ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

An expanded access program of risdiplam for patients with Type 1 or 2 spinal muscular atrophy

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Received: 20 January 2022; Revised: 1 April 2022; Accepted: 2 April 2022

Annals of Clinical and Translational Neurology **2022; 9(6): 810–818**

doi: 10.1002/acn3.51560

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Abstract

Objective: The US risdiplam expanded access program (EAP; NCT04256265) was opened to provide individuals with Type 1 or 2 spinal muscular atrophy (SMA) who had no satisfactory treatment options access to risdiplam prior to commercial availability. The program was designed to collect safety data during risdiplam treatment. **Methods**: Patients were enrolled from 23 non-preselected sites across 17 states and treated with risdiplam orally once daily. Eligible patients had a 5q autosomal recessive Type 1 or 2 SMA diagnosis, were aged ≥2 months at enrollment, and were ineligible for available and approved SMA treatments or could not continue treatment due to a medical condition, lack/loss of efficacy, or the COVID-19 pandemic. **Results**: Overall, 155 patients with Type 1 (n = 73; 47.1%) or 2 SMA (n = 82; 52.9%) were enrolled and 149 patients (96.1%) completed the EAP (defined as obtaining access to commercial risdiplam, if desired). The median treatment duration was 4.8 months (range, 0.3–9.2 months). The median patient age was 11 years (range, 0–50 years), and most patients (n = 121; 78%) were previously treated with a disease-modifying therapy. The most frequently reported adverse events were diarrhea (n = 10; 6.5%), pyrexia (n = 7; 4.5%), and upper respiratory tract infection (n = 5; 3.2%). The most frequently reported serious adverse event was pneumonia (n = 3; 1.9%). No deaths were reported. **Interpretation**: In the EAP, the safety profile of risdiplam was similar to what was reported in pivotal risdiplam clinical trials. These safety data provide further support for the use of risdiplam in the treatment of adult and pediatric patients with SMA.

Introduction

Spinal muscular atrophy (SMA) is a genetic, neuromuscular disease caused by deletion or mutation of the survival of motor neuron 1 (*SMN1*) gene.[1] In most cases, due to a translationally synonymous C-to-T mutation in exon 7, the SMN2 pre-mRNA undergoes alternative splicing that excludes exon 7. The resulting SMNΔ7 protein is unstable and degrades rapidly, leading to reduced levels of the SMN protein and subsequent motor neuron loss.[2] A paralogous SMN gene, *SMN2*, produces functional SMN protein, but at levels that are inadequate to compensate for the lack of *SMN1*.[2]

SMA is characterized by progressive muscle weakness and ranges in severity.[3] For classification purposes, patients are categorized into five subtypes (ranging from 0 to 4, with lower numbers indicating greater severity) based on age at symptom onset and maximum motor milestone achieved.[4] Type 0 SMA is rare, diagnosed in neonates, and usually fatal at birth. Symptom onset with Type 1 SMA occurs before 6 months of age.[5,6] Infants never sit without support, and death typically occurs by 2 years of age. Symptom onset with Type 2 SMA is between 6 and 18 months of age. Children can sit but are unable to stand or walk without support. In Type 3 SMA, symptoms typically manifest after 18 months of age. Individuals can walk but may lose this ability as the disease progresses. Type 4 SMA is rare and has a typical onset in adults aged >21 years; individuals are able to walk into adulthood and generally have a normal life span.[3,6] With better standards of care and the availability of disease-modifying therapies (DMTs) for SMA, individuals are now also being classified by functional ability (non-sitters, sitters, and walkers) rather than just by SMA type.[7]

The current understanding of the pathophysiology of SMA has led to the development of DMTs designed to increase SMN protein expression. To date, three treatments for SMA have been approved by the US Food and Drug Administration (FDA). Nusinersen (SPINRAZA®), an intrathecally administered, *SMN2*-targeting, antisense oligonucleotide therapy, is approved for adult and pediatric patients with SMA.[8] Onasemnogene abeparvovec (ZOLGENSMA®), an intravenously administered, adeno-associated viral vector-based SMN gene-transfer therapy, is approved for the treatment of patients <2 years of age with SMA.[9] Risdiplam (EVRYSDI®), an orally administered SMN2 pre-mRNA splicing modifier, increases the levels of functional SMN protein. Risdiplam is approved for the treatment of individuals with SMA who are aged ≥2 months.[10] As a small molecule, risdiplam is the only oral treatment currently available for patients with SMA. Risdiplam is being investigated in infants, children, and adults with SMA in four clinical studies: RAINBOWFISH (NCT03779334), FIREFISH (NCT02913482), SUNFISH (NCT02908685), and JEWELFISH (NCT03032172).

