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ORIGINAL RESEARCH

Adherence, Persistence, and Safety of Risdiplam in Spinal Muscular Atrophy: A Population-Based Cohort Study

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ABSTRACT

Introduction: Spinal muscular atrophy (SMA) is a rare neuromuscular disorder caused by biallelic SMN1 variants, partially modulated by SMN2 copy number. Risdiplam, an oral SMN2 splicing modifier, has demonstrated efficacy in SMA. However, long-term adherence and persistence are key to sustaining benefit. We evaluated real-world adherence, persistence, and safety of risdiplam in a population-based cohort.

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Methods: This was a retrospective observational study including all genetically confirmed SMA type 1–3 patients treated with risdiplam in Spain between January 2020 and October 2025. Adherence was assessed using the proportion of days covered (PDC) from pharmacy dispensing records and the Morisky–Green questionnaire. Persistence was defined as time to permanent discontinuation or switch. Adverse events (AEs) were extracted from clinical records, and Kaplan–Meier analysis was used to estimate persistence probabilities.

Results: Fifty-three patients were included (38 adults, 15 pediatric patients); 5.7% had SMA type 1, 52.8% type 2, and 41.5% type 3. One pediatric patient with SMA type 1 was presymptomatic at treatment initiation. Median age at risdiplam initiation was 29 years (interquartile range [IQR] 17–42), and 35.8% had prior nusinersen exposure. Adherence was high: median PDC was 100% (IQR 100–100) at 12 months and throughout follow-up; all patients assessed with the Morisky–Green questionnaire (35/53, 66%) were adherent. At 12 months, 92.5% (49/53) remained on treatment (Kaplan–Meier estimate 94.3%; 95% CI 88.3–100.0). Persistence at 24 and 36 months was 87.8% and 80.1%, respectively; later estimates should be interpreted cautiously because of the limited number of patients at risk. Median treatment duration was 28.1 months. Nine patients (17.0%) discontinued treatment. Treatment-related AEs occurred in 4/53 patients (7.5%), including one pediatric case of leukocytoclastic vasculitis requiring permanent discontinuation.

Conclusions: In this real-world population-based cohort, risdiplam showed very high adherence, favorable short- to mid-term persistence, and a favorable safety profile, supporting the feasibility of oral therapy in both pediatric and adult patients with SMA.

PLAIN LANGUAGE SUMMARY

Spinal muscular atrophy is a rare disease that leads to progressive muscle weakness and affects both children and adults. Risdiplam is an oral treatment that can be taken at home, which may be more convenient than other options that require repeated hospital visits or invasive procedures. In this study, we examined how well patients followed this treatment and how long they continued taking it in everyday clinical practice at a specialized center. We included a broad group of patients and followed them over time to better understand how the treatment performs outside clinical trials. We found that most patients took the medication consistently and continued treatment for prolonged periods. Only a small number stopped treatment, mainly due to side effects, lack of perceived benefit, or personal decisions. Overall, the treatment was well tolerated, with most side effects being mild, although one patient experienced a serious skin reaction that required discontinuation of treatment. These findings suggest that risdiplam is a practical long-term option in real-life settings, particularly because it can be taken at home. They also highlight that continuing treatment over time may reflect how patients and clinicians perceive its benefits and risks in daily practice.

Keywords: Adherence; Persistence; Real-world evidence; Risdiplam; Safety; Spinal muscular atrophy

Key Summary Points

Why carry out this study?

Spinal muscular atrophy (SMA) is a chronic, life-limiting neuromuscular disorder requiring long-term disease-modifying therapy, where sustained adherence and persistence are critical to maintaining clinical benefit.

Although risdiplam has shown efficacy and tolerability in clinical trials, long-term real-world data in population-based cohorts remain limited.

We evaluated real-world adherence, persistence, and safety of risdiplam in all genetically confirmed SMA type 1–3 patients treated in a regional population-based cohort in Spain.

What was learned from this study?

In 53 pediatric and adult patients, adherence was very high (median proportion of days covered 100% [interquartile range [IQR] 100–100]). Persistence probabilities were 94.3%, 87.8%, and 80.1% at 12, 24, and 36 months, respectively; estimates at later time points should be interpreted with caution because of the limited number of patients at risk. Treatment-related adverse events were infrequent (4/53, 7.5%), with one case of leukocytoclastic vasculitis requiring discontinuation.

These findings support the long-term feasibility, tolerability, and sustainability of once-daily oral risdiplam in routine clinical practice across a broad SMA population.

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder caused by biallelic deletions or pathogenic variants in the *SMN1* gene, leading to deficiency of survival motor neuron (SMN) protein. Residual production is partially compensated by the paralogous *SMN2* gene, which is able to produce a small amount of functional SMN protein; its variable copy number modulates disease severity in an inverse manner [1]. Progressive degeneration of anterior horn cells in the spinal cord and motor nuclei in the brainstem results in symmetrical, predominantly proximal muscle weakness and atrophy. With an estimated birth prevalence of 1 in 10,000 and a carrier frequency of 1:40–70, SMA represented the leading genetic cause of death in infants prior to the advent of disease-modifying therapies [1–3].

