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Spinal muscular atrophy type 3 and treatment adherence in a changing therapeutic landscape: a national-center experience

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Aim To report on treatment outcomes in adult patients with spinal muscular atrophy type 3 (SMA3) who had their nusinersen treatment initiated in adulthood.

Methods The study enrolled 11 adults treated with nusinersen for SMA3 at the Croatian National Referral Centre for Neuromuscular Disorders from 2019 to 2022. We prospectively collected validated SMA outcome measures: Revised Hammersmith score (RHS), Revised Upper Limb Module, and 6-minute walk test (6MWT) as motor function outcomes and the Individualized Neuromuscular Quality of Life questionnaire. Baseline outcomes were compared with the outcomes after three years of treatment.

Results All patients reported subjective improvement, and 9/11 reported an increased quality of life. Overall, 10/11 patients experienced clinically significant improvement in at least one measured outcome, while the remaining 1 patient reported the absence of disease progression. The mean increase in RHS was 2.7 points ($P=0.062$), and the mean increase in 6MWT was 39.7 m ($P=0.239$). Younger age and shorter disease duration correlated with better treatment outcomes ($r=-0.543$ and $r=-0.666$, respectively). After the approval of risdiplam in 2022, a third of patients chose to switch therapies despite observed subjective and objective positive nusinersen treatment effects.

Conclusion Nusinersen had a positive treatment effect despite missed doses during the COVID-19 pandemic. Although the most significant improvements can be expected in patients treated the earliest, nusinersen treatment can be beneficial even in long-standing SMA.

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Spinal muscular atrophy (SMA) is a progressive, autosomal recessive motor-neuron disease caused by a mutation in the survival motor neuron 1 (*SMN1*) gene leading to insufficient SMN protein expression with muscle weakness and atrophy (1,2).

In 2016, the US Food and Drug Administration approved the first SMA-specific medication, nusinersen. It targets *SMN2* – a gene that encodes a truncated SMN protein, which is dysfunctional due to the exclusion of exon 7 from RNA. Nusinersen binds to premessenger RNA, modifying its splicing to promote the expression of a full-length functional SMN protein (2). SMA is typically classified into five subtypes based on the age at which symptoms appear and motor milestones achieved. SMA type 3 (SMA3) is on the milder end of the spectrum, with symptoms becoming apparent after 18 months of age (3a) or 3 years (3b). SMA3 patients are able to walk independently at least for a time (3). Studies of SMA natural history have revealed a slow and progressive decline in motor functions in all disease subtypes, including ambulatory function in SMA3 (4-7). Nusinersen is most effective when given earlier in the disease (8), with uncertainties and questions regarding treatment effects in adult patients. Our aim was to report the outcomes of adult (>18 years) SMA3 patients, predominantly walkers, in whom nusinersen treatment was initiated in adulthood.

PARTICIPANTS AND METHODS

The study enrolled 11 adults treated with nusinersen for SMA3 at the Croatian National Referral Centre for Neuromuscular Disorders from 2019 to 2022. Validated SMA outcome measures were prospectively collected during nusinersen treatment. All the patients had a confirmed homozygous deletion of the *SMN1* gene and at least two copies of the *SMN2* gene, which is a requirement for nusinersen treatment approval in Croatia. All patients were treated with intrathecal loading doses of 12 mg on day 0, 14, 28, and 63, followed by a maintenance dose on day 180. In winter 2020 and 2021, doses were postponed due to the COVID-19 pandemic. Intrathecal injections were administered using standard access in all patients except one, who underwent fluoroscopy-guided lumbar puncture. Demographics and clinical characteristics were noted, along with patient-reported experiences and adverse events. SMA outcome measures including the Revised Upper Limb Module (RULM), Revised Hammersmith Score (RHS), and 6-Minute Walk Test (6MWT) were collected during routine patient visits before commencing treatment and during treatment. A change in RHS and RULM scores of three points was considered clinically meaningful (2,9), which is why this cut-off was used in other clinical studies (10) and in our study. Regarding the 6MWT, a difference of 30 m was considered clinically meaningful (6,7,11). We reported on the outcomes recorded on the baseline visit and three years after the beginning of treatment.

