ORIGINAL ARTICLE

Risdiplam in Type 1 Spinal Muscular Atrophy

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ABSTRACT

BACKGROUND

Type 1 spinal muscular atrophy is a rare, progressive neuromuscular disease that is caused by low levels of functional survival of motor neuron (SMN) protein. Risdiplam is an orally administered, small molecule that modifies *SMN2* pre–messenger RNA splicing and increases levels of functional SMN protein.

METHODS

We report the results of part 1 of a two-part, phase 2–3, open-label study of risdiplam in infants 1 to 7 months of age who had type 1 spinal muscular atrophy, which is characterized by the infant not attaining the ability to sit without support. Primary outcomes were safety, pharmacokinetics, pharmacodynamics (including the blood SMN protein concentration), and the selection of the risdiplam dose for part 2 of the study. Exploratory outcomes included the ability to sit without support for at least 5 seconds.

RESULTS

A total of 21 infants were enrolled. Four infants were in a low-dose cohort and were treated with a final dose at month 12 of 0.08 mg of risdiplam per kilogram of body weight per day, and 17 were in a high-dose cohort and were treated with a final dose at month 12 of 0.2 mg per kilogram per day. The baseline median SMN protein concentrations in blood were 1.31 ng per milliliter in the low-dose cohort and 2.54 ng per milliliter in the high-dose cohort; at 12 months, the median values increased to 3.05 ng per milliliter and 5.66 ng per milliliter, respectively, which represented a median of 3.0 times and 1.9 times the baseline values in the low-dose and high-dose cohorts, respectively. Serious adverse events included pneumonia, respiratory tract infection, and acute respiratory failure. At the time of this publication, 4 infants had died of respiratory complications. Seven infants in the high-dose cohort and no infants in the low-dose cohort were able to sit without support for at least 5 seconds. The higher dose of risdiplam (0.2 mg per kilogram per day) was selected for part 2 of the study.

CONCLUSIONS

In infants with type 1 spinal muscular atrophy, treatment with oral risdiplam led to an increased expression of functional SMN protein in the blood. (Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT02913482.)

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*A complete list of the investigators in the FIREFISH Working Group is provided in the Supplementary Appendix, available at NEJM.org.

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Spinal muscular atrophy is a rare, progressive, recessive neuromuscular disease that is caused by deletions or loss-of-function mutations in the survival of motor neuron 1 gene (*SMN1*), which result in insufficient levels of SMN protein.[1,2] Humans have a paralogous gene *SMN2* that also codes SMN protein, but exon 7 is excluded during splicing, which results in low levels of functional SMN protein.[3,4] These low levels of functional SMN protein do not compensate for the loss of *SMN1* in patients with spinal muscular atrophy.

Spinal muscular atrophy is categorized into five subtypes (ranging from 0 to 4, with lower numbers indicating greater severity), which are defined according to the maximum motor milestone attained and the age of symptom onset.[1,5] Type 1 spinal muscular atrophy is characterized by the inability to sit without support and by reduced life expectancy.[1,6-8] These infants have a decline in motor function, and most do not survive beyond 2 years of age.[1,7,8] Impaired cough[9] and reduced vital capacity[10] due to neuromuscular weakness are associated with respiratory infections. Swallowing is compromised, and these infants require feeding support or combined feeding and ventilatory support by 12 months of age.[7]

The Food and Drug Administration (FDA) has approved three therapies for spinal muscular atrophy: nusinersen, onasemnogene abeparvovec, and risdiplam. Nusinersen is an intrathecally administered *SMN2*-targeting antisense oligonucleotide therapy for adults and children,[11] and onasemnogene abeparvovec is an intravenously administered adeno-associated virus vector–based gene-transfer therapy for use in patients younger than 2 years of age.[12] Each of these two agents has led to improvements in survival and motor function in patients with spinal muscular atrophy.[13-16]

Risdiplam is a systemically distributed small molecule, administered orally in liquid form, that modifies *SMN2* pre–messenger RNA (pre-mRNA) splicing.[17] It has been approved by the FDA for the treatment of patients with spinal muscular atrophy who are 2 months of age or older.[18] It has been inferred from data about a close analogue of risdiplam (SMN-C5) in fibroblasts obtained from patients with type 1 spinal muscular atrophy that risdiplam could bind selectively to two sites in *SMN2* pre-mRNA: the exonic splicing enhancer 2 in exon 7 and the 5′ splice site in intron 7.[19] Risdiplam promotes the inclusion of exon 7, thereby increasing the expression of full-length *SMN2* mRNA and functional SMN protein.[17] In mouse models of spinal muscular atrophy, risdiplam led to an increase in functional SMN protein levels in the central nervous system and nonneuronal tissues.[17,20]

