. S6A in the Supplementary Appendix). By the cutoff date for the final analysis, 39% of the infants in the nusinersen group and 68% in the control group had died or had received permanent assisted ventilation. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group. Overall, the risk of death or the use of permanent assisted ventilation was 47% lower in the nusinersen group than in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.32 to 0.89; P=0.005).

Secondary End Points

A significantly higher percentage of infants in the nusinersen group than in the control group had a CHOP INTEND response (71% vs. 3%, P<0.001). An increase of at least 1 point from baseline in the CHOP INTEND score was observed in 73% of the infants in the nusinersen group versus 3% in the control group; a decrease in the score was observed in 7% versus 49% (Fig. S7 in the Supplementary Appendix).

A lower percentage of infants in the nusinersen group than in the control group had died by the end of the trial (16% vs. 39%) (Fig. 2B). The risk of death was 63% lower in the nusinersen group than in the control group (hazard ratio, 0.37; 95% CI, 0.18 to 0.77; P=0.004) (Table 2).

An estimated 15% of the infants in the nusinersen group and 8% in the control group had received permanent assisted ventilation at 3 months, and an estimated 31% and 48%, respectively, had received permanent assisted ventilation at 13 months. Overall, 23% of the infants in the nusinersen group and 32% in the control group received permanent assisted ventilation (hazard ratio, 0.66; P=0.13) (Table 2). Because the P value for this end point was not significant, all subsequent end-point analyses in the hierarchical testing strategy were considered to be exploratory. By the end of the trial, 36% of the infants in the nusinersen group and 5% in the control group had had a CMAP response (Table 2). In the subgroup analyses, the likelihood of event-free survival was higher among infants who had a shorter disease duration at screening (≤13.1 weeks) than among those who had a longer disease duration (Table 2). (For details, see Figs. S6 and S8 in the Supplementary Appendix.)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nusinersen Group (N=80)	Control Group (N=41)
Female sex — no. (%)	43 (54)	24 (59)
Age at first dose — days		
Mean	163	181
Range	52–242	30–262
Age at symptom onset — wk		
Mean	7.9	9.6
Range	2–18	1–20
Age at diagnosis of spinal muscular atrophy — wk		
Mean	12.6	17.5
Range	0–29	2–30
Disease duration at screening — wk		
Mean	13.2	13.9
Range	0–25.9	0–23.1
Symptoms of spinal muscular atrophy — no. (%)		
Hypotonia	80 (100)	41 (100)
Developmental delay of motor function	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Limb weakness	79 (99)	41 (100)
Swallowing or feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)
Use of ventilatory support — no. (%)	21 (26)	6 (15)
Use of a gastrointestinal tube — no. (%)	7 (9)	5 (12)
Total HINE-2 score†	1.29±1.07	1.54±1.29
CHOP INTEND score‡	26.63±8.13	28.43±7.56
CMAP amplitude — mV		
Peroneal	0.371±0.31	0.317±0.29
Ulnar	0.226±0.19	0.225±0.12

* Plus–minus values are means ±SD. CMAP denotes compound muscle action potential.
† Scores on Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) range from 0 to 26, with higher scores indicating better motor function.[13,14]
‡ Scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) range from 0 to 64, with higher scores indicating better motor function.[15,16]

Additional Prespecified Analyses

Among infants who were alive at the end of the trial and had been enrolled for at least 6 months, most of the infants in the nusinersen group had an increase from baseline in the HINE-2 score;

Table 2. Primary and Secondary End Points.*

End Point	Nusinersen Group	Control Group	Hazard Ratio (95% CI)	P Value
	no./total no. (%)			
Primary end points				
Motor-milestone response†				
Interim analysis	21/51 (41)	0/27	—	<0.001
Final analysis	37/73 (51)	0/37	—	—
No death or use of permanent assisted ventilation‡	49/80 (61)	13/41 (32)	0.53 (0.32–0.89)	0.005
Secondary end points§				
CHOP INTEND response¶	52/73 (71)	1/37 (3)	—	<0.001
No death	67/80 (84)	25/41 (61)	0.37 (0.18–0.77)	0.004
No use of permanent assisted ventilation‡	62/80 (78)	28/41 (68)	0.66 (0.32–1.37)	0.13
CMAP response‖	26/73 (36)	2/37 (5)	—	—
No death or use of permanent assisted ventilation among those with disease duration ≤13.1 wk at screening‡	30/39 (77)	7/21 (33)	0.24 (0.10–0.58)	—
No death or use of permanent assisted ventilation among those with disease duration >13.1 wk at screening‡	19/41 (46)	6/20 (30)	0.84 (0.43–1.67)	—

