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Research Report

Risdiplam in Spinal Muscular Atrophy: Safety Profile and Use Through The Early Access to Medicine Scheme for the Paediatric Cohort in Great Britain

Nikki Cornell[a], Anne-Marie Childs[b], Elizabeth Wraige[c], Pinki Munot[a], Gautam Ambegaonkar[d], Gabriel Chow[e], Imelda Hughes[f], Marjorie Illingworth[g], Anirban Majumdar[h], Chiara Marini-Bettolo[i], Deepak Parasuraman[j], Stefan Spinty[k], Tracey Willis[l], Mariacristina Scoto[a] and Giovanni Baranello[a,*], On Behalf of the Paediatric UK Risdiplam EAMS Working Group

[a]*The Dubowitz Neuromuscular Centre, Developmental Neuroscience Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, NIHR Great Ormond Street Hospital Biomedical Research Centre & Great Ormond Street Hospital NHS Foundation Trust, UCL Great Ormond Street Institute of Child Health London, UK*
[b]*Leeds Royal Infirmary, Leeds, UK*
[c]*Evelina London Childrens Hospital, London, UK*
[d]*Addenbrookes Hospital, Cambridge, UK*
[e]*Queen's Medical Centre Nottingham, Nottingham, UK*
[f]*Royal Manchester Children's Hospital, Manchester, UK*
[g]*University Hospital Southampton, Southampton, UK*
[h]*Bristol Royal Hospital for Children, Bristol, UK*
[i]*John Walton Muscular Research Centre, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation trust*
[j]*University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK*
[k]*Alder Hey Children's Hospital, Liverpool, UK*
[l]*The Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, UK*

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Abstract.
Background: Spinal muscular atrophy (SMA) is a progressive neuromuscular disease caused by mutations in Survival motor neuron 1 (*SMN1*) gene, leading to reduction in survival motor neuron protein (SMN), key for motor neuron survival and function in the brainstem and spinal cord. Risdiplam is an orally administered *SMN2*-splicing modifier which increases production of functional SMN protein. Risdiplam was offered in the UK under early access to medicines scheme (EAMS) to SMA type 1 and 2 patients aged 2 months and older, not suitable for authorised treatments from September 2020 to December 2021.

*Correspondence to: Giovanni Baranello, The Dubowitz Neuromuscular Centre, Developmental Neuroscience Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, NIHR Great Ormond Street Hospital Biomedical Research Centre & Great Ormond Street Hospital NHS Foundation Trust, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1 N 1EH. UK. Tel.: +44 0 2079052872; Fax: +44 0 2079052832; E-mail: g.baranello@ucl.ac.uk.

Objective: To describe the largest paediatric European real-world set of data on patients' characteristics and short-term safety for risdiplam in Great Britain through EAMS.
Methods: We collated data from SMA REACH UK a national clinical and research network for all patients enrolled onto EAMS and assessed all submitted adverse events.
Results: Of the 92 patients; 78% were Type 2 SMA, mean age 10.9 years, range 0–17 years. 56 were treatment naïve, 33 previously treated; of these 25 had received nusinersen, 3 previous treatment unknown. Sixty adverse events (AEs) were reported occurring in 34 patients. The commonest were respiratory tract infections and gastrointestinal disturbance. Four life-threatening events were reported with 2 deaths and permanent cessation of risdiplam in 3 patients.
Overall, 38/60 AEs were considered unrelated to risdiplam, 10/60 related to risdiplam and for 12/60 causality not specified.
Conclusions: This study found a safety profile similar to clinical trials with no new safety concerns identified. With the restricted eligibility of onasemnogene abeparvovec and complications of nusinersen administration, EAMS allowed access or continued treatment to naïve patients or patients no longer suitable for approved medications. Collection of longitudinal data for this complex population is needed, to provide greater insights into risdiplam's role in addressing patients' needs into the future.

Keywords: Spinal muscular atrophy, risdiplam, treatment, adverse events, safety

INTRODUCTION

Spinal muscular atrophy (SMA) is a progressive neuromuscular disease caused by biallelic mutations in the Survival Motor Neuron 1 (*SMN1*) gene. This leads to a reduction in survival motor neuron (SMN) protein which is key for motor neuron survival and function in the brainstem and spinal cord. Limited levels of functional SMN are produced from the paralogue *SMN2* gene, and the copy number of *SMN2* is inversely correlated with SMA disease severity [1].