Results from FIREFISH, a two-part, open-label study investigating the efficacy and safety of risdiplam in infants with Type 1 SMA and two *SMN2* gene copies, showed benefits in treated infants.[11,12] After 12 months of treatment with risdiplam, 12 of 41 infants (29%) were able to sit without support for ≥5 seconds, a milestone not achieved in untreated natural history cohorts.[12] By 12 months of treatment, 85% of infants (n = 35/41) remained alive and without permanent ventilation. The most common adverse events (AEs) reported in ≥4 infants were upper respiratory tract infection, pneumonia, fever, constipation, diarrhea, and maculopapular rash, and the most common serious AE (SAE) was pneumonia (32%).

SUNFISH is a two-part, placebo-controlled study of risdiplam in participants aged 2–25 years with Type 2 or 3 SMA.[13] The primary endpoint of Part 2, change from baseline in the 32-item Motor Function Measure total score after 12 months, was met, showing a statistically significant difference of 1.55 points between the risdiplam-treated and placebo groups (95% CI: 0.3, 2.81; p = 0.016). AEs more commonly reported with risdiplam versus placebo (≥5% difference) were fever, diarrhea, rash, mouth and aphthous ulcers, urinary tract infection, and arthralgias; the SAE more commonly reported was pneumonia.

Prior to the approval of risdiplam by the FDA in August 2020, an expanded access program (EAP; NCT04256265) was opened to provide access to risdiplam for eligible individuals with SMA in the US who, at the time, could not receive other DMTs, were ineligible for clinical trial participation, or were at risk of lack/loss of treatment efficacy of the current therapy. With the emergence of the SARS-CoV-2 virus at the end of 2019 and the subsequent coronavirus disease 2019 (COVID-19) pandemic, the risdiplam EAP was quickly revised using FDA guidance to include patients who could not receive treatment with an approved DMT due to pandemic-related barriers.[14]

Here, we discuss the design and implementation of the risdiplam EAP and provide a summary of the baseline and safety data.

Methods

Program design

The EAP was designed for eligible patients with Type 1 or 2 SMA prior to commercial availability of risdiplam in the US. The treating physician evaluated a patient to determine whether they met all eligibility criteria during a screening period of ≤4 weeks, after which eligible patients began treatment with risdiplam.

Treatment with risdiplam continued until a lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, commercial availability of risdiplam for the indication of SMA by the FDA, or program closure, whichever occurred first.

Setting and length of program

The EAP was conducted at 23, non-preselected sites in 17 US states via a decentralized design. A full list of the sites

that participated in the program is available in the Supplemental Appendix. The program began on 24 April 2020, and ended on 03 May 2021. Screening of new patients ended the day risdiplam became commercially available in the United States. Patients who already consented at the time of FDA approval were allowed to continue screening and enroll in the program if eligible. At the end of the program, patients were able to transition from the EAP to use of the commercial drug, if desired. To ensure there was no interruption of care, the program allowed for time post commercial approval for all patients who wished to continue treatment with risdiplam to get access to commercial risdiplam. As such, the last patient was able to obtain coverage in May 2021, approximately 9 months after commercial approval of risdiplam.

Patient eligibility

Patients were eligible for the program if they had a confirmed diagnosis of 5q autosomal recessive SMA, including genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene, and clinical history, signs, or symptoms attributable to Type 1 or 2 SMA. Patients were aged ≥2 months at enrollment and were ineligible for available and approved treatments for SMA or could not continue treatment due to a medical condition (e.g., severe scoliosis), risk of lack/loss of treatment efficacy of current therapy as determined by the treating physician, or the COVID-19 pandemic.

Patients were excluded from the program if they received a maintenance dose of nusinersen or another *SMN2*-targeting therapy within 120 days of starting risdiplam or received onasemnogene abeparvovec within 3 months of receiving risdiplam or did not have normal results from liver function tests at 3 months after the administration of onasemnogene abeparvovec. A full list of inclusion and exclusion criteria is available in the Supplemental Appendix.