Clinically, SMA is categorized into phenotypes based on age at onset and maximal motor milestone achieved. Type 0 presents prenatally with respiratory failure at birth; type 1 (Werdnig–Hoffmann disease) manifests before 6 months of age and precludes independent sitting; type 2 (Dubowitz disease) usually arises before 18 months, permitting stable sitting but not independent ambulation; type 3 (Kugelberg–Welander disease) begins after 18 months and allows unaided walking; and type 4 presents in adulthood with the mildest clinical course [2, 3].

The advent of disease-modifying therapies in 2016 marked a turning point in the management of SMA, substantially changing its natural history [2]. The current therapeutic landscape includes nusinersen, an intrathecal antisense oligonucleotide that increases *SMN2* exon 7 inclusion but requires repeated lumbar punctures [4], and onasemnogene abeparvovec, an intravenous single-shot gene therapy delivering a functional *SMN1* transgene, though its use is limited by hepatotoxicity, thrombocytopenia, and eligibility restrictions [5]. Despite their clinical benefits, access limitations, treatment burden, and procedural challenges leave a subset of patients with unmet therapeutic needs.

Risdiplam (Evrysdi®) is the first oral *SMN2* splicing modifier, administered once daily and dosed according to age and body weight, addressing several of the limitations associated with intrathecal or gene-based therapies [6]. Risdiplam has demonstrated clinically meaningful improvements in motor function across different patient populations. Clinical trials, including RAINBOWFISH for presymptomatic patients, FIREFISH for infantile-onset SMA, and SUNFISH for later-onset SMA, have shown efficacy across the disease spectrum, together with a generally favorable safety profile characterized mainly by mild respiratory and gastrointestinal adverse events. This led to regulatory approval for patients with SMA types 1–3 or those with one to four *SMN2* copies [6, 7]. However, despite the advantages of oral administration, concerns remain regarding long-term adherence in a chronic lifelong treatment setting.

As risdiplam becomes integrated into routine clinical practice, real-world data on adherence, persistence, and safety are essential to complement evidence from clinical trials. A recent retrospective study reported high adherence and persistence at 12 months in the United States

[8], but real-world evidence remains limited, particularly with longer follow-up periods and in population-based cohorts.

Therefore, the aim of the present study was to assess real-world adherence, persistence, and safety of risdiplam in a population-based cohort of pediatric and adult patients with SMA types 1–3 treated in the Valencian region of Spain.

METHODS

Study Design and Population

This was a retrospective, observational, multidisciplinary, non-interventional, population-based study including all patients with SMA living in the Valencian region of Spain. The Valencian region has approximately 5,000,000 inhabitants, and all patients with SMA are followed and treated at Hospital Universitari i Politècnic La Fe: pediatric patients (≤ 16 years) in the Pediatrics Department and adult patients (> 16 years) in the Neurology Department.

In Spain, nusinersen has been available since March 2018, with access in selected cases through early access programs from 2017. Risdiplam was first available under compassionate use in 2020 for selected patients without access to nusinersen (e.g., complex spinal anatomy) and became widely available under public reimbursement in 2023. Patients were treated according to the Spanish national treatment protocol established in April 2018 and its subsequent revisions, based on the Spanish Delphi consensus [9]. This protocol defines inclusion, exclusion, and discontinuation criteria, as well as follow-up recommendations. Bridging therapies are not routinely publicly funded in Spain; however, switching between nusinersen and risdiplam is allowed. One patient in our cohort had temporary concomitant exposure during treatment transition.

The study was approved by the Clinical Research Ethics Committee of Hospital Universitari i Politècnic La Fe and conducted in accordance with the Declaration of Helsinki. Due to its non-interventional observational design based on routinely collected data, informed consent was not required, as determined by the Ethics Committee.

Eligible patients were those with genetically confirmed 5q-SMA who initiated risdiplam therapy between January 2020 and January 2025, irrespective of clinical phenotype or disease stage. Both treatment-naïve patients and patients previously treated with other disease-modifying therapies (nusinersen) were included, provided they initiated risdiplam during the study period. Patients lost to follow-up were excluded. No patients with SMA type 4 were identified in the cohort.

The overall follow-up period extended from January 2020 to October 31, 2025, corresponding to a maximum potential observation window of approximately 70 months.

Variables Under Study

Collected variables included demographic data (age and sex), clinical characteristics (SMA type, phenotype, and age at symptom onset), treatment-related variables (previous therapies and duration, age at risdiplam initiation, dosing regimen, treatment discontinuation and reasons), and adherence, persistence, and safety outcomes.

Risdiplam was dispensed monthly as a reconstituted oral solution through the hospital pharmacy. Most patients received 6.7 mL once daily; however, some pediatric patients received lower doses, with a minimum daily dose of 1.7 mL, according to age- and weight-based dosing recommendations. Patients or caregivers received standardized education on correct daily administration and were instructed to maintain a regular dosing schedule. Clinical follow-up visits were performed every 2 to 12 months, depending on patient age and disease severity, including assessment with age- and phenotype-appropriate motor scales and systematic collection of adverse events.