SMA is classified into five subtypes with varying degrees of severity, depending on age of onset and maximum motor milestones achieved. SMA Type 0 is usually fatal in utero or at birth. Type 1 present with hypotonia, weakness, and progressive feeding and respiratory impairment during the first 6 months after birth. Untreated SMA Type 1 children are unable to achieve unsupported sitting and have reduced life expectancy, usually below the age of two years. Type 2 SMA typically present between 6 months and 2 years of age and patients may sit independently but do not achieve independent standing or walking. Type 3 SMA usually presents after 18 months, achieve independent walking but can lose this ability. Type 4 SMA has adult onset, walk independently and a normal lifespan [2–4].

Three disease modifying treatments are now available for SMA. Nusinersen is an antisense oligonucleotide (ASO) administered intrathecally and is available in the UK for SMA Type 1, 2 and 3 [5].

Onasemnogene abeparvovec is an adenoassociated viral vector *SMN1* gene transfer therapy given by single intravenous infusion; approved for infants with 1–3 copies of *SMN2* gene until the age of 2 years in the US or for SMA Type 1 up to a weight of 21 kg in Europe [6].

Risdiplam is an orally administered small molecule *SMN2*-splicing modifier which promotes inclusion of exon 7 in the *SMN2* mRNA transcript thus increasing the production of the functional SMN protein. It is currently available for individuals with SMA Types 1, 2, and 3 with one to four *SMN2* copies [7]. Since December 2021 it has been available under a managed access agreement (MAA) in the UK. Risdiplam has been used in clinical trials since 2015 and was initially offered in the UK under an early access to medicines scheme (EAMS) to SMA type 1 and 2 patients aged 2 months and older, not suitable for authorised treatments.

Risdiplam access through the EAMS was available to eligible patients in the UK from September 2020 to December 2021 when the NICE final guidance for risdiplam implementation was published. Inclusion criteria were a genetically confirmed diagnosis of 5q-SMA Types 1 and 2 in individuals older than two months and not suitable for authorised treatments. Whilst some of these patients may have been eligible for other treatment, after careful consideration and discussions between families and professionals it would have been decided that patients were no longer suitable to continue the previous treatment before they were considered eligible to be recruited into the EAMS scheme. The aim of EAMS was to give UK patients with life-threatening or seriously debilitating conditions access to medicines that were not yet licensed when there was a clear unmet medical need.

In this paper we describe the real-world data on patients' characteristics and short-term safety for risdiplam in Great Britain through the EAMS.

METHODS

For all patients enrolled, specific details were provided to Roche by the referring physician on the EAMS application form. Mandatory data was required, and additional data requested to assist in developing knowledge and understanding of how risdiplam can be used in clinical practice, particularly for patients who have previously received a targeted SMA treatment. Here we report on baseline characteristics, adverse events, and serious adverse events in patients younger than 18 years at enrolment.

RISDIPLAM TREATMENT

The lead neuromuscular consultant for each patient assessed patients' eligibility and suitability to access risdiplam under the EAMS based on the criteria of: Type 1 or 2 SMA patient, older than 2 months and not suitable for any authorised treatment. Assessments and treatment management were the responsibility of the treating physician in accordance with global and local regulatory requirements, including safety data reporting and documentation. All physicians involved were experienced in managing patients with SMA and were part of the SMA REACH (Research and Clinical Hub) UK national network, that includes 17 neuromuscular centres in the UK. All patients and/or legally authorised representatives provided written informed consent to participate in the EAMS. Prior to commencing risdiplam patients were assessed with a full medical history, physical examination, and baseline blood tests including haematology and biochemistry. Such parameters were reviewed when patients attended their routine follow up appointments. Reduced assessment intervals were indicated if any abnormal results or concerns occurred at the leading physician's discretion. Discontinuation criteria included physician decision to stop due to potential harm to the patient, patient needing treatment not allowed on the scheme, scheme being stopped, patient/carer failing to follow the instructions relevant to the child's safe participation in the scheme, and decision to withdraw by patient/carer with no reason required [8].

The dosing scheme was as per the Evrysdi summary of product characteristics. Patients aged 2 months to <2 years received 0.20 mg/kg/day, patients aged ≥ 2 years and less than 20 kg received 0.25 mg/kg/day, and patients aged ≥ 2 years and more than or equal to 20 kg received 5 mg/day [7].

Patients received risdiplam at home and carers were advised to orally administer risdiplam at the prescribed dose at the same time each day, the most common recommended administration being at breakfast.