We conducted an open-label, two-part study of risdiplam in infants 1 to 7 months of age who had type 1 spinal muscular atrophy (FIREFISH). Here, we present the results from the dose-finding part 1 of this study, which had primary outcomes of safety and the pharmacokinetics and pharmacodynamics of risdiplam and the selection of the dose for part 2. Part 1 of the study included post hoc exploratory efficacy outcomes, which were adopted from part 2, including event-free survival and the ability to sit without support for at least 5 seconds. Part 2 includes prespecified clinical outcomes that are not included in part 1.

METHODS

STUDY OVERSIGHT

The study was approved by an ethics committee at each study site and was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent was provided by parents or caregivers. The sponsor, F. Hoffmann–La Roche, provided the study drug, study management and medical monitoring, drug safety management and analysis, data management and statistical analysis, and pharmacokinetic and pharmacodynamic analysis. The sponsor paid for a professional medical writer, who wrote the first draft of the manuscript. Safety data were reviewed by a monitoring committee within F. Hoffmann–La Roche until the start of part 2 of the study and by an independent data and safety monitoring committee thereafter. Confidentiality agreements were in place between the authors and the sponsor. All the authors vouch for the adherence of the study to the protocol (available with the full text of this article at NEJM.org), for the accuracy of the data, and for the complete reporting of adverse events at their study sites. Eight of the authors contributed to the study conception and design. Data collection was performed by nine of the authors. Data analysis and interpretation were performed by all the authors.

PATIENTS AND STUDY DESIGN

Enrolled infants (1 to 7 months of age at enrollment) had symptomatic, genetically confirmed 5q-autosomal recessive spinal muscular atrophy and two copies of *SMN2*. Infants were excluded from the study if they had previously received treatment with other *SMN2*-targeting therapies or gene therapy. The full list of eligibility criteria is provided in the Supplementary Appendix, available at NEJM.org.

OUTCOMES

The primary outcomes of part 1 of the study were safety and the pharmacokinetics and pharmacodynamics of risdiplam and the determination of the dose to be used in part 2, which was powered as an efficacy study. Safety assessments included adverse-event reporting, laboratory assessments, electrocardiography, anthropometric and physical examinations, and vital signs. (Table S1 in the Supplementary Appendix shows the assessment schedule.) Owing to risdiplam-associated retinal toxic effects that have been observed in monkeys,[17] ophthalmologic assessments, including imaging (optical coherence tomography and fundus photography) and evaluation of visual function, were performed every 2 months. Blood samples were obtained for the measurement of the plasma concentration of risdiplam and SMN protein (quantified, respectively, by means of liquid chromatography–tandem mass spectrometry and an immunoassay developed on the Elecsys platform).[21,22]

Risdiplam was administered, once daily, either orally at the assigned dose in infants who were able to swallow or as a bolus through a feeding tube in infants who were unable to swallow. Dose finding was performed in a dose-escalation manner. The doses in part 1 of the study were as follows: 0.00106 mg per kilogram of body weight as a single-dose administration and then 0.0106 mg, 0.04 mg, 0.08 mg, 0.2 mg, and 0.25 mg per kilogram once daily. Dose escalation was based on regular review of pharmacokinetic and safety data, followed by dose adjustments, to reach the protocol-specified target exposure (the mean area under the risdiplam plasma concentration time curve [AUC] over a period of 24 hours at steady state) of 700 ng•h per milliliter in the low-dose cohort and 2000 ng•h per milliliter in the high-dose cohort. Once the safety of risdiplam at the low dose was confirmed in the first five enrolled infants, we had planned that the last (fifth) enrolled infant would change from the low-dose cohort to the high-dose cohort.