* The prespecified interim analysis was conducted on June 15, 2016, and included the 78 infants (51 in the nusinersen group and 27 in the control group) who had been enrolled for at least 6 months. Only motor-milestone response was tested in the interim analysis. All other end points were tested in the final analysis, which was conducted with the use of data collected up to the date of the last patient's last visit (November 21, 2016). For the final analysis, the 121 patients who had undergone randomization and the assigned procedure at least one time were included in time-to-event analyses, and the 110 patients who had been enrolled at least 6 months before the last patient's last visit were included in all other analyses. CI denotes confidence interval.

† Motor-milestone response was defined according to scores on the HINE-2, which assesses the development of motor function through the achievement of motor milestones; in this trial, the scores accounted for seven of the eight motor-milestone categories, excluding voluntary grasp. Infants were considered to have a motor-milestone response if they met the following two criteria: improvement in at least one category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point, an increase in the score for kicking of ≥2 points, or achievement of the maximal score for kicking) and more categories with improvement than categories with worsening (i.e., a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point or a decrease in the score for kicking of ≥2 points).

‡ Permanent assisted ventilation was defined as tracheostomy or ventilatory support for at least 16 hours per day for more than 21 continuous days in the absence of an acute reversible event, as determined by an independent end-point adjudication committee.

§ To control for a type I error rate at 0.05, a hierarchical testing strategy was used, in which statistical significance of the first primary end point was required before inferential conclusions could be drawn about the second primary end point and secondary end points. Testing of subsequent end points for statistical significance was contingent on the achievement of statistical significance for the previous end point analyzed. Secondary end points are listed in hierarchical order. Because the P value for the third secondary end point was not significant, all subsequent end-point analyses in the hierarchical testing strategy were considered to be exploratory. (For details, see the Supplementary Appendix.)

¶ A CHOP INTEND response was defined as an increase of at least 4 points from baseline in CHOP INTEND score at the end-of-trial visit (day 183, 302, or 394).

‖ A CMAP response was defined as an increase in the peroneal CMAP amplitude to at least 1 mV (or maintenance of an amplitude of ≥1 mV) at the end-of-trial visit (day 183, 302, or 394).

16 of the 58 infants in the nusinersen group (28%) had an increase of 5 points or more, whereas only 1 of the 20 infants in the control group (5%) had any increase (Fig. 1). Of the 41 infants who had any increase in the HINE-2 score, 28 (68%) had a shorter disease duration at screening (≤12 weeks). In addition, 6 of the 18 infants (33%) in the nusinersen group who received permanent assisted ventilation during the trial had an increase in the HINE-2 score. Among infants in the nusinersen group, the mean HINE-2 score increased progressively over time.

