ORIGINAL ARTICLE

Risdiplam in Presymptomatic Spinal Muscular Atrophy

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ABSTRACT

BACKGROUND

Risdiplam, an oral pre–messenger RNA splicing modifier, is an efficacious treatment for persons with symptomatic spinal muscular atrophy (SMA). The safety and efficacy of risdiplam in presymptomatic disease are unclear.

METHODS

We conducted an open-label study of daily oral risdiplam (with the dose adjusted to 0.2 mg per kilogram of body weight) in infants 1 day (birth) to 42 days of age with genetically diagnosed SMA but without strongly suggestive clinical signs or symptoms. The primary outcome, assessed in infants with two *SMN2* copies and a baseline ulnar compound muscle action potential (CMAP) amplitude of at least 1.5 mV, was the ability to sit without support at month 12. Natural history studies have shown that the majority of infants with two *SMN2* copies who are untreated would have a severe SMA phenotype (type 1), would never sit independently, would receive permanent ventilation and feeding support, or would die by 13 months of age. Secondary outcomes that were assessed over a period of 24 months included survival, ventilatory support, motor milestones, the development of clinically manifested SMA, feeding, and growth.

RESULTS

A total of 26 infants with two, three, or four or more copies of *SMN2* were enrolled. After 12 months of treatment, 21 infants (81%) could sit unsupported for 30 seconds, 14 (54%) could stand alone, and 11 (42%) could walk alone. A total of 4 of 5 infants (80%; 95% confidence interval, 28 to 100) with two *SMN2* copies and a baseline ulnar CMAP amplitude of at least 1.5 mV were able to sit without support for at least 5 seconds. Three infants were withdrawn from the study by a parent or caregiver after the month 12 visit. Of 23 infants who completed 24 months of treatment, all were alive without the use of permanent ventilation or feeding support. Over a period of 24 months, nine treatment-related adverse events were reported in 7 infants; none of these events were serious.

CONCLUSIONS

Infants up to 6 weeks of age with genetically diagnosed SMA who were treated with risdiplam before the development of clinical signs or symptoms appeared to have better functional and survival outcomes at 12 and 24 months than untreated infants in natural history studies. Larger, controlled studies with longer follow-up are needed to further understand the relative efficacy and safety of presymptomatic treatment of SMA with risdiplam. (Funded by F. Hoffmann–La Roche; RAINBOWFISH ClinicalTrials.gov number, NCT03779334.)

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Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disease caused by deficiency of survival of motor neuron (SMN) protein due to deletions or mutations in the gene *SMN1*.[1,2] Although the gene *SMN2* produces SMN protein, alternative splicing excludes exon 7 from most *SMN2* pre–messenger RNA (mRNA), making it unable to fully compensate for the loss of *SMN1*.[3] SMN deficiency leads to progressive muscle weakness, motor complications, and — in severe cases — respiratory failure and death.[1]

Risdiplam is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases and sustains functional SMN protein levels.[4-6] The safety and efficacy of risdiplam have been shown in children and adults with symptomatic type 1, 2, or 3 SMA.[4,7-9] Enhanced treatment efficacy has been shown with earlier treatment.[4,10-15]

We conducted an open-label, phase 2, single-group, multicenter study (RAINBOWFISH) to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants up to 6 weeks of age with genetically diagnosed SMA but without strongly suggestive clinical signs or symptoms of SMA.

METHODS

STUDY OVERSIGHT

The study was approved by an ethics committee at each study site and 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, designed the study, provided the study drug, and was responsible for study management, medical monitoring, safety management and analysis, data management, and statistical, pharmacokinetic, and pharmacodynamic analyses. Safety data were reviewed by an independent data monitoring committee on an ongoing basis. Confidentiality agreements were in place between the authors and the sponsor.

Four authors employed by the sponsor and five academic authors contributed to the conception and design of the study. Data collection was performed by eight academic authors. Statistical, pharmacokinetic, and pharmcodynamic analyses were performed by three authors employed by the sponsor. All the authors contributed to data interpretation. The authors vouch for the adherence of the study to the protocol, the accuracy and completeness of the data, and complete reporting of adverse events at their study sites. The sponsor placed no restrictions on publication of study results. The sponsor paid Nucleus Global to write the first draft on the basis of a detailed outline agreed on by all the authors and to provide additional writing and editing support with an earlier version of the manuscript. Author contributions are detailed in the Supplementary Appendix, available with the full text of this article at NEJM.org. The study protocol, with three amendments, is also available at NEJM.org.