Post hoc exploratory outcomes were adopted from part 2 of the study and were not prespecified for part 1 (see the protocol). These exploratory outcomes included the following: event-free survival, which was defined as being alive without the use of permanent ventilation (tracheostomy or ventilation [bilevel positive airway pressure] for ≥16 hours per day continuously for >3 weeks or continuous intubation for >3 weeks, in the absence of, or after the resolution of, an acute reversible event), as assessed in infants over a period of 12 months with the use of the Kaplan–Meier method; sitting without support, as assessed with the use of item 22 (sits without support for ≥5 seconds) of the gross motor subscale of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III[23]; sitting attempts were video-recorded, and videos were reviewed and scored by two independent raters who were unaware of the dose assignment); the score on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND; on a scale from 0 to 64, with higher scores indicating better motor function)[24]; motor milestone scores on Section 2 of the Hammersmith Infant Neuromuscular Examination (HINE-2; on a scale from 0 to 26, with higher scores indicating better motor function)[25]; and electrophysiological and nutrition measures (see the Supplementary Appendix). No clinical conclusions can be drawn from these post hoc analyses.

STATISTICAL ANALYSIS

We estimated that a minimum sample of 8 infants in part 1 would provide the study with a greater than 80% chance of detecting an adverse event in at least 1 infant if the known incidence of the adverse event in this population was 20%. To enable dose selection for part 2 of the study (i.e., to assess the variability of pharmacokinetics in infants with different ages or body weights), we estimated that 24 infants could be enrolled in part 1. The change from baseline in the blood SMN protein concentration was calculated for each infant at each time point, and the median and range of these values for each dose cohort are reported.

The percentage of infants who met each end point are presented with the denominator of the

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Low-Dose Cohort (N=4)	High-Dose Cohort (N=17)	All Infants (N=21)
Sex — no. (%)			
Female	4 (100)	11 (65)	15 (71)
Male	0	6 (35)	6 (29)
Median age (range) — mo			
At onset of symptoms	2.7 (2.0–3.0)	1.5 (0.9–3.0)	2.0 (0.9–3.0)
At diagnosis	3.3 (2.5–5.1)	3.0 (0.9–5.4)	3.0 (0.9–5.4)
At enrollment	6.9 (6.7–6.9)	6.3 (3.3–6.9)	6.7 (3.3–6.9)
Motor measures†			
Median CHOP-INTEND score (range)	23.5 (10–25)	24 (16–34)	24 (10–34)
Median HINE-2 score (range)	1 (0–3)	1 (0–2)	1 (0–3)
Respiratory support — no. (%)	0	5 (29)‡	5 (24)‡

* The dose of risdiplam was adjusted per the protocol to the final dose of 0.2 mg per kilogram of body weight before 1 year of treatment in the high-dose cohort and after 1 year of treatment in the low-dose cohort. The three surviving infants in the low-dose cohort subsequently had their dose adjusted at the ages of 24.4 months, 20.6 months, and 20.8 months.
† 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. Scores on Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) range from 0 to 26, with higher scores indicating better motor function. All 21 infants were assessed with the use of the CHOP-INTEND and HINE-2 at baseline. Two infants in the high-dose cohort had 1 item (out of 16) missing in their baseline CHOP-INTEND scores; both these item scores were imputed to 0.
‡ Four of these infants were receiving respiratory support prophylactically.

total number of infants. Confidence intervals that are reported for exploratory measures are post hoc and were not adjusted for multiple comparisons. Confidence intervals were calculated by the complementary log–log transformation method for survival and event-free survival and by the Clopper–Pearson method for other efficacy measures. Infants who did not attain a motor milestone, who did not maintain a milestone that had been reached earlier, who were withdrawn from the study, or who died were classified as not having a response. Missing scores for items in the CHOP-INTEND and HINE-2 were assigned a score of 0.

RESULTS

PATIENTS

A total of 21 infants were enrolled (Fig. S1). The final doses that were established by the dose-escalation method were 0.08 mg per kilogram once daily in the low-dose cohort and 0.2 mg per kilogram once daily in the high-dose cohort. The low-dose cohort included 4 infants: 3 infants received the low dose for at least 12 months before an increase to the high dose, and 1 infant received the low dose but was withdrawn from the study on day 19 and started palliative care owing to progression of the underlying disorder. The fifth enrolled infant died from disease-related complications approximately 3 weeks after enrollment in the study and before the planned dose increase. Therefore, the dose of the fourth infant was increased after approximately 2.5 months of treatment. This fourth infant and all the subsequently enrolled infants composed the high-dose cohort (17 infants).