Risdiplam treatment

Patients were treated with risdiplam orally once daily. Patients aged 2 months to <2 years received 0.20 mg/kg/day, patients aged ≥2 years (<20 kg) received 0.25 mg/kg/day, and patients aged ≥2 years (≥20 kg) received 5 mg/day.

Patient management during the COVID-19 pandemic

Due to the challenges of the COVID-19 pandemic, guidance was provided to sites on the management of patient visits and safety assessments. This was based on the FDA guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (March 2020).[14]

Patients were instructed not to travel against any local restrictions, and no patient was excluded from program participation if they were unable to visit the clinic due to COVID-19 pandemic-related circumstances. When an in-person visit was not possible, site personnel were instructed to contact patients on a regular basis to ask about general health and potential safety issues. AEs and all pertinent information were entered in the case report form.

Data collection and analyses

Medical history and demographic data were collected at screening. All patients were monitored for safety during treatment with risdiplam. Visits were every 3 months for patients <2 years old and/or <20 kg and every 6 months for patients ≥2 years old and ≥20 kg. However, when in-person visits were not possible, regular remote contacts could be conducted instead.

AEs, including SAEs and AEs of special interest, were monitored and recorded. AEs were based on the highest grade in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. The grading scale for events not specifically listed in the NCI CTCAE was based on a scale from 1 to 5, where Grades 1 and 2 were mild or moderate AEs, respectively. A Grade 3 AE was considered severe, medically significant, requiring hospitalization, disabling, or limiting self-care activities of daily living. AEs that were considered life threatening or resulted in death were Grades 4 and 5, respectively. Grades 3, 4, and 5 were reported as SAEs.

Protocol-specified safety assessments, laboratory assessments, vital sign measurements, and physical/neurological examinations were performed. If a patient discontinued from the EAP and did not transition to the use of the commercial drug, safety data continued to be collected for 28 days after the final dose. When a patient discontinued risdiplam due to transition to commercially available risdiplam, no additional safety information was collected after the last risdiplam dose within the EAP. However, the physician was encouraged to report any AEs that they were made aware of while the patient was receiving commercial risdiplam.

Safety analyses were performed on the safety population, defined as all enrolled patients who received at least one dose of risdiplam. Safety was assessed through descriptive summaries of AEs, laboratory test results, and vital signs. Risdiplam exposure data were summarized, including duration and dosage.

Ethics

The program was conducted in full conformance with the International Council for Harmonisation Guideline for Good Clinical Practice; principles of the Declaration of Helsinki; FDA regulations; and applicable local, state, and federal law. Written informed consent was provided by the patient or the patient's legally authorized representative before participation in the program. The protocol, informed consent form, and patient-facing materials were submitted and approved by a central institutional review board (IRB). Sites that could not defer to the central IRB obtained local IRB approval prior to patient participation.

Results

Patient baseline characteristics

The EAP enrolled 155 patients with Type 1 (n = 73; 47.1%) or 2 SMA (n = 82; 52.9%; Table 1). All patients received at least one dose of risdiplam, and 149 patients (96.1%) completed the EAP (defined as obtaining access to commercial risdiplam, if desired). Six patients discontinued the program early due to AEs (n = 3; 1.9%), perceived lack of efficacy (n = 2; 1.3%), or interest in trying a different treatment (onasemnogene abeparvovec; n = 1; 0.6%).

A wide range of ages was represented in the program (Table 1). The median age of patients at the time of screening was 11.0 years (range, 4 months–50 years). Eleven patients (7.1%) were <2 years old, 102 (65.8%) were 2–17 years old, and 42 (27.1%) were ≥18 years old. Most patients had been previously treated with a DMT (Table 2): nusinersen (n = 101; 65.2%), onasemnogene abeparvovec (n = 9; 5.8%), or both (n = 11; 7.1%).

Table 1. Patient demographics and baseline characteristics.