PATIENTS

Eligible infants were 1 day of age (gestational age, 37 to 42 weeks for single births and 34 to 42 weeks for twins) to 42 days of age at the time of the first dose, with genetic diagnosis of 5q-autosomal recessive SMA and no clinical signs or symptoms strongly suggestive of SMA at screening. Eligibility was independent of *SMN2* copy number and continued until at least 5 participants with two copies of *SMN2* and a compound muscle action potential (CMAP) amplitude of at least 1.5 mV were enrolled; such participants served as the primary efficacy population. Full eligibility criteria are provided in the protocol. The study enrolled 26 infants from seven sites across Australia, Belgium, Brazil, Poland, Russia, Taiwan, and the United States. Demographic information was collected by site investigators (see Table S6 in the Supplementary Appendix for details on the representativeness of the patient population).

STUDY PROCEDURES

Infants entered a screening period of up to 42 days of age, which included *SMN2* genotyping, general health examinations, ophthalmologic assessments, and assessments for signs and symptoms of SMA. Once enrolled, all the infants received once-daily risdiplam orally at a dose targeting an average plasma exposure of approximately 2000 ng × hour per milliliter. Treatment was initiated at a dose of 0.04 mg per kilogram of body weight for the first three infants; on the basis of pharmacokinetic data, the dose was adjusted for all the participants to 0.2 mg per kilogram within 3 to 8 weeks after treatment initiation

(see the Supplementary Appendix). Open-label treatment continued until month 24, after which participants entered the open-label extension period. Treatment will continue for a total 5-year duration.

OUTCOMES

The primary outcome, assessed in infants with two *SMN2* copies and a baseline ulnar CMAP amplitude of at least 1.5 mV, was the ability to sit without support for at least 5 seconds at month 12 (Item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, third edition [BSID-III]).[16] See the Supplementary Appendix for more information on the selection of the primary outcome.

Secondary outcomes at month 24 included the development of clinically manifested SMA; survival and permanent ventilation (defined as 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 achievement of motor milestones defined by the Hammersmith Infant Neurological Examination, Module 2 (HINE-2)[17] and BSID-III[16]; scores 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[18]); the achievement in infants of CHOP INTEND stopping criteria (defined as being able to sit without support [BSID-III Item 22] and having a CHOP INTEND total score of ≥60 at two consecutive visits); growth; swallowing and oral feeding; changes in ulnar CMAP amplitude; and pharmacokinetics and pharmacodynamics.

Assessments of BSID-III motor milestones were video recorded at the study site and scored by two independent central readers. For a milestone to be achieved, both central readers had to agree. According to the World Health Organization (WHO) windows for motor milestones,[19] infants should be able to sit without support by approximately 9 months of age. Sitting would not be observed in untreated infants with type 1 SMA and two *SMN2* copies.[20,21]

Clinically manifested SMA was considered to have developed if at least one of the following criteria were met: an inability to sit independently, as assessed by both the HINE-2 (sitting item score of <3 ["Stable sit"]) and BSID-III Item 22 (a score of 0), at month 12; an inability to walk independently, as assessed by both the HINE-2 (walking item score of <3 ["Walking independently"]) and BSID-III Item 42 (a score of 0), at month 24; an age-adjusted weight at the 3rd percentile or less or a decrease of at least two major percentile lines (3rd, 10th, 25th, 50th, 75th, 90th, and 97th) as compared with baseline at the time point, in combination with tongue fasciculation or feeding or swallowing abnormalities; or the placement of a gastric tube for nutritional support in the absence of a non–SMA-related indication at the time point. Patients who died or were withdrawn from the study by a parent or caregiver may be counted as having had clinically manifested SMA (see the Supplementary Appendix for details).

Safety assessments included adverse events, laboratory assessments, and vital signs; the relatedness of adverse events to treatment was determined by the investigators. Owing to retinal toxic effects observed in monkeys, a comprehensive panel of ophthalmologic assessments was performed,[22] including imaging to detect structural changes of the retina and visual-function testing to detect potential functional impairment. Ophthalmologic assessments were performed according to predefined criteria and examined by a central reviewer who provided recommendations for additional assessments in consultation with the site ophthalmologist, if required. A full list of study outcomes and schedule of assessments is provided in the protocol.

