ORIGINAL ARTICLE

# Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls

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## ABSTRACT

### BACKGROUND

Type 1 spinal muscular atrophy (SMA) is a progressive neuromuscular disease characterized by an onset at 6 months of age or younger, an inability to sit without support, and deficient levels of 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 in blood.

### METHODS

We conducted an open-label study of risdiplam in infants with type 1 SMA who were 1 to 7 months of age at enrollment. Part 1 of the study (published previously) determined the dose to be used in part 2 (reported here), which assessed the efficacy and safety of daily risdiplam as compared with no treatment in historical controls. The primary end point was the ability to sit without support for at least 5 seconds after 12 months of treatment. Key secondary end points were a score of 40 or higher on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND; range, 0 to 64, with higher scores indicating better motor function), an increase of at least 4 points from baseline in the CHOP-INTEND score, a motor-milestone response as measured by Section 2 of the Hammersmith Infant Neurological Examination (HINE-2), and survival without permanent ventilation. For the secondary end points, comparisons were made with the upper boundary of 90% confidence intervals for natural-history data from 40 infants with type 1 SMA.

### RESULTS

A total of 41 infants were enrolled. After 12 months of treatment, 12 infants (29%) were able to sit without support for at least 5 seconds, a milestone not attained in this disorder. The percentages of infants in whom the key secondary end points were met as compared with the upper boundary of confidence intervals from historical controls were 56% as compared with 17% for a CHOP-INTEND score of 40 or higher, 90% as compared with 17% for an increase of at least 4 points from baseline in the CHOP-INTEND score, 78% as compared with 12% for a HINE-2 motor-milestone response, and 85% as compared with 42% for survival without permanent ventilation ($P<0.001$ for all comparisons). The most common serious adverse events were pneumonia, bronchiolitis, hypotonia, and respiratory failure.

### CONCLUSIONS

In this study involving infants with type 1 SMA, risdiplam resulted in higher percentages of infants who met motor milestones and who showed improvements in motor function than the percentages observed in historical cohorts. Longer and larger trials are required to determine the long-term safety and efficacy of risdiplam in infants with type 1 SMA. (Funded by F. Hoffmann–La Roche; FIREFISH 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 (SMA) is an autosomal recessive motor neuron disease caused by mutations in the survival of motor neuron 1 gene (*SMN1*) that result in reduced production of functional SMN protein.[1,2] The paralogous gene *SMN2* also encodes SMN protein; however, during splicing of this gene, exclusion of exon 7 occurs in the majority of transcripts, which results in low levels of functional SMN protein.[3] SMA is divided into five subtypes on the basis of the age at onset and the highest motor milestone attained.[4,5] In the case of type 1 SMA, symptoms typically manifest before 6 months of age, and the ability to sit without support is never attained.[4,6,7] Affected infants show a decline in respiratory and swallowing functions and typically receive feeding support or combined feeding and ventilatory support by 12 months of age.[7] Many developmental motor milestones are not reached in these infants,[8] and their motor function declines after diagnosis.[7,9] The majority of untreated infants do not survive beyond 2 years of age.[4,6,7]

Three treatments have been approved by the Food and Drug Administration for SMA. Both nusinersen, an intrathecally administered *SMN2*-targeting antisense oligonucleotide, and onasemnogene abeparvovec-xioi, an intravenously administered adeno-associated virus vector–based gene-replacement therapy, have been associated with improvements in survival and motor outcomes in patients with type 1 SMA.[10,11] The third treatment, risdiplam, is an orally administered, systemically distributed small molecule that promotes the inclusion of exon 7, which increases the expression of full-length *SMN2* messenger RNA and levels of SMN protein.[12] Risdiplam is approved for the treatment of patients 2 months of age or older with SMA.