The age range of the infants at symptom onset was 28 days (i.e., 0.9 months) to 3.0 months. The median age of the infants at enrollment was 6.7 months (range, 3.3 to 6.9) (Table 1). The median baseline CHOP-INTEND score of 24 and HINE-2 score of 1 were consistent with severe disease.[8,13] At baseline, none of the infants were able to sit without support, and 5 of the 21 infants (24%) were receiving respiratory support; 4 of these infants were receiving this support prophylactically. At month 12, the mean age of the infants was 17.7 months. As of the data-cutoff date of February 27, 2019, the median duration of risdiplam treatment among all 21 infants was 14.8 months (range, 0.6 to 26.0).

SAFETY

As of the clinical data-cutoff date, a total of 24 serious adverse events had been reported. The most common serious adverse events were pneumonia (in three infants) and respiratory tract infection, viral respiratory tract infection, acute respiratory failure, and respiratory distress (in two infants each). Overall, 202 adverse events were reported (Tables 2 and S2). Three infants had died at the time of the data cutoff (Table S5). After the data-cutoff date, one infant was withdrawn from risdiplam treatment on day 585 at the request of the parents, and the infant died approximately 3.5 months after withdrawal owing to a respiratory complication related to spinal muscular atrophy. No additional deaths have been reported in part 1 of the study.

One infant had a serious adverse event of grade 4 neutropenia in the context of serious pneumonia. Laboratory results, vital signs, and electrocardiograms that were assessed at prescheduled time points did not show clinically significant adverse findings as compared with baseline. Hematologic variables remained stable over time; any abnormal results were present at baseline or returned to within normal ranges without change to the dose of study medication. Bone marrow suppression was not observed. One event of eczema was ongoing at the clinical data-cutoff date. Other skin events and details about laboratory findings that were related to adverse events are listed in Table S2.

Ophthalmologic assessments showed age-related immaturity of the retina (isolated retinal cysts), which resolved with increasing age. There were no findings suggestive of risdiplam-induced retinal toxic effects, as had been observed in a study in monkeys treated with risdiplam (at higher exposures than were tested in this study).[17]

BLOOD SMN PROTEIN CONCENTRATIONS AND RISDIPLAM EXPOSURE

The baseline median concentration of SMN protein in blood was 1.31 ng per milliliter (range, 0.58 to 4.82) among 4 infants in the low-dose cohort and 2.54 ng per milliliter (range, 1.10 to 6.40) among 16 infants in the high-dose cohort (Fig. 1). In the low-dose cohort, the blood SMN protein concentration increased to its highest median value of 4.49 ng per milliliter (range, 2.61 to 5.55) among 3 infants at 4 weeks, which was a median of 4.5 times (range, 1.2 to 5.4) the baseline value; at 12 months, the median value among these 3 infants was 3.05 ng per milliliter (range, 1.75 to 5.51), which was a median of 3.0 times (range, 1.1 to 3.6) the baseline value. In the high-dose cohort, the blood SMN protein concentration increased to its highest median value of 5.87 ng per milliliter (range, 2.84 to 8.76) among 17 infants at 4 weeks, which was a median of 2.1 times (range, 0.9 to 6.5) the baseline value; at 12 months, the median value among 15 infants was 5.66 ng per milliliter (range, 2.66 to 8.60), which was a median of 1.9 times (range, 0.6 to 7.8) the baseline value. At month 12, the mean AUC of risdiplam among 3 infants in the low-dose cohort was 630 ng•h per milliliter (range, 470 to 800); in the high-dose cohort, the mean value among 16 infants was 2000 ng•h per milliliter (range, 1540 to 2960).

EXPLORATORY EFFICACY OUTCOMES

At month 12, a total of 19 of the 21 infants (90%; 3 infants in the low-dose cohort and 16 in the high-dose cohort) had not had a clinical event as defined in the Outcomes section (Fig. 2). A total of 7 infants (33%), all in the high-dose cohort, were able to sit without support for at least 5 seconds, as assessed by the BSID-III. A total of 9 of the infants in the high-dose cohort were able to maintain upright head control at all times, and 1 infant in the high-dose cohort was able to bear weight in standing, as assessed by the HINE-2; no infants in the low-dose cohort were able to perform these functions. The CHOP-INTEND scores and HINE-2 motor milestones are shown in Tables S3 and S4 and Figure S3. At month 12, a total of 11 infants (52%) had a CHOP-INTEND score of 40 or higher, a score that is rarely observed in patients with type 1 spinal muscular atrophy.[7,8,13,16]

Over the 12-month period, no infant lost the ability to swallow. At month 12, a total of 18 infants (86%; 3 in the low-dose cohort and 15 in the high-dose cohort) were able to feed orally, either exclusively or in combination with a feeding tube. A total of 3 infants were fed by a combination of oral and tube feeding, and 1 infant who was unable to swallow at baseline was still fed exclusively by feeding tube at month 12.