STATISTICAL ANALYSIS

The study had a target sample size of at least 25 infants, including a minimum of 5 infants who met the criteria for the primary efficacy population (two *SMN2* copies and a baseline ulnar CMAP amplitude of ≥1.5 mV). The rationale for the sample size is explained in the Supplementary Appendix. Primary efficacy data (month 12) are presented descriptively with two-sided 95% Clopper–Pearson (exact) confidence intervals. To determine whether the primary efficacy objective was met, the percentage of infants who could sit unsupported at month 12 was compared with a "performance criterion" of 5%. The 5% threshold was chosen on the basis of the natural history of the disease (by definition, patients with type 1 SMA are never able to sit without support) and the assumption that there

is a 97% chance that type 1 SMA will develop in a presymptomatic infant with two *SMN2* copies.[23]

Secondary efficacy and safety analyses (month 24) are reported for all 26 enrolled infants. No adjustments were made for multiple comparisons.

RESULTS

PATIENTS

The first patient was enrolled on August 7, 2019. Of 29 screened infants, 26 were enrolled (Fig. S1). Eight infants had two *SMN2* copies: 5 had a baseline ulnar CMAP amplitude of at least 1.5 mV (primary efficacy population), and 3 had lower CMAP amplitudes (0.5, 0.6, and 1.3 mV). A total of 18 infants had three or more copies of *SMN2*. The median CHOP INTEND score at baseline was 51.5 (range, 35 to 62), and the median ulnar CMAP amplitude was 3.6 mV (range, 0.5 to 6.7). In most infants (77%), SMA was identified by newborn screening. The age at the first dose of risdiplam ranged from 16 to 41 days (Table 1).

The clinical cut-off date for the primary analysis, when all the infants had received treatment

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

Characteristic	Two Copies of *SMN2* (N=8)	Three Copies of *SMN2* (N=13)	Four or More Copies of *SMN2* (N=5)	All Infants (N=26)
Median age at first dose of risdiplam (range) — days	24 (16–35)	28 (20–41)	32 (24–40)	25 (16–41)
Sex — no. (%)				
Female	4 (50)	9 (69)	3 (60)	16 (62)
Male	4 (50)	4 (31)	2 (40)	10 (38)
Race — no. (%)†				
Asian	0	1 (8)	2 (40)	3 (12)
White	8 (100)	11 (85)	3 (60)	22 (85)
Unknown	0	1 (8)	0	1 (4)
SMA identification method — no. (%)				
Newborn screening	4 (50)	11 (85)	5 (100)	20 (77)
Family history	4 (50)	1 (8)	0	5 (19)
Other	0	1 (8)	0	1 (4)
Median body weight (range) — g	3999 (3076–4270)	4000 (3400–5726)	4170 (3275–5620)	4015 (3076–5726)
Median CHOP INTEND score (range)‡	46.5 (35.0–52.0)	55.0 (44.0–62.0)	50.0 (44.0–52.0)	51.5 (35.0–62.0)
Median HINE-2 score (range)§	2.0 (0.0–4.0)	3.0 (1.0–6.0)	1.0 (1.0–4.0)	2.5 (0.0–6.0)
Ulnar CMAP amplitude				
Median (range) — mV	2.0 (0.5–3.8)	4.6 (2.1–6.7)	3.7 (3.4–6.6)	3.6 (0.5–6.7)
<1.5 mV — no. (%)	3 (38)	0	0	3 (12)
≥1.5 mV — no. (%)	5 (62)	13 (100)	5 (100)	23 (88)

* Results are shown according to the number of copies of the gene survival of motor neuron 2 (*SMN2*). Percentages may not total 100 because of rounding. CMAP denotes compound muscle action potential, and SMA spinal muscular atrophy.
† Race was reported by the parent or caregiver.
‡ 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 were assessed in all 26 infants at baseline.
§ Scores on Module 2 of the Hammersmith Infant Neurological Examination (HINE-2) range from 0 to 26, with higher scores indicating better motor function. Scores were assessed in all 26 infants at baseline.

for 12 months or had been withdrawn from the study by a parent or caregiver, was February 20, 2023. The clinical cut-off date for the 24-month analysis was March 27, 2024. All the infants completed the month 12 visit, and 23 completed the month 24 visit; 3 infants with two *SMN2* copies were withdrawn from the study by a parent or caregiver to switch to commercial onasemnogene abeparvovec before month 24.