	All patients (N = 155)
Age at screening, years	
Mean (SD)	13.0 (10.0)
Median	11.0
Range	0–50
Age group, *n* (%)	
<2 years	11 (7.1)
≥2 and <6 years	29 (18.7)
≥6 and < 12 years	43 (27.7)
≥12 and < 18 years	30 (19.4)
≥18 and < 25 years	19 (12.3)
≥25 years	23 (14.8)
Sex, *n* (%)	
Male	73 (47.1)
Female	82 (52.9)
Race, *n* (%)	
Asian	3 (1.9)
Black or African American	4 (2.6)
Native Hawaiian or Other Pacific Islander	0
White	133 (85.8)
Multiple	4 (2.6)
Unknown	11 (7.1)
Ethnicity, *n* (%)	
Hispanic or Latino	13 (8.4)
Not Hispanic or Latino	125 (80.6)
Not stated	4 (2.6)
Unknown	13 (8.4)
Weight at baseline, kg	
Mean (SD)	30.8 (18.6)
Median	27.50
Range	5.9–112.5
SMA type, *n* (%)	
1	73 (47.1)
2	82 (52.9)
SMN2 copy number, *n* (%)	
2	67 (43.2)
3	75 (48.4)
4	3 (1.9)
Missing	10 (6.5)
Ambulatory or non-ambulatory, *n* (%)	
Ambulatory	4 (2.6)
Non-ambulatory	149 (96.1)
Missing	2 (1.3)

SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Treatment exposure

The median risdiplam treatment duration for patients in the EAP was 4.8 months (range, 0.3–9.2 months). A total of 16 patients (10.3%) were treated with risdiplam for <3 months, 111 (71.6%) were treated for ≥3 to <6 months, and 28 (18.1%) were treated for >6 months.

Safety

A total of 173 AEs and 31 SAEs were reported, with 73 patients (47.1%) reporting at least one AE and 14 (9.0%) reporting at least one SAE (Table 3).

The most common AEs included diarrhea (n = 10; 6.5%), pyrexia (n = 7; 4.5%), and upper respiratory tract infection (n = 5; 3.2%; Table 4). Pneumonia (n = 3; 1.9%) and acute respiratory failure, constipation, deep vein thrombosis (DVT), and hypokalemia (n = 2; 1.3%, each) were the most frequently reported SAEs.

No AEs indicative of the retinal toxicity, hematologic toxicity, and skin safety findings seen in preclinical studies were observed. No deaths were reported during the program.

Treatment-related AEs and SAEs

A total of 42 AEs were assessed as related to risdiplam by the treating physician. These occurred in 25 patients

Table 2. Patients who have been previously treated with a DMT.

Previous DMT, *n* (%)	All patients (*N* = 155)
Treatment naive	26 (16.7)
Nusinersen	101 (65.2)
Onasemnogene abeparvovec	9 (5.8)
Both*	11 (7.1)
Unknown	8 (5.2)

*Patients had received both onasemnogene abeparvovec and nusinersen.
DMT, disease-modifying treatment.

Table 3. Summary of AEs.

	All patients (*N* = 155)
Total No. of patients with at least one AE, (%)	73 (47.1)
Total No. of AEs	173
Total No. of deaths	0
Total No. of patients withdrawn due to an AE	3 (1.9)
Total No. of patients with at least one:	
AE with fatal outcome, *n*	0
Serious AE, *n* (%)	14 (9.0)
Serious AE leading to dose modification or interruption, *n* (%)	4 (2.6)
Related SAE, *n* (%)	2 (1.3)
AE leading to dose modification or interruption, *n* (%)	11 (7.1)
Related AE, *n* (%)	25 (16.1)
Related AE leading to dose modification or interruption, *n* (%)	4 (2.6)
Grade 3–5 AE, *n* (%)	13 (8.4)

AE, adverse event; No. number.

(16.1%; Table 5). The most common treatment-related AEs were constipation, diarrhea, and headache (three patients each), followed by dizziness, insomnia, and nausea (two patients each). Most treatment-related AEs were reported as recovered or resolved with ongoing risdiplam treatment, with the exception of pollakiuria and urine output increase, pain in extremity, and insomnia (one patient each), which were ongoing at the time of the data cutoff (07 May 2021).

Two patients (1.3%) reported three SAEs that were considered related to risdiplam, none of which led to discontinuation of treatment (i.e., withdrawal from program). One patient with preexisting constipation experienced a Grade 2 constipation event, which necessitated hospitalization. Medication for constipation (sodium chloride, macrogol 3350, unspecified probiotics, and senna) was provided. Treatment with risdiplam was temporarily interrupted, and the event of constipation resolved after 9 days without further recurrence.