ADVERSE EVENTS REPORTING

All adverse events (AEs) were collected by the prescribing clinician; physicians were also required to report AEs to the medicines and healthcare products regulatory agency via the yellow card scheme [9].

ETHICS

All patients and/or legally authorized representatives provided written informed consent to participate in the EAMS. All recruited patients had been consented to collect data through the SMA-REACH (ethical approval in 2014, IRAS 122521, by the Bromley Research ethics committee).

RESULTS

Patient demographics

Ninety-two paediatric patients (43 male, 47 female, 2 unspecified) received risdiplam through the EAMS and were included in this study. Age ranged from 2 to 18 years with most patients being over 12 years of age (51/92, 55.4%). The mean age was 10.9 years, median age 12 years, range 0–17 years.

The majority of patients were Type 2; 72/92, (78.2%) with 20/92 (22%) Type 1 SMA. The numbers of *SMN2* copy were largely undocumented/unknown (65/92; 72%). The treatment duration ranged from 2 to 21 months, with the median length of 11 months and mean of 12.4 months.

Previous treatment status was known in 89/92 patients: 33/92 were on previous disease modifying treatment (DMT), while 56/92 were treatment naïve. Of the 33 patients previously treated, 75% (25/33) had received nusinersen and 9% (3/33) had received risdiplam under clinical trial. Olesoxime was previously in use by 6% (2/33) in clinical trials, for 3/33 (9%) which DMT was unknown. The commonest reason for switching DMT to risdiplam was difficult

Table 1
Reason for change of treatment

	Number of patients	Percent of total (%)
Difficult nusinersen administration	22	67
Completed trial	5	15
Not meeting nusinersen MAA criteria	2	6
Unknown	2	6
Vomiting post LP for nusinersen	1	3
Adverse event	1	3

administration of nusinersen 67% (22/33). (Table 1 -Reason to change treatment)

SAFETY

A total of 60 adverse events were reported occurring in 34 patients; of these, 15% (9/60) occurred in Type 1 patients and 85% (51/60) in Type 2 patients. Overall, 64% (38/60) AEs were considered not related to risdiplam, 16% (10/60) were considered related to risdiplam and for 20% (12/60) the causality was not specified.

The most common AEs were: Respiratory tract infections (35%), gastrointestinal disturbance (20%) and skin and hair abnormalities (10%). Less common adverse events included headache (5%), pubertal and menstrual abnormalities (5%), weight gain (3%), and mood change with memory and concentration difficulties (3%). The rare adverse events only occurred once, these included back and hip pain, toothache, dysuria, unclear speech, dizziness, and ectopic beats (Table 2 – Adverse events).

Of the 10 AEs deemed possibly related to risdiplam 7/10 (70%) involved the gastrointestinal system; these were a combination of diarrhoea, nausea, and abdominal pain and occurred in patients ranging from 8–16 years. Skin hypersensitivity to sunlight occurred in a 10-year-old male after commencing risdiplam and persisted. Episodes of dizziness after commencing risdiplam occurred in a 13-year-old male but settled after a few doses. One patient paused treatment for a two-week period, two months after commencing risdiplam due to a combination of side effects including menorrhagia, ectopic beats and short-term memory and concentration difficulties, then risdiplam was re-commenced with no further AEs reported.

Unfortunately, baseline status of these patients such as bulbar dysfunction, BiPAP requirement, ventilation via tracheostomy, baseline physiotherapy assessments were not systematically collected in the EAMS program. This data would have assisted in the interpretation of AES and SAEs however this data will be part of the ongoing collection of real-world data in the UK SMA REACH national registry in patients treated with DMTs.

SEVERE LIFE-THREATENING EVENTS

Four severe life-threatening events were reported with 2 subsequent deaths. A 16-year-old male with SMA Type 2, 11 months after commencing risdiplam, whilst on oral antibiotics for a chest infection was found at home having suffered a cardiac arrest. A 1-year-old female with SMA Type 1, a month after