The median change from baseline in the weight-for-age percentiles among all the infants at month 12 was 3 percentiles (range, −66 to 89), and the median weight-for-age percentile was

Table 2. Adverse Events.*

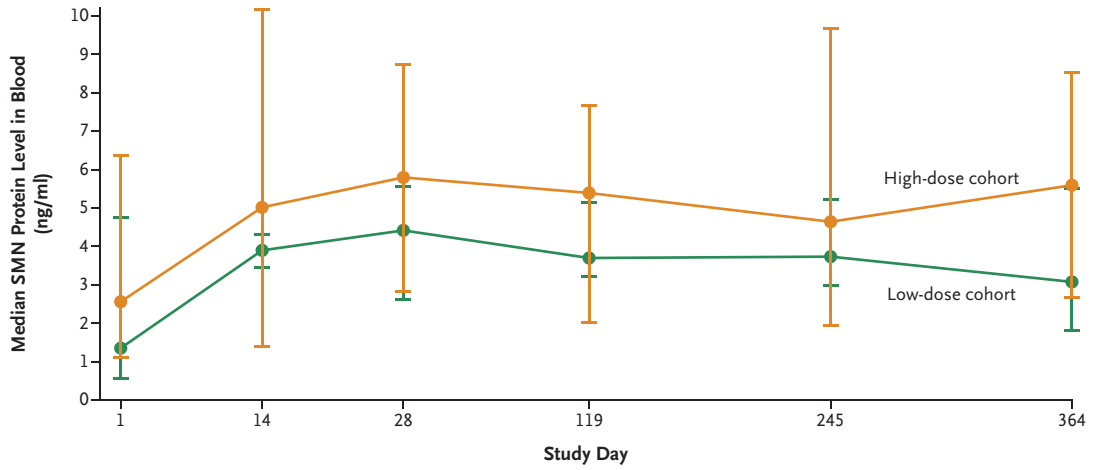
Event	Infants (N=21)
Total no. of adverse events	202
≥1 Adverse event — no. (%)	21 (100)
Total no. of serious adverse events	24
≥1 Serious adverse event — no. (%)	10 (48)
≥1 Adverse event of grade 3–5 — no. (%)	9 (43)
Serious adverse event with fatal outcome — no. (%)†	3 (14)
Most common adverse events — no. (%)‡	
Pyrexia	11 (52)
Upper respiratory tract infection	9 (43)
Diarrhea	6 (29)
Cough	5 (24)
Vomiting	5 (24)
Constipation	4 (19)
Pneumonia	4 (19)
Ear infection	3 (14)
Eczema	3 (14)
Erythema	3 (14)
Nasopharyngitis	3 (14)
Respiratory tract infection	3 (14)
Rhinitis	3 (14)
Teething	3 (14)
Upper respiratory tract inflammation	3 (14)
Serious adverse event — no. (%)	
Pneumonia	3 (14)
Respiratory tract infection	2 (10)
Viral respiratory tract infection	2 (10)
Acute respiratory failure	2 (10)
Respiratory distress	2 (10)
Influenza	1 (5)
Upper respiratory tract infection	1 (5)
Atelectasis	1 (5)
Hypoxia	1 (5)
Pneumonia aspiration	1 (5)
Pneumothorax	1 (5)
Respiratory failure	1 (5)
Neutropenia	1 (5)
Cardiac arrest	1 (5)
Decreased weight	1 (5)
Failure to thrive	1 (5)
Grade 3–5 serious adverse event — no. (%)	
Pneumonia	3 (14)
Viral respiratory tract infection	2 (10)
Acute respiratory failure	2 (10)
Respiratory tract infection	1 (5)
Neutropenia	1 (5)
Influenza	1 (5)
Hypoxia	1 (5)
Pneumonia aspiration	1 (5)
Respiratory distress	1 (5)
Pneumothorax	1 (5)
Atelectasis	1 (5)
Cardiac arrest	1 (5)
Respiratory failure	1 (5)

* Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 21.1.