Table 4. Most common AEs and SAEs.*

	All patients (*N* = 155)
Most common AEs in ≥4 patients, *n* (%)	
Diarrhea	10 (6.5)
Pyrexia	7 (4.5)
Upper respiratory tract infection	5 (3.2)
Abdominal pain	4 (2.6)
Constipation	4 (2.6)
Vomiting	4 (2.6)
Urinary tract infection	4 (2.6)
Dizziness	4 (2.6)
Headache	4 (2.6)
Most common SAEs in ≥2 patients, *n* (%)	
Pneumonia	3 (1.9)
Acute respiratory failure	2 (1.3)
Constipation	2 (1.3)
Deep vein thrombosis	2 (1.3)
Hypokalemia	2 (1.3)

*MedDRA preferred terms, Medical Dictionary for Regulatory Activities.
AE, adverse event; SAE, serious AE.

The second patient experienced signs and symptoms suggestive of systemic inflammatory response syndrome (SIRS; fever, abdominal pain, and elevated white blood cell count) on Day 92. Although sepsis was suspected, no clear source of infection was identified, and the SIRS resolved after 4 days with ongoing risdiplam treatment. The same patient later developed DVT in the left leg following an injury about 1 month after the event of SIRS had resolved. The DVT might have been related to the previous injury, but the possibility that risdiplam played a role could not be excluded as assessed by the treating physician. The dosage of risdiplam remained unchanged, and both the pain in the extremity and DVT were ongoing at the time of data cutoff.

Treatment-related AEs that led to withdrawal or dose modification or interruption

Of the three patients (1.9%) who withdrew from the program due to an AE, two withdrew due to an AE that was deemed related to risdiplam. Abnormal behavior (Grade 1), which was characterized by increased hyperactivity, was noted in one patient on Day 3 of risdiplam. After 1 week, risdiplam treatment was interrupted, and the event was considered resolved the following day. The patient withdrew from the study. Another patient experienced vomiting classified as mild or Grade 1. The patient chose to stop risdiplam, and the vomiting resolved in 3 days. This patient withdrew from the EAP.

Treatment-related AEs in four patients (2.6%) led to dose modification or interruption: abnormal behavior

Table 5. Treatment-related AEs and SAEs.*

	All patients (N = 155)
Treatment-related AEs, *n* (%)	25 (16)
Constipation	3 (1.9)
Diarrhea	3 (1.9)
Headache	3 (1.9)
Dizziness	2 (1.3)
Insomnia	2 (1.3)
Nausea	2 (1.3)
Abdominal discomfort	1 (0.6)
Abdominal pain	1 (0.6)
Abdominal pain upper	1 (0.6)
Abnormal behavior	1 (0.6)
Amenorrhea	1 (0.6)
Chest pain	1 (0.6)
Decreased appetite	1 (0.6)
Deep vein thrombosis	1 (0.6)
Dysgeusia	1 (0.6)
Fatigue	1 (0.6)
Feeling jittery	1 (0.6)
Gastroesophageal reflux disease	1 (0.6)
Heart rate increased	1 (0.6)
Increased appetite	1 (0.6)
Increased bronchial secretion	1 (0.6)
Menstrual disorder	1 (0.6)
Oral discharge	1 (0.6)
Pain in extremity	1 (0.6)
Palpitations	1 (0.6)
Pollakiuria	1 (0.6)
Pyrexia	1 (0.6)
Secretion discharge	1 (0.6)
Systemic inflammatory response syndrome	1 (0.6)
Tachycardia	1 (0.6)
Urinary tract infection	1 (0.6)
Urine output increased	1 (0.6)
Vomiting	1 (0.6)
Treatment-related SAEs, *n* (%)	3 (1.9)
Constipation	1 (0.6)
Deep vein thrombosis	1 (0.6)
Systemic inflammatory response syndrome	1 (0.6)

*MedDRA preferred, Medical Dictionary for Regulatory Activities.
AE, adverse event; SAE, serious AE.

(see above), vomiting (see above), abdominal discomfort, and constipation (see *Treatment-related AEs and SAEs*). Apart from constipation, these AEs were assessed as non-serious. All treatment-related AEs that led to withdrawal or dose modification or interruption were reported as recovered or resolved.