OUTCOMES

Primary Analysis (Month 12)

Overall, 25 of 26 infants (7 of 8 with two *SMN2* copies and 18 of 18 with three or more copies) were able to sit unsupported as assessed by the BSID-III at month 12. Of 5 infants with two *SMN2* copies and a baseline ulnar CMAP amplitude of at least 1.5 mV, 4 (80%; 95% confidence interval, 28 to 100) were able to sit without support for at least 5 seconds (primary end point); this was higher than the 5% performance criterion of the protocol.

Secondary and Subgroup Analyses

All 23 infants who completed the month 24 assessment were alive without any respiratory support, and all maintained swallowing and oral feeding abilities (Table 2). Three infants who were withdrawn from the study before month 24 were not receiving permanent ventilation support and could swallow and feed orally at their most recent assessments.

A total of 21 of 23 infants (91%) were able to stand alone (BSID-III Item 40) and walk alone (BSID-III Item 42) at month 24. When assessed with the use of the HINE-2, a total of 21 of 23 infants (91%) could stand unaided and 20 of 23 (87%) walked independently (Table 2). At month 24, a total of 22 of 23 infants (96%) met the stopping criteria for assessment with the CHOP INTEND (Table 2).

Overall, ulnar CMAP amplitudes increased over a period of 24 months (Table 2). Infants with three or more copies of *SMN2* had higher median changes in CMAP amplitude than those with two copies.

The median SMN protein level was 5.69 ng per milliliter (range, 1.13 to 26.42) at baseline and 7.24 ng per milliliter (range, 2.57 to 13.74) at month 24. Similar increases in SMN protein level were observed across *SMN2* copy-number groups.

By month 24, clinically manifested SMA was considered to have developed in six of eight infants with two *SMN2* copies (Table 2). At month 12, one infant was unable to sit without support and was also withdrawn from the study to switch to an alternative SMA therapy. At month 24, three infants were unable to walk, and two infants were withdrawn to switch to an alternative SMA therapy.

Of five infants with two *SMN2* copies who completed the month 24 assessment, all five (100%) were able to sit for at least 30 seconds (BSID-III Item 26) and three (60%) were able to stand (BSID-III Item 40) and walk (BSID-III Item 42) (Fig. 1). As assessed with the HINE-2, five infants (100%) were able to sit independently, three (60%) were able to stand unaided, and two (40%) were able to walk independently (Table 2). Four of five infants had reached the CHOP INTEND stopping criteria by month 24.

All 18 infants with three or more copies of *SMN2* were able to sit by month 12 and were able to stand and walk by month 24 (Table 2). Most achieved BSID-III milestones at study visits within WHO windows for typically developing children: 12 of 18 (67%) were able to sit for at least 5 seconds; 17 of 18 (94%) were able to stand; and 16 of 18 (89%) were able to walk (Fig. 1).[20] All 18 infants had reached the CHOP INTEND stopping criteria by month 24.

SAFETY

Up to March 27, 2024, a total of 281 adverse events were reported in 25 infants (Table 3). No adverse event led to withdrawal from the study or treatment discontinuation. Nine treatment-related adverse events were reported in 7 infants; none of these events were serious (Table S5).

A total of 11 serious adverse events were reported in 4 infants (Table 3). Neonatal jaundice was reported in 1 infant; constipation, gastroenteritis, lower respiratory tract infection, viral lower respiratory tract infection, and pneumonitis were each reported in a second infant; femur fracture and soft-tissue injury were reported in the third infant; and gastroenteritis and two incidences of urinary tract infection were reported in the fourth infant. No serious adverse events were considered to be drug related by the investigators, although this was not independently adjudicated. Retinal adverse events were reported in 3 infants:

Table 2. Secondary Outcomes at Months 12 and 24.*

Outcome	Two Copies of *SMN2* (N=8)		Three Copies of *SMN2* (N=13)		Four or More Copies of *SMN2* (N=5)		All Infants (N=26)†	
	At Month 12	At Month 24	At Month 12	At Month 24	At Month 12‡	At Month 24	At Month 12‡	At Month 24
BSID-III — no. (%)§								
Able to sit without support for ≥5 sec	7 (88)	5 (62)	13 (100)	13 (100)	5 (100)	5 (100)	25 (96)	23 (88)
Able to sit without support for ≥30 sec	7 (88)	5 (62)	9 (69)	12 (92)¶	5 (100)	4 (80)¶	21 (81)	21 (81)
Able to stand alone	1 (12)	3 (38)	10 (77)	13 (100)	3 (60)	5 (100)	14 (54)	21 (81)
Able to walk alone	1 (12)	3 (38)	8 (62)	13 (100)	2 (60)	5 (100)	11 (42)	21 (81)
HINE-2 — no. (%)								
Able to sit: pivots or rotates	6 (75)	5 (62)	13 (100)	13 (100)	4 (100)	5 (100)	23 (92)	23 (88)
Able to stand								
Does not support weight	4 (50)	1 (12)					4 (16)	1 (4)
Stands with support	3 (38)	1 (12)	3 (23)		2 (50)		8 (32)	1 (4)
Stands unaided	1 (12)	3 (38)	10 (77)	13 (100)	2 (50)	5 (100)	13 (52)	21 (81)
Able to walk								
Cruises‖		2 (25)	3 (23)		1 (25)		4 (16)	2 (8)
Walks independently	1 (12)	2 (25)	9 (69)	13 (100)	2 (50)	5 (100)	12 (48)	20 (77)
Could not be tested	4 (50)	1 (12)	1 (8)		1 (25)		6 (24)	1 (4)
Reached CHOP INTEND stopping criteria — no. (%)**	NA	4 (50)	NA	13 (100)	NA	5 (100)	NA	22 (85)
Feeding and swallowing — no. (%)								
Able to swallow	7 (88)	5 (62)‖	13 (100)	13 (100)	5 (100)	5 (100)	25 (96)	23 (88)††
Able to feed exclusively by mouth	7 (88)	5 (62)‖	13 (100)	13 (100)	5 (100)	5 (100)	25 (96)	23 (88)††

Change from baseline in ulnar CMAP amplitude								
Median (range) — mV‡‡	0.5 (–1.6 to 3.4)	1.0 (0.5 to 2.5)	2.0 (–0.7 to 5.5)	2.5 (–0.5 to 4.5)	2.2 (0.6 to 4.3)	3.5 (0.4 to 6.4)	1.4 (–1.6 to 5.5)	2.5 (–0.5 to 6.4)
Mean — mV‡‡	0.79±1.59	1.24±0.88	2.05±1.74	2.24±1.85	2.54±1.70	3.86±2.51	1.76±1.76	2.43±2.01
Increase from baseline of ≥0.3 mV — no. (%)	4 (50)	4 (50)	11 (85)	10 (77)	5 (100)	5 (100)	20 (77)	19 (73)
Infants alive without permanent ventilation — no. (%)§§	8 (100)	5 (62)	13 (100)	13 (100)	5 (100)	5 (100)	26 (100)	23 (88)
Infants with clinically manifested SMA — no. (%)¶¶	1 (12)	6 (75)	0	0	0	0	1 (4)	6 (23)
SMA neurologic examination: infants with ≥1 abnormal finding — no. (%)‖‖	4 (50)	2 (25)	1 (8)	0	0	0	5 (19)	2 (8)

* Plus–minus values are means ±SD. NA denotes not applicable.
† Percentages are calculated from the intention-to-treat population (26 infants). Three infants were withdrawn from the study by a parent or caregiver before month 24 and did not complete the month 24 assessment.
‡ One of the infants with four or more copies of *SMN2* could not be assessed for the HINE-2 at the 12-month visit, so the denominator for the HINE-2 outcomes at month 12 is 4 for infants with four or more copies of *SMN2* and 25 for all infants.
§ Assessments for the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), were performed by two independent central readers.
¶ Results assessed by the site clinical evaluator differed from those of the two independent central readers. The site evaluator reported that 13 of 13 infants (100%) with three copies of *SMN2* and 5 of 5 (100%) with four or more copies were able to sit without support for at least 30 seconds.
‖ Cruising is taking steps while holding on to furniture.
** Infants met CHOP INTEND stopping criteria in the RAINBOWFISH study if they were able to sit without support for at least 5 seconds at two consecutive visits (BSID-III Item 22) and had a CHOP INTEND total score of 60 or more at the same two consecutive visits.
†† The three infants who were withdrawn from the study before the 24-month assessment were not receiving permanent ventilation support and were able to swallow and feed orally at their last assessments (early withdrawal).
‡‡ Mean and median CMAP values at month 24 were calculated from 22 infants with available data.
§§ Permanent ventilation was defined as tracheostomy or ventilation (bilevel positive airway pressure) for at least 16 hours per day continuously for more than 3 weeks or continuous intubation for more than 3 weeks, in the absence of, or after the resolution of, an acute reversible event.
¶¶ One infant was not able to sit at month 12 and was also withdrawn from the study to switch to another treatment. Three infants were not able to walk at month 24. Two infants were withdrawn to switch to another treatment.
‖‖ At month 24, both abnormal findings were within the deep tendon reflexes.