We conducted an open-label, two-part study that evaluated the safety and efficacy of risdiplam in infants with type 1 SMA who were 1 to 7 months of age at enrollment. In the dose-finding part 1 of the study reported previously in the *Journal*,[13] risdiplam led to increased expression of SMN protein; on the basis of the results of part 1, the dose for part 2 was selected. Here, we present the results from part 2 on the clinical efficacy and safety of risdiplam in infants with type 1 SMA as compared with historical controls. Parts 1 and 2 had the same eligibility criteria but had different study populations; 21 infants were enrolled in part 1, and 41 other infants were enrolled in part 2.

## METHODS

### STUDY OVERSIGHT

The study was approved by an ethics committee at each study site and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines described in the protocol, available with the full text of this article at NEJM.org. Parents or caregivers of the infants provided written informed consent for participation in the study. The sponsor, F. Hoffmann–La Roche, provided the study drug; was responsible for study management, medical monitoring, drug-safety management and analysis, data management, statistical analysis, and pharmacokinetic and pharmacodynamic analysis; and paid for a professional medical writer. An independent data monitoring committee reviewed safety data. There were confidentiality agreements in place between the authors and the sponsor. Two academic authors and 5 authors employed by the sponsor contributed to the study conception and design. Data collection was performed by 11 academic authors. Statistical analysis was performed by 2 authors employed by the sponsor. All the authors vouch for the completeness and accuracy of the data and for the adherence of the study to the protocol. (Details regarding individual author contributions are provided in the Supplementary Appendix, available at NEJM.org.) There were no restrictions by the sponsor on publication of study results by the academic authors.

### PATIENTS

Infants at 14 centers in 10 countries were enrolled. (A list of study sites is provided in the Supplementary Appendix.) Eligibility criteria included a genetic diagnosis of 5q SMA, a clinical diagnosis of type 1 SMA (based on an onset of symptoms between 28 days and 3 months of age), two copies of *SMN2*, and an age of 1 to 7 months at enrollment. Infants were excluded from the study if they were receiving invasive ventilation or awake noninvasive ventilation, had undergone a tracheostomy, or had received treatment with other *SMN2*-targeting therapies or gene therapy. (The full list of eligibility criteria is provided in the protocol.)

### STUDY PROCEDURES

Infants older than 5 months of age received risdiplam at a dose of 0.2 mg per kilogram of body weight per day. For infants younger than 5 months of age, treatment was initiated at a dose of 0.04 or 0.08 mg per kilogram per day and adjusted to 0.2 mg per kilogram per day, generally within 1 to 3 months after the start of treatment and after a review of the pharmacokinetic data; one infant continued to receive a lower dose for a longer period owing to high exposure as determined by the pharmacokinetic monitoring. For infants who were able to swallow, risdiplam was administered orally; for those who were unable to swallow, it was administered as a bolus through a feeding tube.

### END POINTS

The primary end point for the current part 2 of the study was the ability to sit without support for at least 5 seconds after 12 months of treatment, as assessed with the use of item 22 of the gross motor subscale of the Bayley Scales of Infant and Toddler Development, third edition.[14] The assessment was video-recorded at study sites and scored by two trained, independent raters. (Administration of this test is described in the Supplementary Appendix.)

There were four key secondary end points. The first key secondary end point was a score of 40 or higher on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); scores range from 0 to 64, with higher scores indicating better motor function.[15] The second key secondary end point was an increase of at least 4 points from baseline in the CHOP-INTEND score. The third key secondary end point was a motor-milestone response as measured with the use of Section 2 of the Hammersmith Infant Neurological Examination (HINE-2); scores range from 0 to 26, with higher scores indicating better motor function.[16] Infants were classified as having a response if they had more improvement than worsening with respect to motor milestones. An improvement in a motor milestone with the use of this scale was defined as an increase of at least 2 points in the ability to kick (or maximal score) or an increase of at least 1 point in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as a decrease of at least 2 points in the ability to kick (or lowest score) or a decrease of at least 1 point in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp was excluded from the definition. Infants who died or who were withdrawn from the study were classified as not having a response. The fourth key secondary end point was event-free survival, 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).