At each follow-up visit, or earlier if requested by the patient, continuation of risdiplam therapy was re-evaluated. Patients showing lack of clinical benefit, an unfavorable risk–benefit balance as assessed by the clinician and perceived by the patient, or poor adherence as assessed by

the clinician were advised to discontinue treatment or switch to nusinersen.

Follow-up for the present analysis continued until the earliest of permanent treatment discontinuation, death, or the study cutoff date.

Adherence

Adherence to risdiplam was primarily assessed using pharmacy dispensing records to calculate the proportion of days covered (PDC) at 12 months and across the entire follow-up period. A PDC ≥ 80% was considered indicative of good adherence [10]. Because dispensing dates may not perfectly reflect actual medication intake, dispensing delays were additionally assessed using a permissible gap (grace period) of 10 days, selected to reflect the local dispensing cycle (approximately 30–35 days between dispensations). Delays within this grace period were considered compatible with continuous treatment, whereas delays exceeding 10 days were classified as nonadherence episodes unless a clinically justified reason was documented (e.g., intercurrent illness, hospitalization, or temporary medical advice to hold treatment).

As a complementary measure, patients or caregivers completed the four-item Morisky–Green questionnaire, a validated self-report tool assessing medication-taking behavior (forgetfulness, carelessness, stopping treatment when feeling better, and stopping treatment when feeling worse). Each affirmative response scores 1 point, yielding a total score ranging from 0 to 4, with a score of 4 indicating full adherence. The Morisky–Green questionnaire was administered by the hospital pharmacist during routine medication dispensing visits within the 3 months prior to the study cutoff, based on the standard dispensing schedule whereby patients on active treatment collect medication approximately every 3 months.

Persistence and Discontinuation

Treatment persistence was defined as the time from risdiplam initiation to permanent treatment discontinuation or switch to another disease-modifying therapy. Temporary treatment interruptions were considered events for adherence but not for persistence analyses. Patients who remained on treatment at the end of follow-up were censored at their last dispensing or clinical visit.

Kaplan–Meier survival curves were used to estimate treatment persistence probabilities at 12, 24, and 36 months, with corresponding 95% confidence intervals (CIs).

Safety Assessment

All adverse events (AEs) and serious adverse events (SAEs) occurring during risdiplam treatment were collected from caregiver reports and medical records. For this analysis, the frequency and nature of treatment-emergent AEs and SAEs, as well as treatment discontinuations due to adverse events, were summarized.

Statistical Analysis

Statistical analyses were performed using R statistical software version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as median and interquartile range (IQR), and categorical variables as absolute number and percentage. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 55 patients with SMA treated with risdiplam were initially identified. Two patients were excluded because they were lost to follow-up after relocating to another region. Ultimately, 53 patients were included in the analysis: 38 adults and 15 pediatric patients.

Baseline Characteristics

The cohort comprised 53 patients, including three patients with SMA type 1 (5.7%), all of whom were pediatric patients, 28 patients (52.8%) with type 2 (18 adults and 10 pediatric), and 22 patients (41.5%) with type 3 (20

adults and 2 pediatric). No patients with SMA type 4 were identified in the cohort. Among the pediatric patients, one with SMA type 1 was presymptomatic at treatment initiation. Of the 53 patients included, 30 (56.6%) were female and 23 (43.4%) were male. The median age at risdiplam initiation was 29 years (IQR 17–42): 36 years (IQR 28.3–48.8) in adults and 13 years (IQR 8.5–16) in pediatric patients.

Nineteen patients (35.8%) had received prior disease-modifying therapy with nusinersen (14 adults and 5 pediatric), for a median duration of 26.0 months (IQR 16.6–51.0). The median number of nusinersen doses per patient was 12 (IQR 9–16). Baseline motor phenotype was predominantly sitter (29/53, 54.7%), followed by non-sitters (17/53, 32.1%) and walkers (7/53, 13.2%), with similar distributions in adult and pediatric subgroups (Table 1).

Treatment Adherence

Treatment adherence was high across the cohort (Table 2). All patients achieved PDC ≥ 80%. Among patients with available fixed-interval data at 12 months (n = 50), median PDC was 100% (IQR 100–100) in both adults and pediatric

Table 1 Baseline characteristics of patients included in the study. Pediatric patients are those ≤ 16 years of age at the start of risdiplam