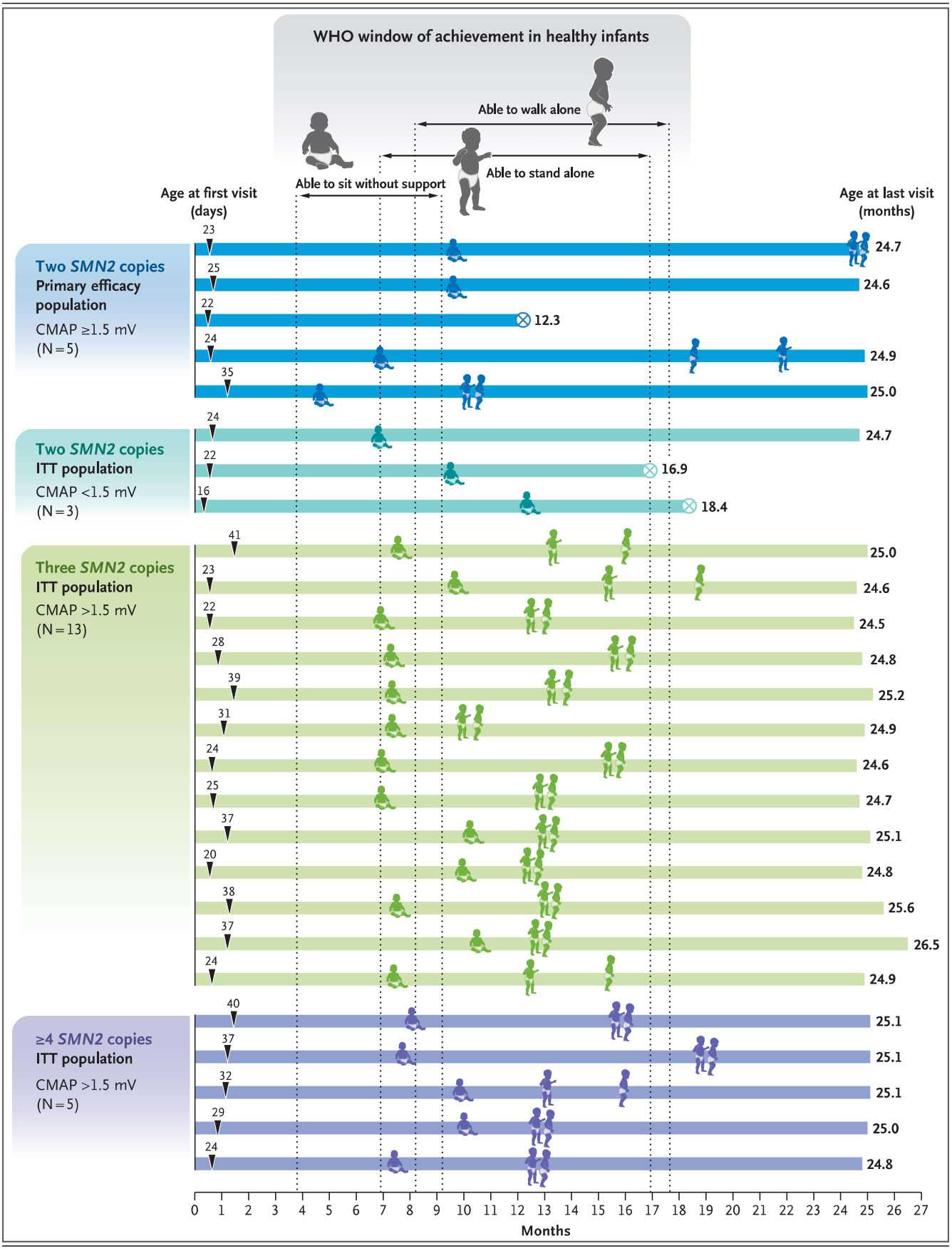

Figure 1 (facing page). Achievement of Motor Milestones to Month 24.