Additional secondary end points that were not included in the hierarchical testing and from which no clinical conclusions can be drawn are listed in the Supplementary Appendix. These end points include survival, freedom from permanent ventilation, and the ability to feed orally at month 12. Amplitudes for compound muscle action

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

| Characteristic | All Infants (N = 41) |
|---|---|
| Median age at enrollment (range) — mo | 5.3 (2.2–6.9) |
| Sex — no. (%) | |
| Female | 22 (54) |
| Male | 19 (46) |
| Median age at onset of symptoms (range) — mo | 1.5 (1.0–3.0) |
| Duration of disease* | |
| Median (range) — mo | 3.4 (1.0–6.0) |
| ≤3 mo — no. (%) | 14 (34) |
| >3 mo — no. (%) | 27 (66) |
| Motor measures† | |
| Median CHOP-INTEND score (range) | 22.0 (8.0–37.0) |
| Median HINE-2 score (range) | 1.0 (0.0–5.0) |
| Able to swallow — no. (%) | 39 (95)‡ |
| No pulmonary care — no. (%)§ | 29 (71) |

* Shown is the time between the onset of symptoms and first treatment.
† 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 the infants were assessed with the use of the CHOP-INTEND and HINE-2 at baseline. One infant had one item missing in the baseline HINE-2 score (walking item, which would be expected to be 0); this item score was imputed to 0. None of the infants had a missing item in the baseline CHOP-INTEND score.
‡ One infant was fed by tube at baseline owing to inadequate weight gain. The ability to swallow had not been assessed after enrollment in the study.
§ No pulmonary care was defined as no ventilatory support or airway clearance.

**Table 2. Primary and Secondary Efficacy End Points in the Hierarchy at Month 12.**

| End Point | Performance Criterion* | All Infants (N=41) | | P Value† |
|---|---|---|---|---|
| | % | *no.* | *% (95% CI)* | |
| **Primary end point‡** | | | | |
| Able to sit without support for ≥5 sec | 5 | 12 | 29 (16–46) | <0.001 |
| **Secondary end points assessed at 12 mo** | | | | |
| CHOP-INTEND score of ≥40 | 17 | 23 | 56 (40–72) | <0.001 |
| Increase of ≥4 points from baseline in the CHOP-INTEND score | 17 | 37 | 90 (77–97) | <0.001 |
| HINE-2 motor-milestone response§ | 12 | 32 | 78 (62–89) | <0.001 |
| Event-free survival¶ | 42 | 35 | 85 (70–93) | <0.001 |

* The performance criterion for the primary end point is based on the natural history of type 1 spinal muscular atrophy (SMA), in which untreated infants are not expected to sit without support.[7,8] The performance criteria for the secondary end points are the upper boundary of the 90% confidence interval from untreated infants with type 1 SMA in two historical studies (Table S1 in the Supplementary Appendix).

† The P values are for the comparison of the percentage of patients in whom an end point was met in the study with the performance criterion from historical data with the use of a two-sided test at a 5% significance level; the lower boundary of the confidence interval for each end point in study infants can be compared with each performance criterion for historical control.

‡ The primary end point was assessed with the use of item 22 of the gross motor subscale of the Bayley Scales of Infant and Toddler Development, third edition.

§ Infants were classified as having a response if they had more improvement than worsening with respect to motor milestones. Improvement was defined as an increase of at least 2 points in the ability to kick (or maximal score) or an increase of at least 1 point in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as a decrease of at least 2 points in the ability to kick (or lowest score) or a decrease of at least 1 point in head control, rolling, sitting, crawling, standing, or walking. A full list of the HINE-2 motor milestones is provided in Table S5.

¶ Event-free survival 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). The data-cutoff date was November 14, 2019.

potential were measured at 12 months, as described in the protocol.