Safety in Type 1 versus 2 patients

A higher percentage of patients with Type 1 (n = 41; 56.2%) than Type 2 SMA (n = 32; 39.0%; Table S1) reported AEs. The frequency of treatment-related AEs was similar between patients with Type 1 (n = 13; 8.4%) versus 2 SMA (n = 12; 7.7%).

In patients with Type 1 SMA, the most common AEs were diarrhea (n = 6; 8.2%), constipation (n = 4; 5.5%), and vomiting (n = 4; 5.5%), while the most common SAEs were constipation and hypokalemia (n = 2; 2.7%, both; Table S2). In patients with Type 2 SMA, the most common AEs were diarrhea and pyrexia (n = 4; 4.9% for each), while the most common SAEs were pneumonia and acute respiratory failure (n = 2; 2.4%, both).

Gastrointestinal events

Overall, 31 patients (20%) experienced a gastrointestinal (GI) AE. Most GI events were mild and resolved or were resolving. The most frequently reported GI events were diarrhea (n = 10; 6.5%), abdominal pain (n = 4; 2.6%), constipation (n = 4; 2.6%), and vomiting (n = 4; 2.6%; Table S1).

Three out of 10 diarrhea events were assessed as related to risdiplam by the treating physician (Table 5). In patients who experienced treatment-related diarrhea, the events occurred within the first month after starting treatment and recovered or resolved during the first 4 months of treatment with no changes to risdiplam treatment. One out of 10 diarrhea events was an SAE that was caused by an enterovirus infection and deemed unrelated to risdiplam by the treating physician.

Four events of constipation were reported, all of which occurred and resolved within the first month after starting treatment. Of the four constipation events, three were deemed related to risdiplam. Two related events were considered non-serious and did not require any changes to the study drug. One related event of constipation was considered an SAE, which required temporary interruption of risdiplam treatment (see *Treatment-related AEs and SAEs*). A fourth constipation event was considered an SAE, required temporary interruption of treatment, and was deemed unrelated to risdiplam.

Discussion

This EAP provided risdiplam access to eligible patients with Type 1 or 2 SMA in the United States, prior to commercial availability. The program provided an opportunity to collect additional risdiplam safety information beyond the pivotal trials. Overall, safety results in this diverse population were similar to those in previous studies, and no new safety signals were observed.[11,12] Diarrhea, pyrexia, and upper respiratory tract infection were the most common AEs observed, which is consistent with AEs stated in the United States label for risdiplam.[15] The most common treatment-related AEs were constipation,

diarrhea, and headache, which all recovered or resolved with ongoing treatment with risdiplam. No patients enrolled in the EAP had AEs indicative of the risdiplam-induced hematologic effects, retinal toxicity, or skin findings observed in preclinical studies. A low percentage of patients withdrew from the program, and only three patients (1.9%) withdrew due to an AE. During the EAP, no deaths were reported.

The unique design of the EAP allowed access to risdiplam in a patient population who otherwise would not have been able to receive treatment for SMA. The decentralized design of the program permitted a large number of sites ($N = 23$) and patients ($N = 155$) to participate. As there were no predetermined sites, the EAP enrolled a relatively heterogeneous group of patients with a broad range of demographic and clinical profiles, including varied functional abilities compared with previous studies of risdiplam. Patients were older (median age, 11.0 years) than those enrolled in the pivotal FIREFISH[11,12] and SUNFISH[13] risdiplam trials. The considerable number of patients who enrolled in the EAP demonstrates the continued unmet need for treatment in the real-world patient population with SMA.

The EAP included patients who were ineligible to receive treatment elsewhere and patients who could no longer receive treatment due to the pandemic. A high percentage of patients (78.1%) were previously treated with a DMT. In previous SMA EAPs for DMTs, enrollment was restricted to patients with Type 1 SMA.[16–20] In some of these programs, further restrictions on eligibility were implemented, so that only infants with early onset of symptoms (at <6 months of age), who were thought to benefit the most from treatment, could enroll.[18,19] These previous limitations on access to treatment based on age have led to an emotional burden among caregivers of ineligible patients.[21]

