BMC Neurology

RESEARCH

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Risdiplam treatment in adults with spinal muscular atrophy: a single-center, real-world study

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Abstract

Background Spinal muscular atrophy (SMA) is a progressive, degenerative neuromuscular disease caused by mutations in the survival motor neuron 1 (*SMN1*) gene leading to muscle weakness and respiratory impairments. Risdiplam is an oral disease-modifying therapy approved for the treatment of SMA in both pediatric and adult patient populations; however, real-world data on the treatment of adults with SMA are limited.

Methods This real-world, retrospective study analyzed data from 11 patients with Types 2, 3, and 4 SMA who had been treated with risdiplam at a single center in Slovenia and had up to 30 months of follow-up. Disease progression was assessed using motor and respiratory outcome measures.

Results At baseline, patients had a mean (SD) age of 51 (20) years; range, 27–82 years. Baseline motor and respiratory function varied across the patient group. From baseline to month 30, stable motor function was observed for most patients over the treatment period, with no significant overall effect of time for Revised Upper Limb Module ($F=1.44$, $p=0.23$) or Revised Hammersmith Scale ($F=0.54$, $p=0.74$). Respiratory function was generally stable over 30 months of treatment with risdiplam: from baseline to month 30, no significant overall effect of time was observed for vital capacity ($F=1.20$, $p=0.32$), forced vital capacity ($F=0.93$, $p=0.47$), peak expiratory flow ($F=0.94$, $p=0.46$), maximal inspiratory pressure ($F=0.65$, $p=0.66$), maximal expiratory pressure ($F=1.25$, $p=0.31$), and sniff nasal inspiratory pressure ($F=1.10$, $p=0.38$).

Conclusions This real-world study suggests that risdiplam treatment for adults with Types 2, 3, and 4 SMA generally stabilizes motor and respiratory function over 30 months. These results add to the limited database of risdiplam treatment outcomes in adults with SMA, support the continued use of risdiplam for adults with SMA, and may help patients and clinicians to understand and assess treatment options.

Keywords Spinal muscular atrophy, Risdiplam, Adults with SMA, Motor function, Respiratory function, Real-world study

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Background

Spinal muscular atrophy (SMA) is a degenerative neuromuscular disease affecting approximately 1 in 3,900–16,000 newborns, characterized by progressive muscle weakness and wastage, respiratory complications, and eventual death [1, 2]. The autosomal recessive disease is caused by homozygous mutations in the survival motor neuron 1 (*SMN1*) gene that prevent or reduce expression of the SMN protein, resulting in degeneration of alpha motor neurons [1, 2].

To date, there are three disease-modifying therapies for the treatment of SMA, each with distinct mechanisms of action, that have received regulatory approval by the European Medicines Agency, the US Food and Drug Administration, and other health authorities worldwide [2]. These therapies all act by increasing SMN protein expression: the intravenously administered gene therapy onasemnogene abeparvovec delivers a functional *SMN1* gene copy to motor neurons; the intrathecally administered antisense oligonucleotide nusinersen alters pre-mRNA *SMN2* splicing; and the orally administered risdiplam modifies *SMN2* mRNA splicing to promote the inclusion of exon 7 [1–3]. Availability of these treatment options has improved patient quality of life and increased survival times, changing the clinical phenotype of SMA, including in the older patient population [2].

Risdiplam was the first oral disease-modifying therapy approved for the treatment of SMA in both pediatric and adult patient populations; however, efficacy is best understood in the pediatric population, with most clinical trial data collected from infants [3–7]. Adult efficacy has been evaluated in the JEWELFISH (NCT03032172; enrolled non-treatment-naïve patients aged 6 months–60 years) and SUNFISH (NCT02908685; enrolled patients aged 2–25 years) clinical trials [3, 5, 6]. Over 24 months of treatment with risdiplam, post-hoc analyses in the JEWELFISH study found that motor function stabilized in patients aged 25–60 years, while exploratory efficacy measures in the SUNFISH study showed stabilization or improvement of motor function, with greater improvements observed in younger patients (aged 2–11 years) versus older patients (12–25 years) [3, 5].