The RHS was used instead of Hammersmith Functional Motor Scale Expanded, since the RHS is more sensitive in recording changes in functionally stronger patients, such as those included in our study (12). The quality of life was assessed with Individualized Neuromuscular Quality of Life questionnaire (INQoL), a questionnaire validated in muscle disease (13). A lower INQoL score indicates a higher quality of life. The research was approved by the Ethics Committee of University Hospital Center Zagreb. The informed consent for the study was waived because all procedures were part of routine clinical care and performed as standard practice within the medical institution.

Statistical analysis

The normality of distribution was assessed with a Shapiro-Wilk test. A paired-samples *t* test and Wilcoxon signed-rank test were used to assess the significance of changes in the measured parameters before and after the intervention. Pearson correlation coefficient was calculated to assess the relationship between specific characteristics and clinical outcomes. The correlation was interpreted as follows: very weak (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80-1.00). The level of significance was set at $P < 0.05$. The statistical analysis was performed with SPSS, version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline demographics and characteristics

The study enrolled 11 patients (seven men) with a median age of 30 years (range 23-42 years). All but one patient were able to walk independently (defined as being able to walk at least five steps without assistance) (Table 1). All patients reported normal bulbar function and no history of respiratory issues or impairment. The mean baseline RHS score was 44.3 out of 69 (SD 16.5; range 19-65). The mean baseline RULM score was 33.7 out of 37 (SD 5.2; range 23-37). The baseline 6MWT was completed by eight patients who could walk more than

five steps. The mean score was 338 m (SD 72.3; range 166 m-413 m). One patient was excluded from further analysis as he was unable to complete the follow-up test due to a femur fracture (Table 2). The mean baseline INQoL score was 66.4 (SD 27.6; range 31-105).

Treatment effects

All patients were treated with nusinersen for three years. All reported subjective improvement, most frequently an impression of reduced fatigue (10/11; Figure 1). The mean RHS score increased from 44.3 (SD 16.5) to 47.1 (SD 16.1) after three years of treatment (+2.7 mean increase, $P=0.062$). The mean RULM score increased from 33.7 (SD 5.2) to 34.1 (SD 5.2; +0.4 mean increase, $P=0.317$). The mean 6MWT increased from 337.7 m (SD 72.3) to 377.4 m (SD 98.5), with a change of +39.7 m (SD 80.3, $P=0.239$). None of the changes were statistically significant. The mean change in INQoL was -7.8, but it was not significant ($P=0.073$).

Six patients did not experience clinically significant change in RHS, but five experienced a significant improvement, two of whom had an impressive 10-point increase. Patients with an increased RHS score experienced improved hip flexion/extension/adduction. Two patients regained the ability to get up from a chair. Three patients had a two-point improvement in RULM, with seven of the eight remaining patients maintaining the score over the three years. Regarding 6MWT, five out of seven patients who were able to perform the follow-up test showed clinically significant improvement. Two patients who were considered walkers but were unable to walk for six minutes improved their walking distance to 10 m (Table 2). All patients reported side effects, most frequently post-lumbar puncture headache (Figure 1).