The rapid adaptation of the protocol on the management of patients and their safety assessments due to the COVID-19 pandemic ensured that patients in the EAP were able to continue risdiplam until they could transition to the use of the commercial drug (if desired). Additionally, eligible patients unable to continue nusinersen due to the pandemic were considered for the EAP. This amendment to the protocol was consistent with a recent publication on recommendations for care during the pandemic, which emphasized that patients receiving treatment for SMA should not have their treatment delayed or interrupted and that treatments should not be considered optional.[22]

The administration of risdiplam was not impacted by the pandemic. Its oral, at-home dosing regimen allowed patients to receive treatment without leaving their homes. In addition, the COVID-19 pandemic did not significantly impact the ability to monitor and manage patient safety during the conduct of the EAP due to the ability to conduct virtual/telephone visits.

A limitation of the program was the limited treatment duration, which may have prevented the capture of rare or long-term safety signals. Data to examine any correlative safety patterns in patients who were previously treated with a DMT were not collected, as the main focus of the program was patient access. Another limitation of this study was the lack of a racially diverse patient population. Although White patients in North America have higher carrier frequencies of the *SMN1* mutation compared with other races,[23,24] other non-White patients with SMA were not highly represented in the patient population of the EAP. Minority racial groups are often underrepresented in clinical trials due to a variety of reasons, one of which includes differences in the access to health care between different races.[25] This decentralized risdiplam EAP demonstrated the possibility of monitoring and collecting data from patients at home. This program serves as an example of how EAPs can be designed to overcome travel difficulties, which may increase access to treatment in these underrepresented patient groups.

With nearly every patient completing the program (defined as obtaining access to commercial risdiplam, if desired), a large part of the EAP's success was attributed to the lack of predetermined sites, the program's flexibility during the pandemic, and the oral at-home dosing of risdiplam. The observed risdiplam safety profile in patients with Type 1 and 2 SMA, including those who had previously received treatment with other DMTs, was consistent with the safety profiles of the pivotal risdiplam trials.[11–13] Thus, this program provides additional data to support risdiplam as a viable treatment option for pediatric and adult patients with SMA.

Acknowledgments

The authors would like to thank all the patients and families who participated in the risdiplam expanded access program, the program sites, and staff members. A full list of members of the EAP Working Group, who served as clinical investigators in the risdiplam EAP, is available in the Supplement Appendix. This program was funded by Genentech, Inc. The authors also thank Michelle B. Kim, PhD, of MediTech Media for providing medical writing support, which was funded by Genentech, Inc in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

For eligible studies qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing this request platform is Vivli (https://vivli.org/ourmember/roche/). For

up to date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in the risk of patient re-identification.

Author Contributions

BA, SBW, TLD, JH, HL, and YY contributed to the study conception and design. JMK, KA, NK, HCP, CS, KJS, AV, and VM collected the data. Analysis and interpretation were performed by all authors. All authors reviewed and commented on previous versions of the manuscript, read and approved the final manuscript.

Conflict of Interest

JMK was a site principal investigator for the risdiplam EAP; she is currently the site principal investigator for Novartis clinical trials for which her institution receives research funding for clinical trial coordination. She has served on an SMA medical advisory board for Scholar Rock, Inc. NK serves on medical advisory boards for Astellas, Biogen, Novartis, Roche, Sarepta, and PTC Therapeutics. KJS has received research grant support from Biogen. AV has received compensation for ad-hoc advisory boards/consulting activity with Biogen, Novartis, AveXis, Sarepta Therapeutics, PTC Therapeutics, Scholar Rock, and Fibrogen; and research/grant support from Muscular Dystrophy Association, Parent Project Muscular Dystrophy, Sarepta, Pfizer, Fibrogen, Genentech, Octapharma, Impax Laboratories, Lilly Pharmaceuticals, and Teva Pharmaceuticals. VKR has received personal fees from AveXis, Biogen, Genentech-Roche, Scholar Rock, PTC Therapeutics, NSPharma, Regenxbio, Sarepta Therapeutics, France Foundation, Cure SMA, and MDA outside of the submitted work. BA, SBW, TLD, JH, HL, and YY are employees and shareholders of Genentech/F. Hoffmann-La Roche. KA, HCP, and CS have no COIs to disclose.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. EAP working group.
Inclusion criteria.
Exclusion criteria.
Table S1 Adverse events reported in ≥2 patients.
Table S2 Serious adverse events reported in ≥2 patients.