Safety assessments included adverse events, laboratory assessments, electrocardiograms, anthropometric measurements, and vital signs. (A full schedule of assessments is provided in the protocol). Owing to findings of retinal toxic effects that were observed in monkeys,[12] ophthalmologic safety assessments were performed by ophthalmologists throughout the study and were centrally reviewed by independent ophthalmologists. Blood samples were obtained for the measurement of risdiplam plasma concentration and SMN protein. (Additional details are provided in the Supplementary Appendix.)

### STATISTICAL ANALYSIS

To allow for comparisons of the results observed in the infants treated with risdiplam, we defined "performance criteria" on the basis of data from historical cohorts. For the primary end point, the performance criterion was not derived with the use of one specific historical cohort but was based on the natural history of type 1 SMA, in which untreated infants are not expected to sit without support[7,8]; we chose an arbitrary conservative criterion of 5% who are expected to attain this milestone for comparison with the treated group.

For the four key secondary end points included in the hierarchical statistical analysis, the performance criteria were derived from two historical cohorts of untreated infants with type 1 SMA that were similar to the population in this study: 16 infants in the NeuroNEXT (National Network for Excellence in Neuroscience Clinical Trials) study who had two copies of *SMN2*[9,17] and 24 infants with type 1B SMA (infants with SMA who had symptom onset by 3 months of age).[8] These performance criteria were the upper limits of the 90% confidence intervals around the percentage of historical controls who met each milestone, as derived with the complementary log–log transformation for the percentage of infants with event-free survival and the Clopper–Pearson method for the other end points. (A list