Characteristics	All ($N = 53$)	Adults ($N = 38$)*	Pediatric patients ($N = 15$)*
Sex, *n* (%)			
Male	23 (43.4)	16 (42.1)	7 (46.7)
Female	30 (56.6)	22 (57.9)	8 (53.3)
Age at start of risdiplam (years), median (IQR)	29 (17–42)	36 (28.3–48.8)	13 (8.5–16)
Age at symptom onset (months), median (IQR)	12 (7–24)	15 (8–34.5)	7 (5.8–13.5)
Type of SMA, *n* (%)			
Type 1	3 (5.7)	–	3 (20.0)
Type 2	28 (52.8)	18 (47.4)	10 (66.7)
Type 3	22 (41.5)	20 (52.6)	2 (13.3)
Phenotype, *n* (%)			
Walkers	7 (13.2)	5 (13.2)	2 (13.3)
Sitters	29 (54.7)	20 (52.6)	9 (60.0)
Non-sitters	17 (32.1)	13 (34.2)	4 (26.7)
Discontinuation, *n* (%)	9/53 (17)	7/38 (18.4)	2/15 (13.3)
Prior nusinersen, *n* (%)	19/53 (35.8)	14/38 (36.8)	5/15 (33.3)
Concomitant nusinersen, *n* (%)	1/53 (1.9)	–	1/15 (6.7)
Switch to nusinersen, *n* (%)	3/53 (5.6)	1/38 (2.6)	2/15 (13.3)
Nusinersen doses, median (IQR)	12 (9–16)	12 (9–16.5)	12 (7.5–13.5)

SMA spinal muscular atrophy

* Percentage by age group

patients. Variable-interval PDC across the entire follow-up period was also high, with a median of 100% (IQR 100–100) in adults and 100% (IQR 100–100) in pediatric patients. Two pediatric patients showed slightly lower total PDC values (97.9% and 93.2%), while all remaining patients achieved a total PDC of 100%.

The Morisky–Green questionnaire was available for 35 patients (66% of the cohort), all of whom were classified as fully adherent (score = 4). The questionnaire was administered by the hospital pharmacist during routine medication dispensing visits in the 3 months prior to the study cutoff; at that time, nine patients were receiving medication through other hospitals and nine had already discontinued treatment, which precluded questionnaire administration. One pediatric patient experienced a temporary treatment interruption of approximately 3 weeks due to logistical issues related to medication storage during travel; this interruption was captured through dispensing records but did not result in permanent treatment discontinuation.

Treatment Persistence and Discontinuation

The median time on treatment was 28.1 months in the overall cohort, with 28.3 months (IQR 22.8–31.3) in adult patients and 27.2 months (IQR 16.8–50.9) in pediatric patients (Fig. 1, Table 2).

At 12 months, 49 of 53 patients (92.5%) remained on treatment; three patients discontinued risdiplam during the first year, one patient had not yet completed 12 months of treatment. Kaplan–Meier analysis estimated a 12-month persistence probability of 94.3% (95% CI 88.3–100.0). Discontinuations during the first year included one pediatric patient due to leukocytoclastic vasculitis and two adult patients: one due to gastrointestinal adverse events and one due to clinical deterioration. The latter patient died 8 months after risdiplam discontinuation for complications of the disease.

At 24 months, treatment persistence was assessable in 36 of 53 patients (67.9%), as 10 patients (7 adults and 3 pediatric) had not yet reached 24 months of follow-up. Three additional discontinuations occurred during the second year: two adults (one due to gastrointestinal adverse events and one after patient decision) and one pediatric patient due to nonadherence related to medication storage issues.

At 36 months, 11 patients had reached this time point. Three additional patients

Table 2 Adherence and persistence outcomes

Characteristics Adherence	All *N* = 53	Adults *N* = 38	Pediatric patients *N* = 15
PDC after 12 months, % (IQR)	100 (100–100)	100 (100—100)	100 (100–100)
Total PDC % (IQR)*	100 (100–100)	100 (100–100)	100 (100–100)
Persistence			
Number of patients, *n* (%)▲			
At 12 months	49/53 (92.5)	35/38 (92.1)	14/15 (93.3)
At 24 months	36/53 (67.9)	26/38 (83.9)	10/15 (66.7)
At 36 months	11/53 (20.8)	6/38 (15.8)	5/15 (33.3)
Time on treatment (months)	28.1 (18.9–28.1)	28.3 (22.8–31.3)	27.2 (16.8–50.9)

Abbreviations: *PDC* proportion of days covered

* During the study period (January 2020 to– October 31, 2025)

▲ Patients with ongoing treatment at each time point. Percentage of patients relative to the initial cohort included in the study