Pearson correlation coefficient was calculated to assess the relationship between specific clinical characteristics and outcomes. No significant correlation was observed

TABLE 1. Patients' baseline characteristics

Patient	*SMN2* copies	Age at disease onset (years)	Disease duration before treatment (years)	Age at first application
1	4	9	23	32
2	3	2	24	26
3	4	16	13	29
4	4	18	11	29
5	3	3	27	30
6	4	17	6	23
7	3	9	23	32
8	4	14	28	42
9	4	12	30	42
10	4	7	15	22
11	4	10	31	41

TABLE 2. Nusinersen treatment effects as assessed by Revised Hammersmith Score (RHS), Revised Upper Limb Module (RULM), Six-minute Walk Test (6MWT), and Individualized Neuromuscular Quality of Life (INOQoL)

Patient	RHS baseline	RHS 3 years in treatment	RHS change	RULM baseline	RULM 3 years in treatment	RULM change	6MWT baseline	6MWT 3 years in treatment	6MWT change	QOL baseline	QOL 3 years in treatment	QOL change	Therapy switch
1	54	64	+ 10	37	37	0	280	409	+ 129 m	49	14	-35	
2	26	32	+ 6	23	23	0				96	79	-17	yes
3	64	65	+ 1	37	37	0	413	519	+ 106 m	105	104	-1	
4	65	65	0	37	37	0	397	440	+ 43 m	76	74	-2	
5	27	37	+10	37	37	0				96	93	-3	
6	60	64	+ 4	37	37	0	398	280	- 118 m	33	28	-5	
7	19	19	0	25	27	+ 2				79	88	9	yes
8	51	49	- 2	35	37	+ 2	352	421	+ 69 m	57	50	-7	yes
9	52	51	- 1	37	37	0	304	338	+ 34 m	42	26	-16	
10	37	36	- 1	31	29	- 2	166			60	74	14	
11	33	36	+ 3	35	37	+ 2	220	235	+ 15 m	31	30	-1	yes

between age at treatment initiation or disease duration and changes in RHS scores. A moderate negative correlation was identified between the age at disease onset and RHS change (r = -0.466).

A moderate negative correlation was found between changes in RHS and QOL (r = -0.558), as well as between disease duration and changes in 6MWT (r = -0.543). Additionally, a strong negative correlation was observed between age and 6MWT change (r = -0.666). A moderate negative correlation was noted between changes in QOL and 6MWT (r = -0.426). However, none of these correlations reached statistical significance.

Treatment administration deviations and patient adherence

All of the patients received intrathecal loading doses followed by a maintenance dose on day 180. In winter 2020 and 2021, doses were postponed due to the COVID-19

TABLE 3. Nusinersen dosing schedule and missed applications during the COVID-19 pandemic

Patient	Loading doses	Maintenance dose 1	Maintenance dose 2 (autumn 2020)	Maintenance dose 3 (winter 2020/2021)	Maintenance dose 4	Maintenance dose 5 (winter 2021/2022)	Maintenance dose 6	Maintenance dose 7
1	✓	✓	✓	✓	✓	✓	✓	✓
2	✓	✓	✓		✓	✓	✓	✓
3	✓	✓	✓	✓	✓		✓	✓
4	✓	✓	✓	✓	✓		✓	✓
5	✓	✓	✓		✓		✓	✓
6	✓	✓	✓		✓		✓	✓
7	✓	✓	✓		✓		.	.
8	✓	✓	✓		✓		✓	✓
9	✓	✓			✓		✓	✓
10	✓	✓			✓		✓	✓
11	✓	✓			✓		✓	✓