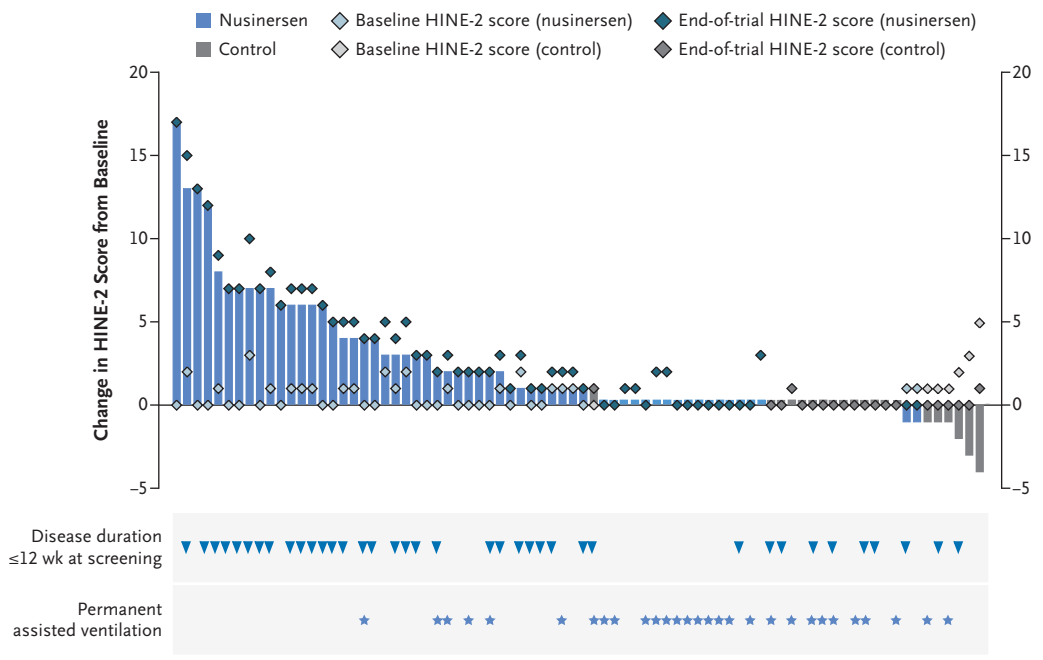

Figure 1. HINE-2 Scores.

Shown are the scores on Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) at baseline and at the end-of-trial visit (on day 183, 302, or 394) (diamonds), as well as the change in HINE-2 score from baseline through the end-of-trial visit (bars), for the 78 infants who were alive, attended an end-of-trial visit, and were included in the final analysis. (Of the 110 infants who were included in the final analysis, 29 died [13 in the nusinersen group and 16 in the control group] and 3 were withdrawn for a reason other than death [2 in the nusinersen group and 1 in the control group] and therefore were not included in this analysis.) The HINE-2 assesses the development of motor function through the achievement of motor milestones; scores on the HINE-2 range from 0 to 26, with higher scores indicating better motor function. The scores shown here account for seven of the eight motor-milestone categories, excluding voluntary grasp. For the infant in the control group who had a 1-point increase, the increase was in the score for kicking, and therefore the infant was not considered to have a motor-milestone response. The shortest bars indicate a value of 0. Triangles indicate infants who had a disease duration of 12 weeks or less at screening. Stars indicate infants who received permanent assisted ventilation during the trial.

(For details, see Figs. S3A and S5A in the Supplementary Appendix.)

SAFETY

The overall incidence of adverse events was similar in the nusinersen group and the control group (96% and 98%, respectively) (Table 3). A lower percentage of infants in the nusinersen group than in the control group had a severe adverse event (56% vs. 80%), a serious adverse event (76% vs. 95%), or an adverse event that led to discontinuation of nusinersen or the control procedure (16% vs. 39%) (Table 3). All the adverse events that led to discontinuation had fatal outcomes (Table S2 in the Supplementary Appendix). Adverse events that were reported within 72 hours after the administration of nusinersen or the sham procedure and adverse events that were reported in more than 5% of the infants in the nusinersen group are listed in Tables S3 and S4 in the Supplementary Appendix, respectively. Otherwise, there were no meaningful between-group differences in the types of adverse events reported. Laboratory test results did not reveal a specific pattern among infants who received nusinersen. (For details about adverse events and laboratory test results, see the Safety Assessments Section in the Supplementary Appendix.)

DISCUSSION

In the ENDEAR trial, among infants with spinal muscular atrophy, those who received intrathecal nusinersen were more likely to have improvements