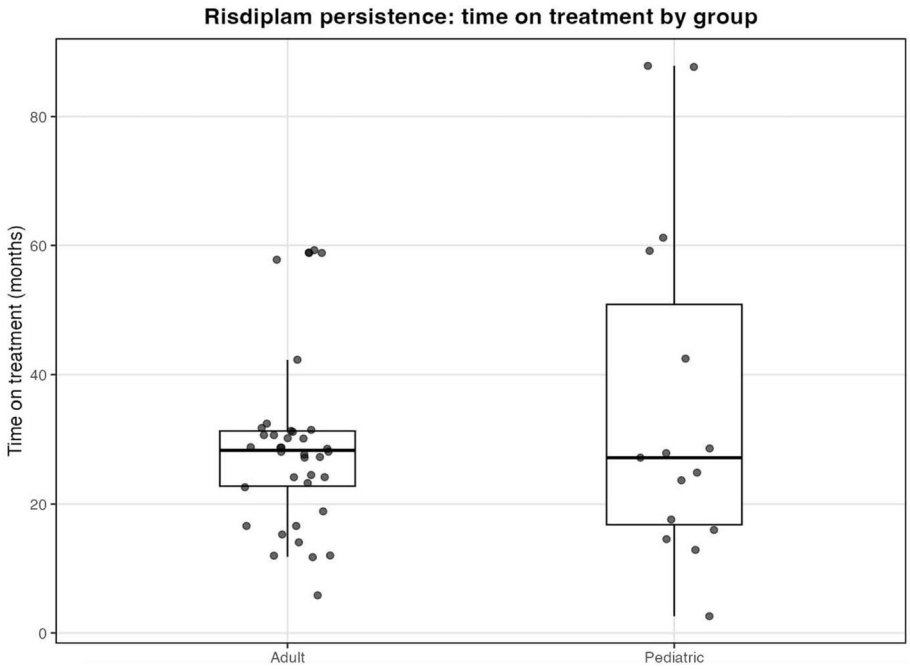

Fig. 1 Persistence with risdiplam treatment during the entire study period

discontinued treatment during the third year due to loss of clinical benefit.

Overall, nine patients (17.0%) permanently discontinued risdiplam during the study period: four due to lack or loss of clinical benefit as assessed by the physicians, three due to adverse events (two gastrointestinal and one leukocytoclastic vasculitis), one due to poor adherence, and one after patient decision against clinical recommendation because of lack of perceived benefit. Persistence probabilities at 12, 24, and 36 months were 94.3%, 87.8%, and 80.1%, respectively (Table 3, Fig. 2). These estimates should be interpreted with caution, particularly at later time points, due to the decreasing number of patients at risk and the increasing proportion of censored observations. A flow diagram summarizing patient selection, follow-up, and treatment status at each time point is provided in Fig. 3.

Safety

Risdiplam-related adverse events were identified in four patients (7.5%). Reported events included gastrointestinal symptoms (diarrhea, $n = 2$) and pyrexia ($n = 1$) in adults, and leukocytoclastic vasculitis in one pediatric patient. All events were considered mild except for leukocytoclastic vasculitis, which required

Table 3 Kaplan–Meier estimates of treatment persistence

Time point (months)	Treatment persistence (%)	95% confidence interval	Number of patients at risk	Number of discontinuations
12	94.3	88.3–100.0	49	3
24	87.8	79.0–97.5	36	3
36	80.1	69.1–92.9	11	3