Real-world evidence of risdiplam treatment in adults with SMA is limited by both number of studies and patients, particularly in those aged > 25 years, despite approximately one third of the SMA population being adults [8]. One single-center study found that, over 30 months of treatment with risdiplam in the real-world setting, 14 patients with SMA aged 18–57 years achieved clinically meaningful improvement on assessments of motor function, and respiratory function stabilized [7]. Similar results of improved or stabilized motor and respiratory function were observed in a study of 18 patients with Types 2, 3, and 4 SMA with a mean (SD) age of 38.6 (13.5) years, treated with risdiplam for up to 24 months [9]. Another study of six adult patients with SMA, aged 21–65 years, found sustained improvement in motor function up to 27 months of risdiplam treatment [10]. Motor function improvements have similarly been observed in non-sitter patients treated with risdiplam (six patients aged 17–46 years), with stabilized or improved respiratory outcomes also demonstrated after 1 year [11].

A greater resource of real-world evidence for risdiplam treatment in adults with SMA is needed to help patients and clinicians understand and assess treatment options. This study aimed to assess motor function and respiratory outcomes in adult patients aged > 25 years treated with risdiplam for up to 30 months at a single center in Slovenia.

Methods

Study design

This retrospective study analyzed data from previously treatment-naïve patients with Types 2, 3, and 4 SMA, who had been treated with risdiplam at a single center in Slovenia and had up to 30 months of follow-up between May 2022 and April 2025. The study was conducted at the Institute of Clinical Neurophysiology, Division of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the National Medical Ethics Committee of Republic of Slovenia (0120–293/2019/8). Clinical trial number: not applicable.

Functional outcomes were measured using the Revised Upper Limb Module (RULM) and Revised Hammersmith Scale (RHS). The RULM is a 20-item clinical scale (one entry item and 19 functional tasks) that measures motor performance in the upper limbs of individuals with SMA [12]. Excluding the entry item, tasks are scored on a scale from 0 to 2, resulting in a total score range of 0 to 37, with higher scores indicating better functionality [12]. A change in the RULM score of 2–3 points is considered to be clinically meaningful [13]. The RHS is a 36-item clinical scale, developed to assess gross motor function in individuals with SMA [14]. Scores range from 0 to 69 (33 items scored from 0 to 2, and three items scored from 0 to 1), where higher scores reflect better motor function [14].

Respiratory outcomes were evaluated through % predicted vital capacity (VC), forced vital capacity (FVC), and peak expiratory flow (PEF), sniff nasal inspiratory pressure (SNIP), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP).

Patients were assessed every 6 months from baseline to month 30, although not all patients contributed data at every time point.

Table 1 Number of patients followed up from baseline to month 30

Parameter, n	Baseline	6 months	12 months	18 months	24 months	30 months
Functional outcomes						
RULM	11	11	10	10	10	9
RHS	11	7	7	7	5	10
Respiratory outcomes						
VC	11	10	9	9	9	9
FVC	11	10	9	9	9	9
MEP	10	10	9	8	6	8
MIP	10	10	9	8	6	8
SNIP	11	10	9	9	9	9
PEF	11	10	9	9	9	9

Abbreviations: FVC forced vital capacity, *MEP* maximal expiratory pressure, *MIP* maximal inspiratory pressure, *PEF* peak expiratory flow, *RHS* Revised Hammersmith Scale, *RULM* Revised Upper Limb Module, *SNIP* sniff nasal inspiratory pressure, *VC* vital capacity

Statistical analyses

Data were analyzed using a linear mixed-effects model to account for the longitudinal nature of the study and the inherent correlation between repeated measurements within the same patient. All analyses were performed in R (version 4.5.3) using the lme4 and lmerTest packages. For each clinical parameter for each 6-month period, time (month) was entered as a fixed effect, and patient ID was included as a random effect (random intercept) to account for baseline variability between participants. The overall effect of time on each parameter was evaluated using Type III Analysis of Variance with Satterthwaite's method for approximating degrees of freedom. To identify specific time points where parameters significantly deviated from baseline, the fixed-effects coefficients of the model were examined, using the baseline (month 0) as the reference category.