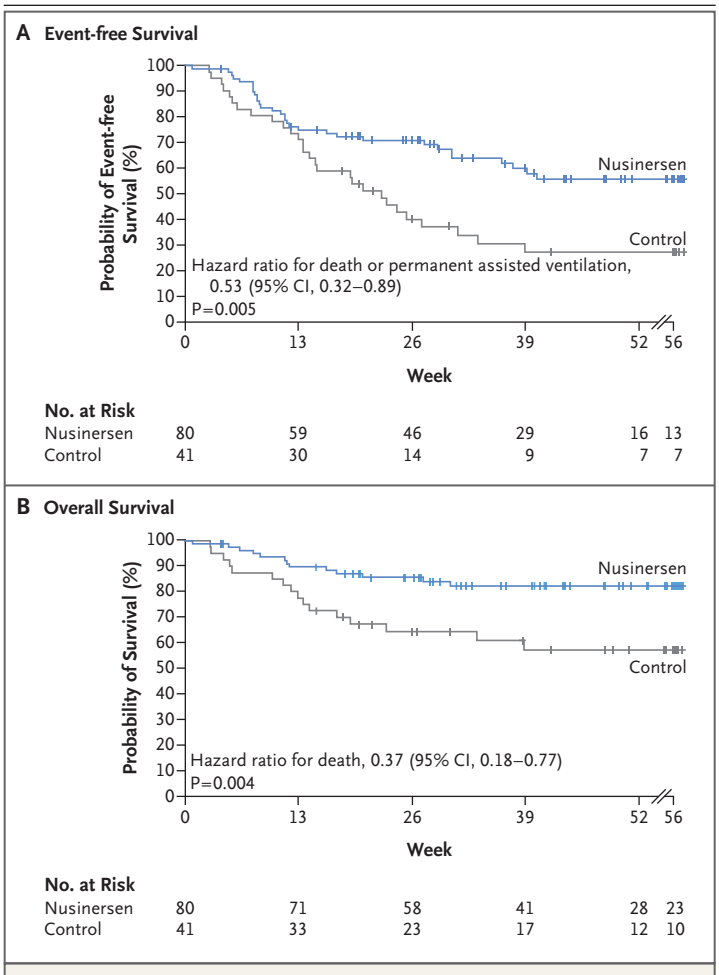

Figure 2. Event-free Survival and Overall Survival.

Panel A shows the probability of event-free survival (the proportion of infants who were alive without the use of permanent assisted ventilation) and Panel B shows the probability of overall survival (the proportion of infants who were alive) in the nusinersen group and the control group. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group; the median time to death was not reached in either group.

in motor function and to be alive without the use of permanent assisted ventilation than those who underwent a sham procedure. These results validate the results of an open-label, phase 2 study of nusinersen in infantile-onset spinal muscular atrophy.[12] Although the baseline characteristics of the infants were generally balanced between the nusinersen group and the control group, infants in the nusinersen group had earlier symptom onset and greater disease burden at baseline than did those in the control group. The between-group difference in the proportion of infants who had a motor-milestone response (based on the HINE-2 score) increased over time. Most infants with spinal muscular atrophy type 1 are unable to achieve or maintain most motor milestones.[6] Several of the infants in the nusinersen group achieved clinically meaningful motor milestones. The increase in the CHOP INTEND score and the CMAP amplitude among infants who received nusinersen confirms that nusinersen improves neuromuscular function.

The definitions of response with respect to HINE-2 and CHOP INTEND were selected to measure deviations from the expected trajectory of motor-function decline that was established in published natural-history studies for spinal muscular atrophy (see the Supplementary Appendix).[5,6,12,15,16] Although the HINE-2 was not specifically developed to assess motor function in infants with spinal muscular atrophy,[13] it can be used to identify incremental changes in the achievement of motor milestones that are relevant among infants with spinal muscular atrophy type 1,[12] and the HINE-2 assessment can be performed reliably in a multicenter study.[14] Infants who received nusinersen had a significantly higher likelihood of event-free and overall survival than infants who underwent a sham procedure, despite the fact that more infants in the nusinersen group than in the control group were receiving ventilatory support at baseline. In the final analysis, the between-group difference in the percentage of infants who received permanent assisted ventilation was not significant; however, data were censored for infants who had died. Because the proportion of infants who had died in the control group was more than twice that in the nusinersen group, this analysis may have masked the treatment effect of nusinersen on the use of permanent assisted ventilation. Approximately half the infants in the nusinersen group who received permanent assisted ventilation did so within 13 weeks after they received the first dose; this result indicates that a minimum treatment time is required to see the full benefits of nusinersen. This result, as well as our finding that infants with a disease duration at screening longer than the median duration of 13.1 weeks were more likely than those with a disease duration no longer than the median duration to need permanent assisted ventilation, suggests that early initiation of treatment may maximize its efficacy.