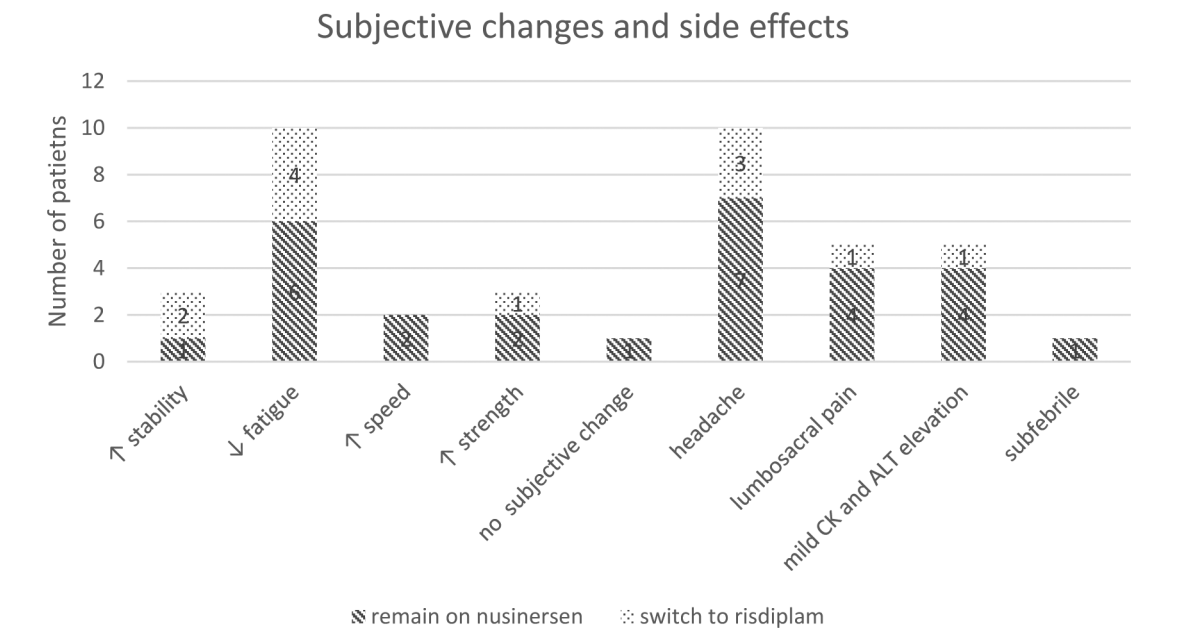

FIGURE 1. Subjective changes and side-effects in patients who remained on nusinersen and those who switched to risdiplam.

pandemic. Seven out of 11 patients had two seven-month pauses between the maintenance doses. Only one patient received all doses according to schedule (Pt 1). However, treatment was not delayed solely by the pandemic; five patients requested a delayed administration due to personal reasons (travel, other medical treatments, intensive rehabilitation programs) (Table 3). In 2022, when risdiplam was approved for SMA treatment, four patients switched therapy. Reasons for therapy change were intrathecal application discomfort (n = 3) and the preference for an independent administration (n = 1). All four patients experienced subjective improvement and improvement measured by SMA outcome scales and were considered treatment responders (Pt 2, Pt 7, Pt 8, Pt 11) (Table 2).

DISCUSSION

All of the treated patients in our group reported subjective improvement, and the majority of patients reported an improved quality of life. Ten out of 11 experienced a clinically significant improvement in at least one measured outcome, and the remaining one patient reported an absence of disease progression. In other studies, the results of nusinersen treatment in adults with SMA2 and SMA3 ranged from no change (14) to meaningful improvement (15-24). Because of predicted continued loss of function in this age group, we regard no worsening to be a beneficial outcome (4,5,25,26).

In our study, patients with an earlier disease onset had better outcomes. This might reflect greater functional weakness in adult patients with earlier disease onset in our group, which is easier to quantify with functional scales (ceiling effect in functionally stronger patients). Improvement in motor functions and endurance correlated with increased quality of life. Younger patients with shorter disease duration had greater improvements in 6MWT, however no significant correlations were observed between age at treatment initiation or disease duration and changes in motor function scores (RHS). This is in line with a meta-analysis by Coratti et al, which found that treated patients reported positive motor function changes irrespective of age, SMA type, or functional level (19). Maggi et al also found that treatment effect in adults was not clearly correlated with disease duration. They emphasized the relevance of baseline motor function in predicting the response to nusinersen (27).

This report has several limitations. Treatment administration regularity was affected by the pandemic, and the sample size was small. However, our cohort was homogenous (mostly ambulant adult SMA 3 patients aged 23-42 with treatment started in adulthood) and our findings are consistent with previous studies and comparable to reported treatment effects globally.