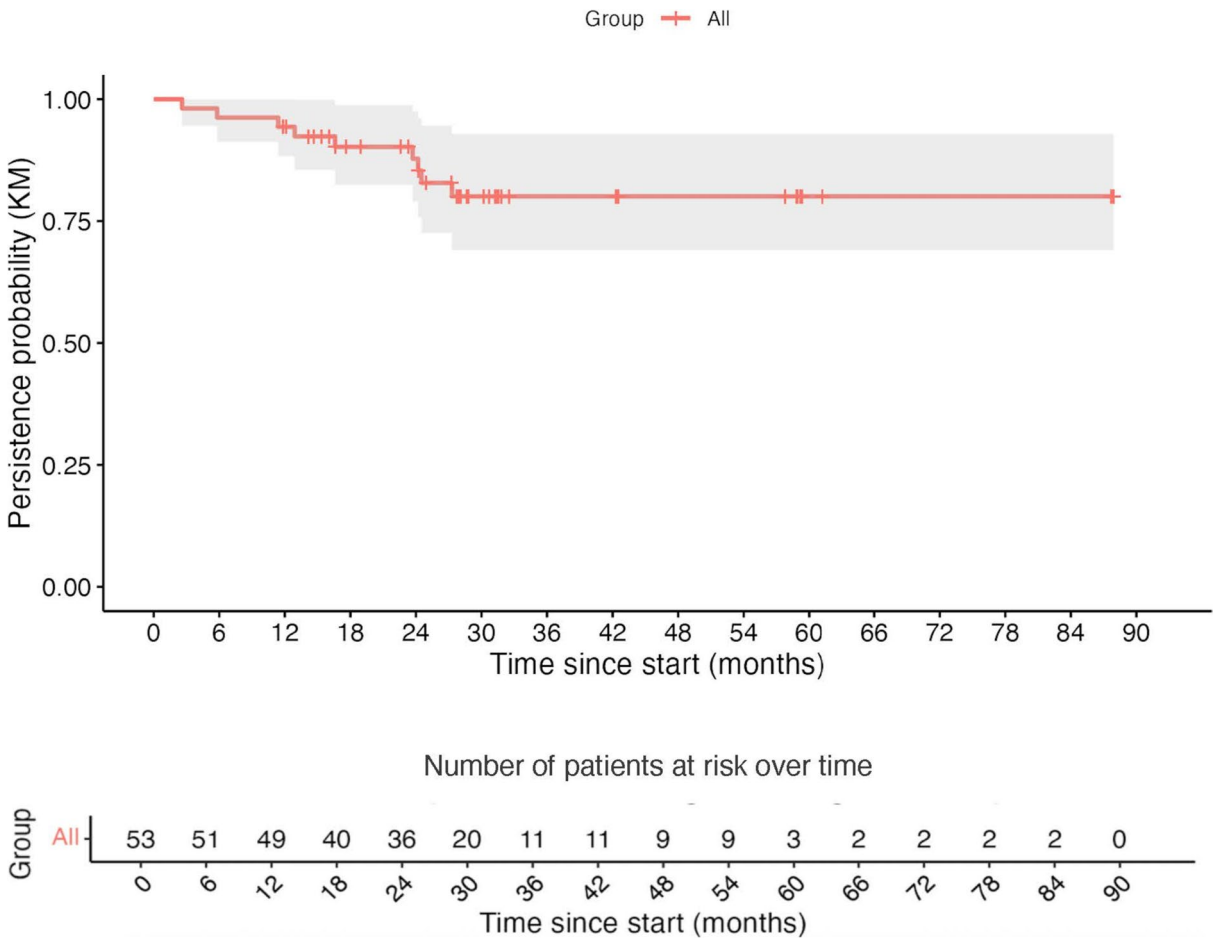

Fig. 2 Kaplan–Meier estimate of treatment persistence with risdiplam. The curve depicts the probability of remaining on risdiplam treatment over time. Shaded areas represent 95% confidence intervals. Vertical ticks indicate censored patients (i.e., those still on treatment at their last follow-up)

permanent treatment discontinuation. Three of the four adverse events led to permanent withdrawal of risdiplam. The case of leukocytoclastic vasculitis was reported to the Spanish Agency of Medicines and Medical Devices (AEMPS) and was subsequently incorporated as a post-marketing adverse drug reaction in the summary of product characteristics. Symptoms resolved after risdiplam discontinuation.

DISCUSSION

In this real-world, population-based cohort of patients with SMA treated at a tertiary care center, risdiplam demonstrated high and sustained adherence and persistence, together with a favorable safety profile after long-term follow-up. These findings support the feasibility of risdiplam as a long-term treatment option in routine clinical practice and suggest that the benefits observed in pivotal clinical trials may also translate to real-life settings. However, persistence estimates at later time points should be interpreted cautiously because of the limited number of patients at risk and the increasing impact of censored observations.

The high adherence and persistence observed in our cohort may partly reflect the structured multidisciplinary care model in our setting, including standardized patient and caregiver