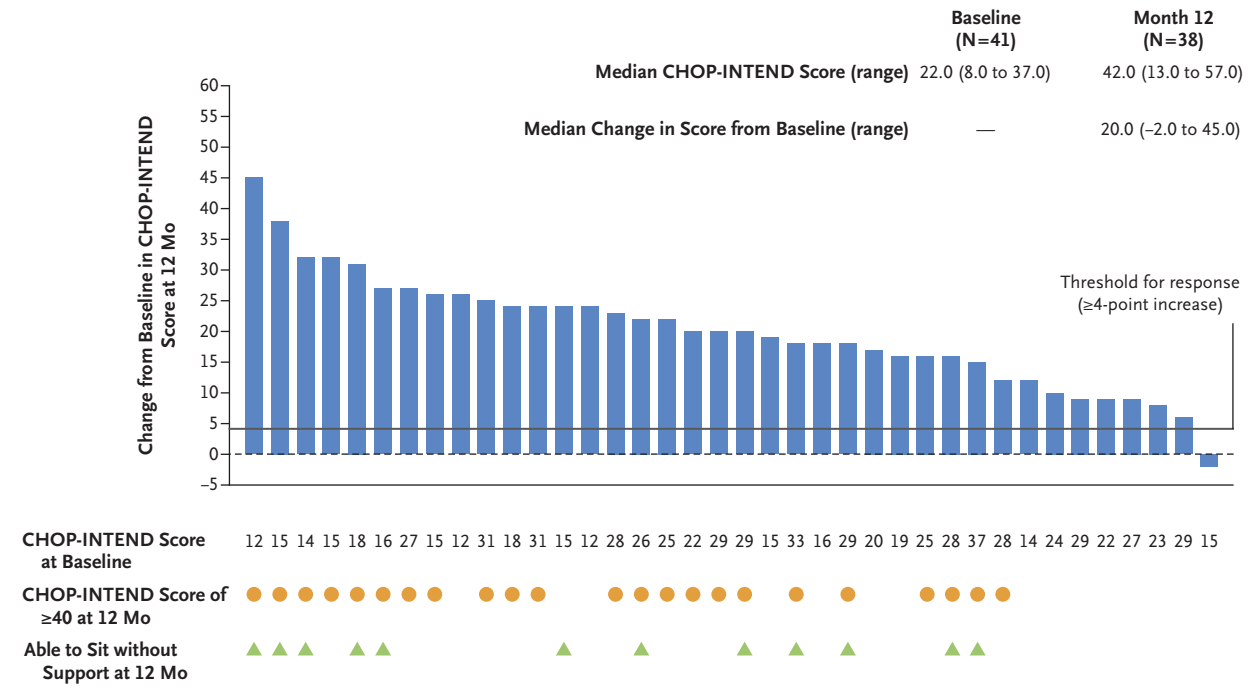


**Figure 1. Motor Function after 12 Months of Risdiplam Treatment.**

Individual patient data at month 12 were available for 38 of 41 infants; the other 3 infants had died. Shown are the scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at baseline (with scores ranging from 0 to 64 and higher scores indicating better motor function), the change from baseline in CHOP-INTEND scores, and data on infants with a score of 40 or higher after 12 months of treatment (orange circles). None of the infants had a missing item in the score at month 12. All except 1 of these 38 infants had an increase of at least 4 points from baseline in the CHOP-INTEND score. Data on infants who were able to sit without support for at least 5 seconds after 12 months of treatment are also shown (green triangles). The data-cutoff date was November 14, 2019.

of the end points for which a predefined performance criterion was derived and the sources used is provided in Table S1 in the Supplementary Appendix.)

When a predefined performance criterion could be determined for an end point, the original statistical plan was for hypothesis testing to be performed with a one-sided significance level of 5%, comparing the percentage of infants in whom an end point was met in the study with the performance criterion. Although 90% confidence intervals and one-sided tests were prespecified in the protocol, 95% confidence intervals and two-sided tests are presented here for the primary and secondary efficacy end points. An exact binomial test was performed for the primary end point and the CHOP-INTEND and HINE-2 end points, and a z-test was performed for event-free survival after 12 months of treatment.

To control for multiple testing across end points, a hierarchical testing approach was implemented that was prespecified at a one-sided significance level of 5% for each step across the primary end point and the four key secondary end points. Infants who did not meet a milestone, who did not maintain a milestone that had been met 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

The clinical cutoff date for the primary analysis, at which time all the infants had received treatment for 12 months or had been withdrawn or died, was November 14, 2019. A total of 41 in-

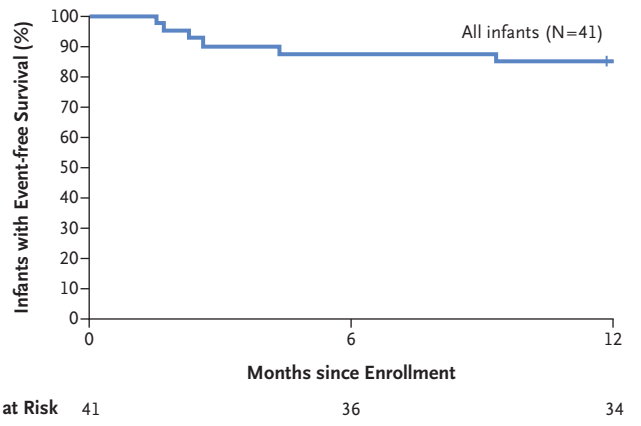


**Figure 2. Event-free Survival after Risdiplam Treatment.**

Event-free survival 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). One infant attended the month 12 visit a few days early (at which point the infant's data were censored [vertical line]) and therefore had not yet reached 12 months from enrollment as of the data-cutoff date (November 14, 2019). The median time to death or permanent ventilation could not be estimated because few infants had an event.

fants were enrolled (Fig. S1). The median age at enrollment was 5.3 months (range, 2.2 to 6.9), and 54% of the infants were female (Table 1). The median CHOP-INTEND score at baseline was 22.0 (range, 8.0 to 37.0), and the median HINE-2 score was 1.0 (range, 0.0 to 5.0). At baseline, 39 of 41 infants (95%) were able to swallow, and 29 of 41 (71%) were not receiving pulmonary care (ventilatory support or airway clearance). Of the 12 infants receiving pulmonary care, 11 received this prophylactically. No infants were able to sit without support at baseline. One infant had one item missing in the baseline HINE-2 score (walking item, which would be expected to be 0); this item score was imputed to 0. None of the infants had a missing item in the baseline CHOP-INTEND score.