Table 2 Patient demographics and baseline characteristics

Demographic and baseline characteristic	All patients (*N* = 11)
Age, mean (SD), years	51 (20)
Sex, n (%)	
Male	2 (18.2)
Female	9 (81.8)
SMA type, n (%)	
Type 2	2 (18.2)
Type 3	8 (72.7)
Type 4	1 (9.1)
SMN2 copy number, n (%)	
3	4 (36.4)
4	4 (36.4)
Unknown	3 (27.3)
Ambulatory status, n (%)	
Ambulatory	2 (18.2)
Non-ambulatory	9 (81.8)
RULM, mean (SD), points	14 (11)
RHS, mean (SD), points	7 (11)
Ventilation use, n (%)	
Non-invasive nighttime ventilation	4 (36.4)
Invasive ventilation	1 (9.1)
No ventilation support	6 (54.5)
VC, mean (SD), % predicted	59 (36)
FVC, mean (SD), % predicted	60 (36)
PEF, mean (SD), % predicted	60 (28)
SNIP, mean (SD), cmH_2O	71 (31)
MIP, mean (SD), cmH_2O	67 (32)
MEP, mean (SD), cmH_2O	61 (35)

Abbreviations: FVC forced vital capacity, *MEP* maximal expiratory pressure, *MIP* maximal inspiratory pressure, *PEF* peak expiratory flow, *RHS* Revised Hammersmith Scale, *RULM* Revised Upper Limb Module, *SMA* spinal muscular atrophy, *SMN2* survival motor neuron 2, *SNIP* sniff nasal inspiratory pressure, *VC* vital capacity

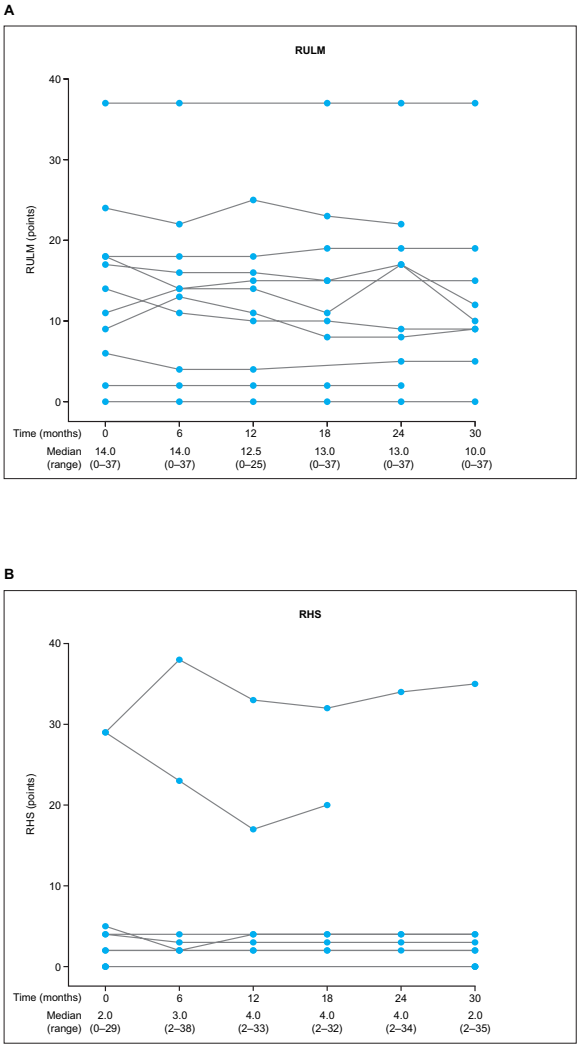

Fig. 1 RULM and RHS scores over 30 months of treatment with risdiplam. *Abbreviations*: *RHS* Revised Hammersmith Scale, *RULM* Revised Upper Limb Module