The ENDEAR trial was terminated early because of the results of the interim analysis and ethical consideration for the infants in the control group. Not all the patients underwent the assigned procedure for 13 months; for many end points, data obtained on day 183, 302, or 394 were used for the final analysis, which could result in outcome variability. Because increasing gains were seen up to the last data point collected for several outcome measures and because the trial was concluded prematurely at the interim analysis, the maximum response in the trial population is not yet clear.

The majority of the reported adverse events were consistent with those expected in a population of infants with spinal muscular atrophy and were similar to those reported in an open-label study in infantile-onset spinal muscular atrophy.[12,18] No serious safety concerns were identified during the close monitoring that followed the intrathecal injections. Because the infants who were enrolled in this trial were nonverbal, adverse events that are typically reported by the patient (particularly adverse events associated with the post–lumbar puncture syndrome, such as back pain and headache) may not have been captured. However, adverse events associated with the post–lumbar puncture syndrome increase in frequency with increasing age and are less common in children than adults.[19] (For additional discussion of adverse events, see the Supplementary Appendix.)

An inherent risk associated with international multicenter trials is that differences in standards of care among the sites could affect patient outcomes. However, standard-of-care guidelines[18,20] were incorporated into the trial design to minimize site-to-site variations, and we therefore propose that the control group is an accurate representation of the natural history of infantile-onset spinal muscular atrophy. Several of the infants who received nusinersen died, none achieved normal motor development, and some needed continued feeding and ventilatory support; these findings indicate that nusinersen is not a cure in symptomatic patients. Infants who were enrolled in the ENDEAR trial have been enrolled in the open-label extension study SHINE, which is designed to assess the effects of longer treatment duration on motor function and quality of life.

Table 3. Adverse Events.

Event	Nusinersen Group (N=80)	Control Group (N=41)
	no. (%)	
Any adverse event*	77 (96)	40 (98)
Adverse event leading to discontinuation	13 (16)	16 (39)
Severe adverse event†	45 (56)	33 (80)
Serious adverse event‡	61 (76)	39 (95)
Serious adverse event with fatal outcome‡	13 (16)	16 (39)
Respiratory disorder§	7 (9)	12 (29)
Cardiac disorder	2 (2)	3 (7)
General disorder	2 (2)	1 (2)
Nervous-system disorder	2 (2)	0
Adverse event that occurred in ≥20% of infants in either group§		
Pyrexia	45 (56)	24 (59)
Constipation	28 (35)	9 (22)
Upper respiratory tract infection	24 (30)	9 (22)
Pneumonia	23 (29)	7 (17)
Respiratory distress	21 (26)	12 (29)
Respiratory failure	20 (25)	16 (39)
Atelectasis	18 (22)	12 (29)
Vomiting	14 (18)	8 (20)
Acute respiratory failure	11 (14)	10 (24)
Gastroesophageal reflux disease	10 (12)	8 (20)
Decreased oxygen saturation	10 (12)	10 (24)
Cough	9 (11)	8 (20)
Dysphagia	9 (11)	9 (22)
Serious adverse event that occurred in ≥10% of infants in either group‡§		
Respiratory distress	21 (26)	8 (20)
Respiratory failure	20 (25)	16 (39)
Pneumonia	19 (24)	5 (12)
Atelectasis	14 (18)	4 (10)
Acute respiratory failure	11 (14)	9 (22)
Pneumonia aspiration	8 (10)	5 (12)
Cardiorespiratory arrest	5 (6)	5 (12)
Respiratory arrest	5 (6)	4 (10)
Viral upper respiratory tract infection	3 (4)	6 (15)
Bronchial secretion retention	1 (1)	5 (12)

* For infants who had more than one adverse event, only the event of the highest severity was counted.
† Severe adverse events were defined as symptoms that caused severe discomfort, incapacitation, or substantial effect on daily life.
‡ Serious adverse events were defined as any untoward medical occurrence that resulted in death or a risk of death, hospitalization or prolonged hospitalization, persistent or substantial disability or incapacity, or a congenital anomaly or birth defect.
§ These events could plausibly be linked to spinal muscular atrophy.

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APPENDIX

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