Table 2
Adverse events

Adverse event	Number of events recorded	Percent of AEs	Number of events deemed 'related' to risdiplam
Respiratory tract infection	21	35%	0
Gastrointestinal disturbance	12	20%	7
Skin and hair abnormalities[a]	6	10%	1
Life threatening episode[b]	4	7%	0
Headache	3	5%	0
Pubertal/menstrual abnormalities[c]	3	5%	1
Weight gain	2	3%	0
Mood change, memory and concentration difficulties	2	3%	1
Superior Mesenteric Artery Syndrome – post spinal surgery	1	1.7%	0
Hip and back pain	1	1.7%	0
Dizziness	1	1.7%	0
Urinary symptoms	1	1.7%	0
Unclear speech	1	1.7%	0
Dental pain	1	1.7%	0
Ectopic beats[d]	1	1.7%	0

a – 3 x rash and itching, 1 x hair thinning, 1 x increased hypersensitivity to sunlight, 1 x peri-orbital erythema. b – see paragraph below. c – menorrhagia, missed menstruation, premature adrenarche. d-Palpitations reported and 24hour ECG showed ectopic beats.

commencing risdiplam, suffered a cardio-respiratory arrest due to a blocked tracheostomy tube leading to hypoxic brain injury and subsequent death. An 8-year-old female suffered a hypoxic episode, one month after starting risdiplam. The hypoxic episode was preceded by overuse of her cough assist machine (8 cycles), and this was deemed by the treating clinician to be the main cause of the patient's hypoxia. Five months after commencing risdiplam a 2-year-old male had a three-week admission to PICU following a respiratory arrest requiring cardiopulmonary resuscitation; occurring on a background of decreased saturations and respiratory symptoms. All severe life-threatening events were deemed not related to risdiplam by the treating clinicians.

CESSATION OF RISDIPLAM

Permanent cessation of risdiplam treatment during EAMS occurred in 3% of patients enrolled (3/92). Two were due to death. One patient decided to permanently cease treatment after seven months of taking risdiplam due to two months of missed menstruation.

Risdiplam treatment was temporarily stopped in 6 patients during some AEs. One patient missed a dose during a vomiting illness, and another stopped for two days due to a chest infection. There were some longer breaks including a patient who developed superior mesenteric artery syndrome after spinal surgery; risdiplam was stopped whilst the child was nil by mouth as part of the management of this post operative complication. During a covid infection one patient decided to stop risdiplam for two weeks; in another case risdiplam was stopped for three weeks whilst the patient received treatment on PICU after a severe life-threatening episode of reduced level of consciousness and severe respiratory distress. One patient paused treatment for a two-week period, two months after commencing risdiplam due to a combination of side effects including menorrhagia, ectopic beats and short-term memory and concentration difficulties, then risdiplam was re-commenced with no further AEs reported.

DISCUSSION

We report real-world data from a large cohort of paediatric patients treated with risdiplam under the EAMS in England, Scotland and Wales. The majority of patients had Type 2 SMA and were older than 11 years.

The SMA type and age distribution can be explained by a combination of factors. A great proportion of patients were already treated and continued to be treated with nusinersen which was available under the MAA in the UK since July 2019 for Type 1, 2 and 3 SMA [10]. Additionally, gene replacement therapy onasemnogene abeparvovec was approved in March 2021 for type 1 SMA patients in the UK, a few months before the EAMS recruitment closure date, providing an alternative option for type 1 SMA patients younger than 13 months, further explaining the reduced number of young type 1 patients recruited to the scheme at this time.

The majority of patients included in the EAMS (61%, 56/92) were treatment naïve; this can be explained by the fact that the EAMS aimed to fill the unmet need of a proportion of patients who could not access approved treatments due to not fulfilling eligibility criteria [8]. Not surprisingly, of the 33 patients previously treated, 75% (25/33) had received nusinersen. The commonest reason for switching DMT to risdiplam was difficult administration of nusinersen (67%). Intrathecal administration of nusinersen can become technically difficult due to the complex anatomical changes occurring with severe scoliosis, and this can be a relatively common challenge as non-ambulant SMA types have an 80% lifetime risk of developing scoliosis [11]. No longer meeting the existing MAA criteria for another DMT (i.e., increased respiratory support with non-invasive ventilation for more than 16 hours per day) was another reason for switching to risdiplam (6%). Although rare, the EAMS provided a treatment option in this group of patients that would otherwise have become ineligible for an approved medication. Unlike previous studies, there were no cases reporting lack of efficacy as the reason for switching. This is likely due to the criteria to access the EAMS of being not eligible to receive an approved medication, while the lack of efficacy was not considered a criterion.