† As of the data-cutoff date (February 27, 2019), three infants had died. Viral respiratory tract infection occurred in a female infant who had been 7 months of age at enrollment. The first symptoms started on day 5 of the study, and she died on study day 21. The event was complicated by bilateral atelectasis. A fatal cardiac arrest and respiratory failure occurred on study day 236 in a female infant who had been 7 months of age at enrollment and who was receiving concurrent mechanical ventilation at night (bilevel positive airway pressure for <16 hours per day) in the context of suspected aspiration. A respiratory tract infection with onset on study day 386 occurred in a female infant who had been 5 months 3 weeks of age at enrollment. In the absence of fever and owing to moderate symptoms (nasal congestion and labored breathing) that seemed to abate, the infant was not hospitalized; the infant died 1 day after the onset of respiratory tract infection. One additional infant died after the data-cutoff date. (Table S5 provides full descriptions of the fatal adverse events.)

‡ The most common adverse events are those that were reported in three or more infants.

the 27th (range, 7 to 90). The median change from baseline in the length- or height-for-age percentiles among all the infants at month 12 was –11 percentiles (range, –57 to 69), and the median length- or height-for-age percentile was the 69th (range, 9 to 100). Other exploratory measures, including the percentage of infants who had an increase from baseline of 0.3 mV or more in the negative peak amplitude for compound muscle action potential, are shown in Table S4.



No. of Patients						
High-dose cohort	16	13	17	15	15	15
Low-dose cohort	4	3	3	3	3	3
Median SMN Protein Level in Blood (range) — ng/ml						
High-dose cohort	2.54 (1.10–6.40)	5.01 (1.42–10.22)	5.87 (2.84–8.76)	5.44 (2.03–7.71)	4.64 (1.95–9.67)	5.66 (2.66–8.60)
Low-dose cohort	1.31 (0.58–4.82)	3.87 (3.45–4.37)	4.49 (2.61–5.55)	3.67 (3.24–5.21)	3.71 (2.97–5.24)	3.05 (1.75–5.51)

Figure 1. SMN Protein Concentration in Whole Blood.

Blood was mixed with lysis buffer in a 1:1 ratio. I bars indicate the range. The data-cutoff date was February 27, 2019. SMN denotes survival of motor neuron.

DISCUSSION

In this trial of risdiplam in infants with type 1 spinal muscular atrophy, 24 serious adverse events had been reported as of the clinical data-cutoff date. The most common serious adverse events were infections of the respiratory tract, and 4 infants died of respiratory complications; these findings are consistent with the neuromuscular respiratory failure that characterizes spinal muscular atrophy. The risdiplam-associated retinal toxic effects that had been previously observed in monkeys[17] were not observed in the current study. One infant had a serious adverse event of neutropenia that occurred in the context of pneumonia. We did not observe effects of the drug on epithelial tissues, particularly parakeratosis, or hematologic findings that have been associated with bone marrow suppression, as has been observed in animals treated with risdiplam at higher exposures than were tested in this study (owing to the effect of risdiplam on other splice targets).[17] Adverse events involving the skin that were observed in this study may have been attributable to the drug but resolved during ongoing risdiplam treatment, in contrast to dermatologic adverse events that worsened with continued treatment in studies in animals.[17]

In this study, a median SMN protein level of 2.1 times the baseline level was observed within 4 weeks after the initiation of treatment in the high-dose cohort (i.e., the selected therapeutic dose for part 2), but there was variation between measurements in individual infants. The mean exposure to risdiplam at which this increase was observed was the highest mean exposure of risdiplam that did not lead to retinal toxic effects in toxicologic studies in animals.[17] On the basis of the pharmacokinetic data, the selected dose for part 2 of this study was 0.2 mg per kilogram.

Exploratory clinical measures that were adopted from the ongoing part 2 of the study were not formally included in part 1. These included, at month 12 (when the mean age of the infants was 17.7 months), that 90% of the infants in the current part of the study were event-free, which was defined as being alive without use of permanent ventilation (meaning they did not have a tracheostomy or ventilation such as bilevel positive airway pressure for ≥16 hours per day for