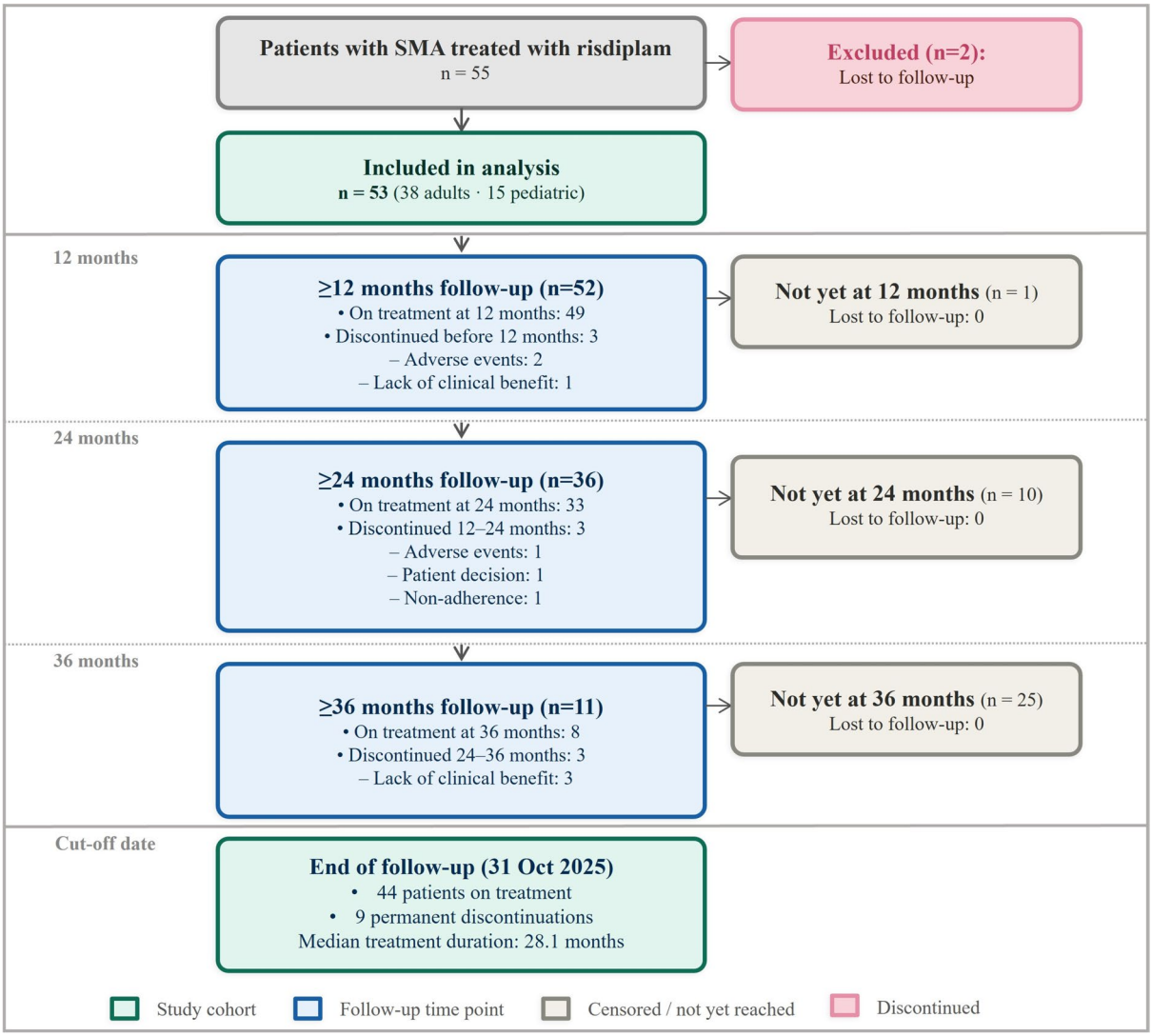

Fig. 3 Flow diagram of patient selection, follow-up, and treatment status. The diagram shows the number of patients with sufficient follow-up at 12, 24, and 36 months, those remaining on treatment, those who discontinued treatment (with reasons), and those not yet reaching each time point due to insufficient follow-up. No patients were lost to follow-up after inclusion

education, regular hospital-pharmacy dispensing, and clinician-led reassessment of treatment continuation. These features may favor treatment continuity in routine practice and should be considered when interpreting the results and their generalizability to other settings.

In the SUNFISH parts 1 and 2 studies, 5-year data in patients with SMA types 2 and 3 showed very high adherence (mean PDC close to 100%) and persistence, with only 11.7% of patients discontinuing treatment after 5 years [11]. In addition, most adverse events reported in these trials were mild, and no treatment-related adverse events led to permanent withdrawal. Some real-world studies support these findings. A short center-based observational study found strong persistence, with treatment interruptions being infrequent [12]. In a study capturing ≥ 98% of pharmacy claims for risdiplam-treated individuals in the United States, Pineda et al. reported adherence rates of 97–98% and 12-month persistence of 365 days (IQR 365–365)

using both > 60-day and > 90-day gap definitions [8].

Conversely, other real-world analyses have reported lower adherence estimates. Using a US health insurance claims database (IQVIA PharMetrics® Plus), Patel et al. observed lower adherence at 12 months (mean 0.98 and PDC 83.7%) in patients with SMA types 1–4, although persistence remained high during the first year (82.3–100%) [13]. In that study, adherence was lowest among patients with SMA type 4, who accounted for 23% of the study population, compared with approximately 1–2% of patients with SMA in most cohorts [14]. This overrepresentation of type 4 patients may partly explain the lower adherence observed and highlights the importance of unbiased population-based studies.

Although no head-to-head trials have directly compared risdiplam with nusinersen or onasemnogene abeparvovec, indirect evidence from real-world studies allows some considerations. In contrast to the high adherence and persistence observed with risdiplam, several real-world studies have reported lower persistence rates with nusinersen. In US claims-based analyses, only 61–70% of patients remained persistent at 12 months, with persistence declining to below 50% at 24 months and a median time to discontinuation of approximately 15 months [15, 16]. Other center-based and population-based studies have similarly shown treatment delays or interruptions in up to two thirds of adolescent and adult patients, frequently related to administration procedure burden, which becomes increasingly challenging with age, scoliosis, and complex spinal anatomy [17]. In adults with later-onset SMA, clinical progression may be slow and patients may not perceive deterioration over long periods; treatment benefits are therefore often subtle. In this context, long-term adherence and persistence can serve as real-world indicators of perceived benefit–risk balance and treatment sustainability.

Data from our own center, with a mean follow-up of 7 years, have also suggested a marked dichotomy in nusinersen persistence between younger children and older patients. Persistence remained high among patients who initiated treatment before adolescence, whereas it declined substantially in those starting therapy at older ages. In particular, the discontinuation rate was 75% among patients older than 12 years, compared with 5% in those younger than 12 years; notably, this 5% reflects a single case of a girl who died from causes unrelated to treatment. The median time to discontinuation in the overall cohort was 34 months [18]. This difference is likely attributable to the intrathecal route of administration, which requires repeated lumbar punctures, often under anesthesia, and becomes increasingly challenging with age, scoliosis, and complex spinal anatomy. By contrast, risdiplam offers the advantage of once-daily oral administration at home, which likely contributes to the high adherence and persistence observed in both pediatric and adult patients in our cohort.

Onasemnogene abeparvovec, while administered as a single intravenous dose, is reimbursed in Spain only for patients below a specific age and weight threshold (< 9 months of age and ≤ 13.5 kg), which restricts its use to a limited subgroup of individuals with SMA [5]. As a result, risdiplam represents a particularly relevant long-term option for a broad spectrum of patients who are not eligible for gene therapy or for whom intrathecal treatment is not feasible or accepted.