Results

Patients

A total of 11 patients with SMA, nine females and two males, were followed for up to 30 months after initiation of treatment with risdiplam (Table 1). Of the 11 patients, two had Type 2 SMA, eight had Type 3 SMA, and one had Type 4 SMA. Prior to treatment with risdiplam, all patients were treatment naïve. Patients did not receive other supportive therapy such as organized physiotherapy. The mean (SD) age at baseline was 51 (20) years; range, 27–82 years (Table 2). One female patient aged 75 years died following pneumonia, heart failure, and multiorgan failure after 24–30 months of risdiplam treatment. This event was not attributed to risdiplam treatment . Another female patient was followed for only 24 months.

Mean (SD, range) RULM score at baseline was 14 (11, 0–37) points. Median (Q1–Q3, range) RHS score at baseline was 2 (0–5, 0–29) (did not pass normality test). Four patients had an RHS score of 0 points and four patients had RHS scores of >0 to <5 points.

Respiratory function varied across the patient group. Mean (SD) % predicted VC, FVC, and PEF at baseline were 59 (36) %, 60 (36) %, and 60 (28) %, with a range of 10–135%, 9–135%, and 12–103%, respectively. SNIP, MIP, and MEP had mean (SD) baseline values of 71 (31) cmH_2O, 67 (32) cmH_2O, and 61 (35) cmH_2O, with a range of 16–121 cmH_2O, 18–110 cmH_2O, and 20–130 cmH_2O, respectively.

Functional outcomes over 30 months

From baseline to month 30, RULM and RHS scores were stable for most patients over the treatment period. At month 30, seven (11%) patients remained stable on the RULM from baseline, while four (36%) patients experienced a decline of ≥2 points from baseline. The overall effect of time was not significant for either RULM ($F=1.44$, $p=0.23$) or RHS ($F=0.54$, $p=0.74$) (Fig. 1A). Only six of the patients followed to month 30 could complete the RHS (three patients were unable to perform any task on the test, so scored 0 points at all visits). One patient (who was followed for 24 months only) had their last RHS assessment at month 18. Five of the six patients followed to month 30 had baseline RHS scores of <5 points and had stable scores at month 30. The remaining patient with 30-month follow-up, as well as the patient followed for 24 months only, had baseline RHS scores of 29 points, which fluctuated over time and did not follow a specific trend, with last recorded RHS scores of 35 points at month 30 and 20 points at month 18, respectively (Fig. 1B).

Respiratory outcomes over 30 months

Respiratory function was generally stable over 30 months of treatment with risdiplam. From baseline to month 30, there was no statistically significant overall effect of time for VC ($F=1.20$, $p=0.32$), FVC ($F=0.93$, $p=0.47$), and PEF ($F=0.94$, $p=0.46$) (Fig. 2A–C). Similarly, no significant overall effect of time was observed for MIP ($F=0.65$, $p=0.66$), MEP ($F=1.25$, $p=0.31$), and SNIP ($F=1.10$, $p=0.38$) (Fig. 2D–F). MIP and MEP were not routinely measured at all outpatient visits: the number of patients with available data across time points ranged from 6 to 10, with eight patients with available data at month 30.

Discussion

The findings of this study add to the currently limited data available for real-world evidence of risdiplam treatment in adults with SMA. Natural history data show patients with SMA typically experience a mild but progressive decline in upper limb function over 24 months without treatment [15]. Over 30 months of treatment