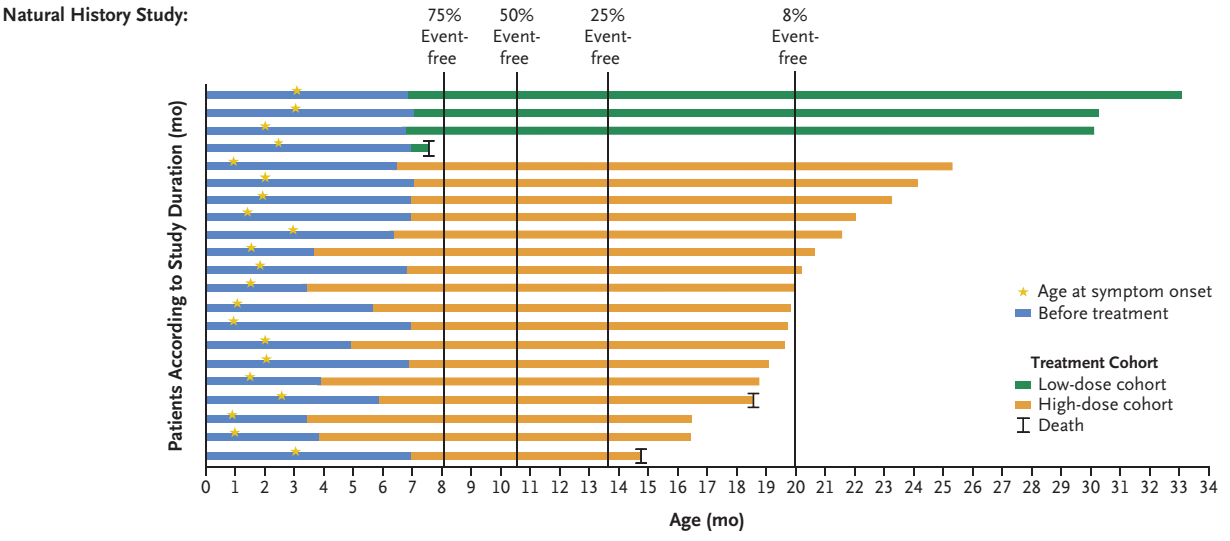


Figure 2. Event-free Survival.

Event-free survival was defined as being alive and not receiving permanent ventilation (tracheostomy or ventilation [bilevel positive airway pressure] for ≥16 hours per day continuously for >3 weeks or continuous intubation for >3 weeks, in the absence of, or after the resolution of, an acute reversible event). The percentages of patients who were event-free in a previous natural history study of spinal muscular atropy[7] are shown at the top of the graph for comparison. The median age at the combined outcome among patients in the previous study who had two copies of *SMN2* was 10.5 months (interquartile range, 8.1 to 13.6); event-free survival in that study was defined as being alive and not receiving noninvasive ventilation for 16 hours or more per day continuously for 2 or more weeks. The duration of our study was measured from the date of enrollment to the data-cutoff date. As of the data-cutoff date, three infants (one in the low-dose cohort and two in the high-dose cohort) had died; one additional infant in the high-dose cohort died after that date (Table S5).

>3 weeks or have continuous intubation for >3 weeks, in the absence of, or after the resolution of, an acute reversible pulmonary event). In a historical cohort of infants with spinal muscular atrophy with two copies of *SMN2*, the median age at the time of death or at the time of receiving at least 16 hours of noninvasive ventilation support per day for at least 14 days was 10.5 months.[7] In our study, no surviving infant was receiving permanent ventilation at month 12, and 7 of the 21 infants were able to sit without support, which is not expected in patients with type 1 spinal muscular atrophy, according to historical experience.[1,6,8] The infants who were enrolled in our study were older and had a longer duration of disease at baseline than patients in other clinical trials in type 1 spinal muscular atrophy.[13,16] Risdiplam is being investigated in trials involving patients with spinal muscular atrophy type 2 or 3 (ClinicalTrials.gov number, NCT02908685); patients with spinal muscular atrophy who have previously received treatment with RG7800 (also known as RO6885247), nusinersen, olesoxime, or onasemnogene abeparvovec (NCT03032172); and infants who are presymptomatic (NCT03779334).

In the current study, treatment with risdiplam increased levels of functional SMN protein in the blood, which implies that risdiplam shifts mRNA splicing toward the expression of full-length *SMN2* mRNA. It cannot be stated with confidence that there was clinical benefit of the agent because the exploratory clinical end points were analyzed post hoc and can only be qualitatively compared with historical cohorts. Part 2 of the study is ongoing to evaluate the longer-term safety and effect of risdiplam in type 1 spinal muscular atrophy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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