Icons represent the ages of individual patients at the scheduled study visit when they were first able to demonstrate the corresponding motor milestone (data-cutoff date, March 27, 2024). Assessments were carried out at baseline; 1 month; 2, 4, 7, 10, and 12 months; and then every 3 months up to 24 months. Infants may have achieved the milestone between study visits. The ability to sit without support for at least 5 seconds, the ability to stand alone, and the ability to walk alone were assessed with Item 22, Item 40, and Item 42, respectively, of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, third edition. For the infant with two copies of the gene survival of motor neuron 2 (*SMN2*) who was 24.9 months of age at the last visit, there was disagreement between the independent central readers and the site clinical evaluator at the week 78 visit for the ability to stand alone, but the ability to walk alone was confirmed; the ability to stand alone was not confirmed until the week 92 visit. The windows of achievement in healthy infants are from the World Health Organization (WHO) Multicentre Growth Reference Study Group.[19] Risdiplam was administered at a daily dose of 0.2 mg per kilogram of body weight. Four infants started risdiplam treatment at a daily dose of 0.04 mg per kilogram, and two infants started treatment at a daily dose of 0.08 mg per kilogram; in all these infants, the daily dose was adjusted to 0.2 mg per kilogram within 3 to 8 weeks after treatment initiation (see the Supplementary Appendix for details). Withdrawal from the study by a parent or caregiver is indicated by a circled "X." CMAP denotes compound muscle action potential, and ITT intention to treat.

cystoid macular edema, retinal pigmentation, and retinal vascular disorder in 1 infant each. For each of these events, the central reviewer either could not confirm the event or considered that the findings were present before treatment initiation. Additional safety information is provided in the Supplementary Appendix.

DISCUSSION

This study of risdiplam in infants with presymptomatic SMA showed that most infants (seven of eight) with two *SMN2* copies had the ability to sit within 12 months. Without treatment, approximately 79% of infants with two *SMN2* copies would go on to have type 1 SMA and would not attain the ability to sit.[24] Three of these infants were able to walk at month 24, as assessed with BSID-III Item 42. Most infants with three or more copies of *SMN2* in this study achieved sitting, standing, and walking milestones within the WHO windows of typical development.[19] Type 2 SMA is predicted to develop in more than half of persons with three *SMN2* copies, with symptom onset before 18 months. Without treatment, they typically are able to sit and may stand with support but cannot walk.[20,24] Type 3 or 4 SMA is more likely to develop in persons with four or more copies of *SMN2*, with onset after 18 months of age, and persons with this copy number are likely to achieve walking.[20,21,24]

These efficacy findings are largely aligned with results for other disease-modifying treatments in presymptomatic SMA (NURTURE and SPR1NT studies).[10-13] The SPR1NT study evaluated the safety and efficacy of onasemnogene abeparvovec, a gene therapy, and the NURTURE study evaluated the safety and efficacy of nusinersen, an intrathecally administered *SMN2* antisense oligonucleotide. However, direct cross-trial comparisons cannot be made, because the studies differed in inclusion criteria and efficacy outcomes, with distinct assessment protocols and timings (Table S7). One noteworthy difference in the RAINBOWFISH study was that achievement of motor milestones was documented during study visits, whereas the SPR1NT study allowed home-video capture of milestones.[10,11] Therefore, infants in the RAINBOWFISH study may have achieved milestones earlier than documented, between visits. The RAINBOWFISH study also had broader inclusion criteria, with no restrictions on *SMN2* copy number or baseline CMAP amplitude. The NURTURE and SPR1NT studies enrolled infants with two or three copies of *SMN2*, whereas the RAINBOWFISH study included five infants with four or more copies, who may not show symptoms as early as 24 months of age.[20,21,25] In the NURTURE study, the threshold for baseline ulnar CMAP amplitude was at least 1 mV, whereas the SPR1NT study used a threshold for tibial CMAP amplitude of at least 2 mV.[10,11,13] This heterogeneity in baseline characteristics, and the development of subtle SMA features during the period between birth and treatment initiation, may underlie some observed differences in efficacy across studies of presymptomatic SMA.[26,27]

Although infants were considered to be presymptomatic because of the absence of clinical signs or symptoms of SMA at screening or baseline, degeneration of motor neurons begins before symptom onset.[15,28,29] In type 1 SMA, motor-