### OUTCOMES

A total of 12 of 41 infants (29%; 95% confidence interval [CI], 16 to 46) were able to sit without support for at least 5 seconds after 12 months of treatment (primary end point); the percentage was significantly higher than the performance criterion of 5% from natural-history data (P<0.001) (Table 2). With respect to the four key secondary end points, after 12 months of treatment, 23 of 41 infants (56%; 95% CI, 40 to 72) had a CHOP-INTEND score of 40 or higher, as compared with the performance criterion of 17% (P<0.001) (Fig. 1, Table 2, and Fig. S3), and 37 of 41 infants (90%; 95% CI, 77 to 97) had an increase of at least 4 points from baseline in the CHOP-INTEND score, as compared with the performance criterion of 17% (P<0.001). At month 12, a total of 32 of 41 infants (78%; 95% CI, 62 to 89) were classified as having a HINE-2 motor-milestone response, as compared with the performance criterion of 12% (P<0.001) (Table 2). A total of 35 of 41 infants (85%; 95% CI, 70 to 93) were event-free at month 12 (age range, 14.5 to 18.9 months), as compared with the performance criterion of 42% (P<0.001) (Fig. 2). (Descriptions of fatal events are provided in Table S2, and descriptions of the infants who met the criteria for permanent ventilation are provided in Table S3.) No additional deaths in part 2 of the study were observed as of this writing.

Exploratory analysis of the blood SMN protein concentration showed that the median concentration at baseline was 2.91 ng per milliliter (range, 0.42 to 4.51) (Fig. S2). The blood SMN protein concentration increased to its highest median value of 6.75 ng per milliliter (range, 1.03 to 9.83) at 17 weeks; the median value at 12 months was 5.17 ng per milliliter (range, 0.76 to 9.39). Results with respect to amplitudes for compound muscle action potential are presented in the Supplementary Appendix.

### SAFETY

Overall, 48 serious adverse events were reported (Table 3 and Table S6); the most common such events were pneumonia (in 13 infants) and bronchiolitis, hypotonia, and respiratory failure (in 2 infants each). A total of 254 adverse events were reported (Table 3). Three infants had fatal respiratory complications that are characteristic of type 1 SMA. Safety laboratory results, vital signs, and electrocardiograms did not show any clinically significant adverse findings. The preclinical findings of epithelial effects (e.g., parakeratosis) and hematologic effects were not observed.[12] Ophthalmologic assessments did not show risdiplam-associated retinal toxic effects, which had been observed in monkeys treated with risdiplam at higher exposures than those tested in our study.[12]

**Table 3. Adverse Events.**

| Event | All Infants (N=41) |
|---|---|
| Total no. of adverse events | 254 |
| ≥1 Adverse event — no. (%) | 41 (100) |
| Total no. of serious adverse events | 48 |
| ≥1 Serious adverse event — no. (%) | 24 (59) |
| Adverse event with fatal outcome — no. (%)* | 3 (7) |
| ≥1 Serious adverse event leading to withdrawal from treatment — no. (%) | 0 |
| ≥1 Serious adverse event leading to dose modification or interruption — no. (%) | 1 (2) |
| ≥1 Adverse event leading to withdrawal from treatment — no. (%) | 0 |
| ≥1 Adverse event leading to dose modification or interruption — no. (%) | 2 (5) |
| ≥1 Adverse event of grade 3–5 — no. (%) | 22 (54) |
| Most common adverse events — no. (%)† | |
| Upper respiratory tract infection‡ | 28 (68) |
| Pneumonia | 16 (39) |
| Pyrexia | 16 (39) |
| Constipation | 8 (20) |
| Diarrhea | 4 (10) |
| Maculopapular rash | 4 (10) |
| Most common serious adverse events — no. (%)§ | |
| Pneumonia | 13 (32) |
| Bronchiolitis | 2 (5) |
| Hypotonia | 2 (5) |
| Respiratory failure | 2 (5) |