Compared with previous studies, our population-based cohort confirms very high adherence and favorable persistence of risdiplam, with a persistence rate of 87.8% at 24 months. These findings likely reflect a favorable overall benefit–risk balance and support the feasibility of once-daily oral treatment in routine clinical practice. Although treatment discontinuation was uncommon, two pediatric patients discontinued therapy: one due to poor adherence related to medication storage issues and one due to leukocytoclastic vasculitis. Notably, the patient who discontinued because of poor adherence had a relatively mild early phenotype [19], suggesting that individual clinical or practical factors may still affect treatment continuation in selected cases. While the results are encouraging, caution is warranted when extrapolating them to longer-term outcomes.

Regarding safety, our findings confirm the good tolerability profile of risdiplam observed

in clinical trials and are consistent with pharmacovigilance studies reporting a more favorable hepatic and renal toxicity profile compared with other treatment options [20]. In pivotal trials, up to 14% of patients experienced treatment-related adverse events—mainly infections and gastrointestinal disorders—whereas the incidence in our cohort was lower, approximately half that reported rate (4/53, 7.5%). However, three of these four cases required permanent treatment discontinuation. Reported adverse events were consistent with the product label [6], except for one case of leukocytoclastic vasculitis in a pediatric patient, which prompted regulatory notification and subsequent inclusion in the summary of product characteristics.

These findings are in line with previous real-world reports [21–23]. Sitas et al. described good tolerability in a cohort of 31 patients, with 74% experiencing no adverse events and only mild, transient effects such as headache and oral ulcers [19, 23]. In a compassionate use program including 111 patients, Hahn et al. reported gastrointestinal disorders as the most frequent adverse events, followed by headache, oral ulcers, constipation, and nausea [22]. Sever et al. reported adverse events in a small cohort of six previously treated patients, including diarrhea (67%), photosensitivity (67%), transient transaminase elevation (50%), and nephrolithiasis (33%) [21]. Although one case of cholelithiasis and one case of nephrolithiasis were observed in our study, a causal association with treatment could not be confirmed; consequently, they were not included in the reported treatment-related adverse event rate.

Overall, our data suggest that the oral formulation of risdiplam, its suitability for home administration, and the avoidance of invasive procedures are key differentiating factors that likely contribute not only to high adherence but also to patient satisfaction and long-term treatment sustainability. Nevertheless, certain logistical challenges were identified, particularly the need for refrigerated storage, which some patients perceived as inconvenient and would have preferred to manage independently at home. Enhanced patient education and empowerment to reconstitute the medication themselves, together with the future availability of alternative formulations (such as tablets), may further improve usability and adherence in routine clinical practice.

This study has limitations inherent to its observational design, including the absence of a control group, potential underreporting of mild adverse events, and the relatively small sample size, reflecting the rarity of SMA. Nevertheless, the cohort captures nearly all patients with SMA in the Valencian Community, partially mitigating the impact of the limited sample size and supporting the representativeness of the findings. In addition, adherence was partly assessed using the Morisky–Green questionnaire, a self-reported measure that may be subject to recall and social desirability bias, although this was complemented by a review of dispensing records to improve the robustness of adherence evaluation. Furthermore, the decreasing number of patients at risk at longer follow-up time points, together with the increasing proportion of censored observations, may limit the robustness of long-term persistence estimates, which should therefore be interpreted with caution.

CONCLUSIONS

Risdiplam demonstrated very high adherence and favorable short- to mid-term persistence in a heterogeneous population-based cohort of pediatric and adult patients with spinal muscular atrophy types 1–3, supporting the feasibility of long-term oral therapy in routine clinical practice. The treatment showed a favorable safety profile, with adverse events being infrequent and mostly mild, although continued pharmacovigilance remains warranted given the occurrence of rare but clinically relevant events. Overall, these findings highlight the value of population-based real-world studies in complementing clinical trial data and in supporting optimal treatment selection among the currently available disease-modifying therapies for spinal muscular atrophy. Additional long-term real-world evidence is needed to further characterize treatment durability and to inform individualized therapeutic decision-making.

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Declarations

Conflict of Interest. Maria Chovi-Trull has nothing to disclose. Nancy C. Ñungo-Garzón receives funding from the CUIDAME project (2019-027-1). Karolina A. Aragon-Gawinska is funded by the CIAPOT/2023/25. The Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) is an initiative of Instituto de Salud Carlos III. Inmaculada Pitarch-Castellano is a member of the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD) and has received personal fees for consulting and training activities from Biogen, Roche, and Novartis outside the submitted work. Asunción Albert-Marí has nothing to disclose. Javier García-Pellicer has nothing to disclose. José L. Poveda-Andrés has nothing to disclose. María D. Edo-Solsona has nothing to disclose. Juan F. Vázquez-Costa is a member of the advisory board of CUIDAME. He is funded by grants from the Instituto de Salud Carlos III (PI24/01512, DTS23/00112) and has received personal fees from Biogen, Roche, and Novartis outside the submitted work.

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