Table 3. Adverse Events.*

Event	All Infants (N=26)
Total adverse events — no.	281
Any adverse event — no. of infants (%)	25 (96)
Adverse event related to treatment — no. of infants (%)†	7 (27)
Total serious adverse events — no.	11
Serious adverse event — no. of infants (%)‡	4 (15)
Adverse event with fatal outcome — no. of infants (%)	0
Serious adverse event related to treatment — no. of infants (%)	0
Adverse event leading to withdrawal from the study — no. of infants (%)	0
Adverse event leading to dose modification or interruption — no. of infants (%)§	5 (19)
Grade 3–5 adverse event — no. of infants (%)¶	5 (19)
Most common adverse events — no. of infants (%)‖	
Teething	11 (42)
Gastroenteritis	10 (38)
Coronavirus disease 2019	9 (35)
Diarrhea	9 (35)
Eczema	8 (31)
Pyrexia	8 (31)
Constipation	6 (23)
Upper respiratory tract infection	6 (23)
Vomiting	6 (23)
Nasal congestion	5 (19)
Nasopharyngitis	5 (19)
Respiratory tract infection, viral	5 (19)
Rhinitis	5 (19)
Viral infection	5 (19)

* Included are adverse events with an onset from first dose of the study drug up to the data-cutoff date (March 27, 2024). The relatedness of adverse events to treatment was determined by the investigators.

† Seven infants had a total of nine treatment-related adverse events; none were serious. The most frequent treatment-related adverse events were skin and subcutaneous tissue disorders in three infants (dermatitis atopic, eczema, and skin discoloration) and eye disorders in two infants (retinal pigmentation and retinal vascular disorder).

‡ A total of 11 serious adverse events were reported in four infants, and all resolved. Neonatal jaundice was reported in one infant; constipation, gastroenteritis, lower respiratory tract infection, viral lower respiratory tract infection, and pneumonitis were each reported in a second infant; femur fracture and soft-tissue injury were reported in the third infant; and gastroenteritis and two incidences of urinary tract infection were reported in the fourth infant.

§ Events that led to dose interruption were two incidences of accidental overdose (1-day interruption each), two incidences of gastroenteritis (interruption for 1 and 2 days), and one incidence each of overdose (1-day interruption), lower respiratory tract infection (1-day interruption), and viral lower respiratory tract infection (1-day interruption).

¶ There were no grade 4 or 5 adverse events.

‖ Shown are adverse events reported in five or more infants.

neuron loss often occurs rapidly within weeks after birth, with substantial loss before symptoms manifest,[30,31] and there is evidence for prenatal motor-neuron loss and delayed myogenesis.[32-35] A decrease in CMAP amplitude may represent subclinical loss of functional motor neurons, indicative of prodromal disease onset in presymptomatic newborns, and is predictive of greater disease progression and reduced treatment efficacy.[20,27,28,31,36] Although CMAP amplitudes of less than 1.5 mV are typically indicative of symptomatic SMA,[37] all the infants had an SMA neurologic examination at day –1; the SMA neurologic examination was not strongly suggestive of SMA abnormalities according to the assessment of the primary investigator in any infant. All three infants in the RAINBOWFISH study with baseline ulnar CMAP amplitudes of less than 1.5 mV were able to sit by month 12. Overall, infants in the RAINBOWFISH study with more *SMN2* copies had greater changes from baseline in CMAP amplitude than infants with fewer *SMN2* copies.

In real-world studies, approximately 50% of patients identified by newborn screening with two *SMN2* copies had some SMA symptoms at treatment initiation.[38] Four infants in our study with two *SMN2* copies met criteria for clinically manifested SMA owing to not achieving motor milestones. There is no clear explanation why these infants were unable to sit without support (one infant at month 12) or walk (three infants at month 24) (see the Supplementary Appendix).

This study showed that infants in whom type 1 SMA was predicted to develop who were treated presymptomatically with risdiplam within the first 6 weeks after birth survived without assisted ventilation and achieved motor milestones over a period of 24 months. These functional outcomes have not been attainable with supportive care alone.[20,39] The apparent effects of risdiplam were evident across the spectrum of patients treated, but infants with higher *SMN2* copy numbers and CMAP amplitudes appeared to have more favorable responses. Target drug-exposure levels were achieved, and the majority of adverse events were not considered to be treatment related and resolved over time. Risdiplam may be a therapeutic option for treatment of presymptomatic SMA, with the advantage of rapid initiation of oral administration at home. Larger comparative trials with longer follow-up are warranted to further understand its relative safety and efficacy.

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