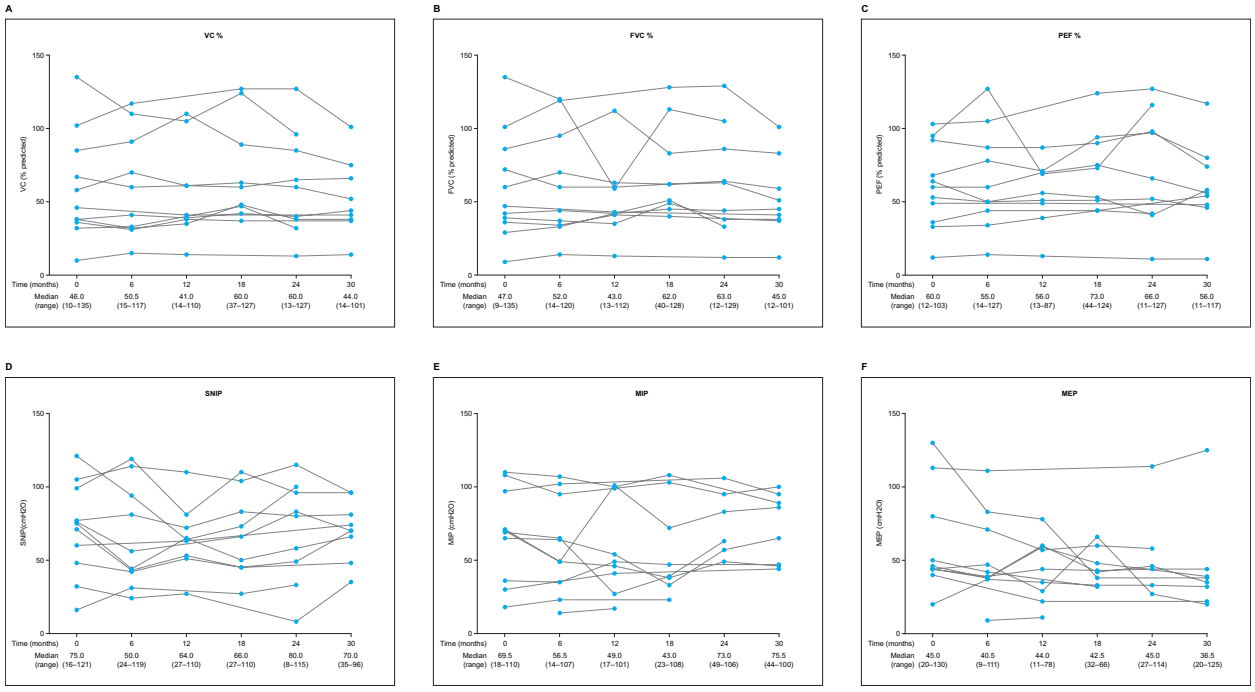

Fig. 2 Respiratory function over 30 months of treatment with risdiplam (**A**) VC%, **B** FVC %, **C** PEF %, **D** SNIP, **E** MIP, **F** MEP. *Abbreviations:* , forced vital capacity, *MEP*, maximal expiratory pressure, *MIP*, maximal inspiratory pressure, *PEF*, peak expiratory flow, *SNIP,* sniff nasal inspiratory pressure, *VC*, vital capacity

with risdiplam, the 11 previously treatment-naïve patients in this study appeared to generally experience stable motor function, as measured by the RULM. While there was no control group for direct comparisons and to allow specific assessment of treatment effect, this stabilization of motor function suggests a divergence from expected natural history [15, 16]. Further follow-up of the trend in this patient group is necessary to give clinically important insight into disease progression over time. While the RHS was limited to only six patients with follow-up to month 30, scores were generally stable over 30 months for patients with lower baseline scores and showed no specific trend for patients with higher baseline scores. In 2026, Parmova O. et al. reported real-world evidence in 59 adults with 5q-SMA treated with risdiplam, 15 of whom had previously received treatment with nusinersen [17]. They observed that RULM results improved during the first 6 months of risdiplam treatment and remained stable for 2–3 years [17]. While Parmova O. et al. noted an early improvement in motor function, the current findings demonstrated generally stabilized scores over 30 months [17]. Given the progressive decline expected in adults with SMA, patient-reported outcome studies have found that adult patients aged 19–64 years have identified stability of motor function as an important treatment goal, to allow maintenance of independence, suggesting that the results from the present study may be meaningful to these patients, although no patient-reported outcomes were collected, and a direct treatment effect cannot be concluded in the absence of a control arm [18]. While previous studies have reported improvement of motor function with long-term risdiplam treatment in adults, given the heterogeneity of patients followed in this real-world study, namely in age, SMA type, and baseline motor function, the identification of trends and understanding of outcomes in more specific populations were limited; it is understood that baseline motor function, age, and previous treatments can significantly impact treatment responses [7, 9–11, 19]. Of note, all patients in this study were treatment naïve prior to treatment with risdiplam.