Although our observations should be interpreted with caution due to sample size, despite long disease duration (average 11 years), we observed a clinically significant improvement in at least one measured outcome in the majority of patients and the absence of disease progression in the remaining patient. This is in line with the results from other studies that showed disease stabilization or small clinical improvement in patients who received regular doses (19,27). However, it is difficult to directly compare our results with those of other studies due to different patient populations and baseline values. The most significant improvements can be expected in patients treated the earliest, however in our experience, nusinersen treatment was beneficial in adult patients with a long-standing disease as well.

After the approval of risdiplam, our experience showed that the choice of therapy was not affected only by treatment effectiveness. Adults with SMA3 frequently lead active lifestyles and chose therapy based on administration route and treatment administration frequency, which warrants a more personalized treatment approach.

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Declaration of authorship all authors conceived and designed the study; MH, BS, HB, KB acquired the data; MH, BS, EB authors analyzed and interpreted the data; MH, BS drafted the manuscript; HB, JN, KB, EB critically reviewed the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

Competing interests MH, BS, HB and EB have received honoraria for lectures, presentations, or educational events from Biogen and Roche. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

1 Nance JR. Spinal muscular atrophy. CONTINUUM: Lifelong Learning in Neurology. 2020;26:1348-68. Medline:33003005

2 Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018;378:625-35. Medline:29443664 doi:10.1056/NEJMoa1710504

3 Zerres K, Rudnik-Schöneborn S, Forrest E, Lusakowska A,

Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997;146:67-72. Medline:9077498 doi:10.1016/S0022-510X(96)00284-5

4 Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol. 2018;25:512-8. Medline:29194869 doi:10.1111/ene.13534

5 Montes J, McDermott MP, Mirek E, Mazzone ES, Main M, Glanzman AM, et al. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. Singh RN, editor. PLoS ONE. 2018 Jun 26;13(6):e0199657.

6 Dunaway Young S, Montes J, Kramer SS, Marra J, Salazar R, Cruz R, et al. Six-minute walk test is reliable and valid in spinal muscular atrophy: 6MWT in SMA. Muscle Nerve. 2016;54:836-42. Medline:27015431 doi:10.1002/mus.25120

7 McDonald CM, Henricson EK, Abresch RT, Florence JM, Eagle M, Gappmaier E, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve. 2013;48:343-56. Medline:23681930 doi:10.1002/mus.23902

8 Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377:1723-32. Medline:29091570 doi:10.1056/NEJMoa1702752

9 Swoboda KJ, Scott CB, Crawford TO, Simard LR, Reyna SP, Krosschell KJ, et al. SMA CARNI-VAL trial part i: double-blind, randomized, placebo-controlled trial of l-carnitine and valproic acid in spinal muscular atrophy. Boutron I, editor. PLoS ONE. 2010 Aug 19;5(8):e12140.

10 Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, et al. Revised upper limb module for spinal muscular atrophy: development of a new module. Muscle Nerve. 2017;55:869-74. Medline:27701745 doi:10.1002/mus.25430

11 Montes J, Dunaway Young S, Mazzone ES, Pasternak A, Glanzman AM, Finkel RS, et al. Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy. Muscle Nerve. 2019;60:409-14. Medline:31298747 doi:10.1002/mus.26633

12 Ramsey D, Scoto M, Mayhew A, Main M, Mazzone ES, Montes J, et al. Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. PLoS One. 2017;12:e0172346. Medline:28222119 doi:10.1371/journal.pone.0172346

13 Vincent KA, Carr AJ, Walburn J, Scott DL, Rose MR. Construction and validation of a quality of life questionnaire for neuromuscular disease (INQoL). Neurology. 2007;68:1051-7. Medline:17389311 doi:10.1212/01.wnl.0000257819.47628.41

14 Moshe-Lilie O, Visser A, Chahin N, Ragole T, Dimitrova D, Karam C. Nusinersen in adult patients with spinal muscular atrophy: Observations from a single center. Neurology. 2020;95:e413-6. Medline:32665408 doi:10.1212/WNL.0000000000009914