* As of the data-cutoff date (November 14, 2019), three infants had died. Acute respiratory failure with a fatal outcome was reported on study day 68 in a male infant who had been 210 days of age at enrollment; pneumonia with a fatal outcome was reported on study day 51 in a male infant who had been 135 days of age at enrollment; and pneumonia with a fatal outcome was reported on study day 79 in a male infant who had been 139 days of age at enrollment. The events were considered by the investigator to be unrelated to risdiplam and to be caused by SMA-related respiratory complications.
† Shown are adverse events that were reported in four or more infants.
‡ Included are events involving upper respiratory tract infection, nasopharyngitis, respiratory tract infection, rhinitis, influenza, pharyngitis, viral respiratory tract infection, and viral upper respiratory tract infection.
§ Shown are serious adverse events that were reported in two or more infants.

## DISCUSSION

In this study involving infants with type 1 SMA, 29% were able to sit without support for at least 5 seconds after 12 months of treatment (primary end point), a milestone that is not attained in this disorder.[7,8] The point estimates for the percentages of all infants in whom the secondary end points were met after 12 months of treatment differed significantly from the historical performance criteria that were obtained from the upper boundary of the confidence interval for point estimates for each end point. All the infants who were alive except for one had an increase of at least 4 points from baseline in the CHOP-INTEND score, and 56% of all infants had a CHOP-INTEND score of 40 or higher, a finding different from the decline in this score observed in historical cohorts of untreated infants.[7,9,10,11,18,19] Higher percentages of infants were event-free and were classified as having a motor-milestone response at month 12 than in historical cohorts. The median increase in SMN protein levels observed over the 12-month treatment period was consistent with the results reported in part 1 of the study.[13]

As of this writing, three infants had died from SMA-related respiratory complications. The most

common serious adverse events, excluding hypotonia, were related to the respiratory system, which is typical of SMA. Ophthalmologic monitoring did not detect retinal toxic effects that had been observed in monkeys treated with higher doses of risdiplam than those used in our study.[12]

Historical cohorts were used to derive performance criteria for comparisons with the percentage of study patients in whom an end point was met. Although the historical cohorts were chosen to be as similar as possible to this study population, there may be differences in patient characteristics. The historical cohorts were also small; for example, the NeuroNEXT study population included only 16 infants with two copies of *SMN2*.[9] The use of historical controls does not allow comparisons to be made to study outcomes with the same confidence as comparisons in a randomized trial. However, given the high mortality among infants with type 1 SMA, it was not considered appropriate to include a control group in the study. An open-label design was considered to be justified because the ability to sit without support (primary end point) is never attained in patients with type 1 SMA.[7,8] Although variation in standards of care among countries that enrolled infants in the study may have affected patient outcomes, standard-of-care guidelines were considered during the selection of study sites, and the exploratory clinical results from part 1 and the results from the current part 2 were similar.[13]

There are two other approved therapies for SMA, but the results of our study cannot be compared with those from studies pertaining to these agents owing to differences in study populations, study designs, varying durations of treatment, and changes in standards of care and available treatment options at the time of study initiation. Open-label risdiplam treatment for 24 months, followed by a 36-month open-label extension, is ongoing. In addition, studies of risdiplam in presymptomatic infants (ClinicalTrials.gov number, NCT03779334), patients with type 2 or 3 SMA (NCT02908685), and patients with SMA who have previously received treatment with RG7800 (also known as RO6885247),[20] nusinersen, olesoxime, or onasemnogene abeparvovecxioi (NCT03032172) are ongoing.

Oral risdiplam treatment over a period of 12 months in patients with type 1 SMA resulted in higher percentages of infants who met motor milestones, survived without need for ventilation, and showed improvements in motor function than the percentages in natural-history cohorts. Longer and larger trials are required to determine the long-term effects of risdiplam in type 1 SMA.

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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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