Natural history respiratory data for adult patients with SMA are limited, but it has been observed that % predicted PEF typically declines by 1–2% per year in patients with Types 2 and 3 SMA, although relative stabilization is often observed in adulthood [20]. In this study, patients showed stable respiratory function over 30 months of risdiplam treatment, as measured by % predicted VC, FVC, PEF, and SNIP, in alignment with previous reports of adult risdiplam treatment, including by Parmova O. et al., who observed stabilization in respiratory function over up to 3 years in adults with SMA [7, 9, 11, 17]. One single-center study of adult treatment-naïve patients with Types 2, 3, and 4 SMA demonstrated that treatment with risdiplam over 24 months resulted in divergence from expected decline in respiratory function calculated from retrospective data [9]. The loss of respiratory function is reported as one of the most frequent concerns for adult

patients with SMA, suggesting that maintenance of respiratory function over the length of this study is an important outcome for patients [18].

Previous real-world reports of treatment with risdiplam in adults with SMA are limited, particularly in older adults aged > 25 years. The current study, which followed a significantly older patient group with a mean (range) age of 51 (27–82) years, contributes to this gap in the understanding of treatment in this population, providing valuable insight into functional and respiratory treatment outcomes for older adults with SMA who have not previously received disease-modifying therapy.

This study is limited by the small patient group, as well as the lack of a control group. Not all patients were able to complete all outcome measures, and not all patients had follow-up to 30 months, limiting our understanding of disease progression across the patient group. It should be noted that patients in the current study did not receive any organized physical therapy, which could have impacted treatment outcomes. Safety data were not systematically collected in this study, limiting the overall assessment of risdiplam therapy in this population in terms of both efficacy and safety.

The patients in this study will continue to be followed over the longer term to add to our understanding of the trends observed. Future studies should continue to collect longitudinal data on risdiplam treatment in adults with SMA, particularly those aged > 25 years, to build upon the real-world evidence available.

Conclusions

Treatment outcomes following risdiplam therapy in adults with SMA are not well understood due to limited long-term data availability. This real-world study suggests that motor and respiratory function, which are important treatment outcomes for this patient population, are generally stable over 30 months of treatment with risdiplam in adults aged 27–82 years with Types 2, 3, and 4 SMA. Our findings add to the available data of risdiplam treatment outcomes in adults, particularly in an older, treatment-naïve population, and support the continued use of risdiplam for adults with SMA.

Abbreviations

FVC	Forced vital capacity
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
PEF	Peak expiratory flow
RHS	Revised Hammersmith Scale
RULM	Revised Upper Limb Module
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SNIP	Sniff nasal inspiratory pressure
VC	Vital capacity

Acknowledgments

Medical writing and editorial assistance were provided by Emily Turner, BSc, CMPP, of Nucleus Global, in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022), funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Authors' contributions

Lea Leonardis, Pija Pukšič Šimek, Sara Kadenšek, and Blaž Koritnik contributed equally to the study design, data collection, data analysis and interpretation. All authors contributed to manuscript writing, critically reviewed the final version, approved the submitted manuscript, and agreed to be accountable for all aspects of the work.

Funding

This study was funded by The Republic of Slovenia Research Agency, grant number P3-0338.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted at the Institute of Clinical Neurophysiology, Division of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the National Medical Ethics Committee of Republic of Slovenia (0120–293/2019/8). Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 31 October 2025 / Accepted: 19 May 2026
Published online: 30 May 2026

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