Importantly, the overall safety profile in this heterogeneous paediatric population was similar to what was previously reported, and no new safety signals were observed. No patients had AEs indicative of the risdiplam induced haematologic effects or retinal toxicity observed in preclinical studies. Two deaths were reported during the EAMS due to cardiac or cardiac-respiratory arrest during an acute respiratory event, that were not considered related to risdiplam. Only one patient withdrew from the program due to an AE. Similar to the previous clinical trials and the limited real-world experiences, respiratory tract

infections and gastrointestinal disturbances were the most commonly reported AEs [12, 13]. Respiratory complications are common comorbidities in SMA, and the relatively high rate reported in the EAMS likely reflect the underlying fragility of the recruited population of SMA 1 and SMA 2 patients [14]. Gastrointestinal symptoms occur in SMA but usually manifest as constipation and gastroesophageal reflux with laxatives often being required regularly in these patients [15]. Therefore, the prevalence of diarrhoea in these patients was considered to be likely related to risdiplam. Likewise, skin abnormalities are rare in SMA and the reported events here were considered as possibly related to risdiplam, although they were mild and managed with simple treatments or resolved.

Our EAMS safety data has similar results to a pooled safety analysis from the FIREFISH, SUNFISH, JEWELFISH and RAINBOWFISH clinical trials that assessed safety data in 465 SMA patients who received risdiplam in these clinical trials. The most common related AEs were diarrhoea, nausea, rash, and headache, with pneumonia the most common SAE [16]. Likewise, similar AE results were obtained from the expanded access program in the United States where the most frequently reported adverse events were diarrhoea, pyrexia, and upper respiratory tract infection, with pneumonia as the most reported SAE [4].

Garzon et al. have shown that risdiplam can be safe and effective in SMA type 2 patients over 16 years in a recent analysis of a small cohort of patients on an early access programme. Clinically meaningful improvements were seen in all patients in at least one scale with only one 16 year old patient reporting mild AEs [17].

Preclinical studies point out the potential risks to male fertility related to risdiplam use, however this data was not systematically collected in our paediatric cohort. We recognise that our retrospective review of demographics and adverse events in this study has some limitations. Our real-world collection of data could have led to missing data and variations between sites. Retrospective collection of data may have resulted in information bias and may have underestimated adverse events. Programs like the EAMS are mainly aimed to provide compassionate use-based access to unapproved therapies and are not designed for the systematic collection of data or to answer scientific questions. For this reason, and for the relative short duration of patients' follow up and heterogeneity of the recruited population, data on efficacy were not systematically collected. However, our data provide further evidence on the real-world safety profile of risdiplam that can be helpful in counselling patients and guiding decision making.

CONCLUSION

Observations on SMA Type 1 and 2 patients on risdiplam via the EAMS has been presented here as the largest paediatric European real-world set of data. This real-world data confirms risdiplam's safety profile is similar to that reported in clinical trials and no new safety concerns have been identified. Risdiplam is currently approved for use in several countries, and it is expected to become available to larger numbers of patients worldwide in the near future, this data may provide further guidance to clinicians when counselling patients and caregivers.

The relatively high number of paediatric patients included in this program highlights the unmet medical need for an additional treatment option. More than 50% of these patients were not receiving any disease modifying treatment prior to enrolment on this scheme. Nearly one third of patients who were receiving a disease modifying treatment were experiencing difficulties with administration leading to potential discontinuation. With the restricted eligibility of onasemnogene abeparvovec and complications of administration of nusinersen the EAMS enabled the treatment gap for some patients to be reduced. Collection of longitudinal data for this complex population is recommended, to provide greater insights into the role of risdiplam in addressing patients' unmet needs.

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DATA AVAILABILITY

The data supporting the findings of this study are available within the article and/or its supplementary material.

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CONFLICT OF INTEREST

GB is PI of clinical trials Sponsored by Roche, Novartis, Sarepta, Pfizer, NS Pharma, Reveragen, Scholar Rock, and has received speaker and/or consulting fees from Sarepta, PTC Therapeutics, Pfizer, Biogen, Novartis Gene Therapies, Inc. (AveXis), and Roche, and grants from Sarepta, Roche and Novartis Gene Therapies.

NC has received sponsorship to attend conferences from Roche

AC has led symposia and participated in Ad boards for Roche and Biogen in the last 3 years and is PI for the Sapphire Study (Scholar Rock).

EW has undertaken consultancy for Roche and sponsored to attend meetings

IH has received Honoraria from Roche

DP is PI for Jewelfish study at UHB Birmingham and has been on temporary advisory board for Roche and sponsored to attend meetings by Roche.

TW has been on an advisory board for Roche

MS is involved as principal investigator in clinical trials from Roche, Biogen and Novartis.

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