15 Arslan D, Inan B, Kilinc M, Bekircan-Kurt CE, Erdem-Ozdamar S, Tan E. Nusinersen for adults with spinal muscular atrophy. Neurol Sci. 2023;44:2393-400. Medline:36854931 doi:10.1007/s10072-023-06698-9

16 Walter MC, Wenninger S, Thiele S, Stauber J, Hiebeler M, Greckl E, et al. Safety and treatment effects of nusinersen in longstanding adult 5q-SMA type 3 – a prospective observational study. J Neuromuscul Dis. 2019;6:453-65. Medline:31594243 doi:10.3233/JND-190416

17 Schreiber-Katz O, Siegler HA, Wieselmann G, Kumpe M, Ranxha G, Petri S, et al. Improvement of muscle strength in specific muscular regions in nusinersen-treated adult patients with 5q-spinal muscular atrophy. Sci Rep. 2023;13:6240. Medline:37069197 doi:10.1038/s41598-023-31617-5

18 Vázquez-Costa JF, Povedano M, Nascimiento-Osorio AE, Moreno Escribano A, Kapetanovic Garcia S, Dominguez R, et al. Nusinersen in adult patients with 5q spinal muscular atrophy: A multicenter observational cohorts' study. Eur J Neurol. 2022;29:3337-46. Medline:35872571 doi:10.1111/ene.15501

19 Coratti G, Cutrona C, Pera MC, Bovis F, Ponzano M, Chieppa F, et al. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis. 2021;16:430. Medline:34645478 doi:10.1186/s13023-021-02065-z

20 Elsheikh B, Severyn S, Zhao S, Kline D, Linsenmayer M, Kelly K, et al. Safety, tolerability, and effect of nusinersen treatment in ambulatory adults with 5q-SMA. Front Neurol. 2021;12:650535. Medline:34093395 doi:10.3389/fneur.2021.650535

21 Daimee M, Shakti N. Nusinersen initiation in adults with spinal muscular atrophy (4906). Neurology. 2020;94(15 Supplement):4906. doi:10.1212/WNL.94.15_supplement.4906

22 Hagenacker T, Wurster CD, Günther R, Schreiber-Katz O, Osmanovic A. Petri Set al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol. 2020;19:317-25. Medline:32199097 doi:10.1016/S1474-4422(20)30037-5

23 Veerapandiyan A, Eichinger K, Guntrum D, Kwon J, Baker L, Collins E, et al. Nusinersen for older patients with spinal muscular atrophy: A real-world clinical setting experience. Muscle Nerve. 2020;61:222-6. Medline:31773738 doi:10.1002/mus.26769

24 De Wel B, Goosens V, Sobota A, Van Camp E, Geukens E, Van Kerschaver G, et al. Nusinersen treatment significantly improves hand grip strength, hand motor function and MRC sum scores in adult patients with spinal muscular atrophy types 3 and 4. J Neurol. 2021;268:923-35. Medline:32935160 doi:10.1007/s00415-020-10223-9

25 Deymeer F, Serdaroglu P, Parman Y, Poda M. Natural history of

SMA IIIb: Muscle strength decreases in a predictable sequence and magnitude. Neurology. 2008;71:644-9. Medline:18725590 doi:10.1212/01.wnl.0000324623.89105.c4

26 Zerres K, Rudnik-Schöneborn S. Natural history in proximal spinal muscular atrophy: clinical analysis of 445 patients and suggestions for a modification of existing classifications. Arch Neurol. 1995;52:518-23. Medline:7733848 doi:10.1001/archneur.1995.00540290108025

27 Maggi L, Bello L, Bonanno S, Govoni A, Caponnetto C, Passamano L, et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3. J Neurol Neurosurg Psychiatry. 2020;91:1166-74. Medline:32917822 doi:10.1136/jnnp-2020-323822