

# Evaluation of real-life outcome data of patients with spinal muscular atrophy treated with nusinersen in Switzerland

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## Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive disorder causing progressive proximal muscular, respiratory, and bulbar weakness. We present outcome data on motor function, ventilation, nutrition, and language development of SMA patients treated with nusinersen in Switzerland. This multicenter, observational study included 44 patients. At treatment initiation, after 2 months and then every 4 months we assessed motor function with the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Functional Motor Scale expanded (HFMSE) and 6-Minute Walk Test (6MWT). At treatment initiation, patients were 0.1–44.6 years old, treatment duration ranged from 6 to 41 months. All 11 SMA type 1 children achieved higher CHOP-INTEND scores at the last assessment compared to treatment initiation, 4 acquired stable sitting. Six type 1 children were <18 months-old at treatment initiation. Two of them did not need ventilation or nutritional support at the last assessment; three had delayed language development and 3 articulation difficulties. 5/21 SMA type 2 patients achieved higher HFMSE scores. All ambulant type 3 patients showed a gain in the 6MWT. Nusinersen is an effective treatment, with gains in motor function occurring particularly in children and SMA type 1, but also in type 2 and 3, adolescents and adults. © 2022 The Authors. Published by Elsevier B.V.

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## 1. Introduction

Chromosome 5q-associated spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by loss of alpha motor neurons in the spinal cord and lower bulbar motor neurons leading to progressive muscular weakness, atrophy, respiratory and bulbar impairment and tongue fasciculation [1,2]. Classification of SMA distinguishes SMA types 0 to 4 based on age of symptom onset and maximal motor function of historical, untreated patients [3–5]. SMA is caused by a homozygous deletion (95%) or heterozygous deletion in combination with a point mutation (5%), or two different point mutations of the SMN1 (survival motor neuron 1) gene, mapped on chromosome 5q11.1-13.3. SMN1 encodes the protein survival motor neuron [6]. Correlation between the clinical severity of SMA and the copy number of the SMN2 gene, a low-functioning paralogue of SMN1, has been described [7,8]. A single nucleotide change creates an exonic splicing silencer in exon 7 of SMN2, which leads to exclusion of exon 7 in most transcripts [9]. This altered mRNA results in the production of a truncated version of the SMN protein, which is degraded. Only 10% full-length SMN protein is produced by SMN2 compared to SMN1.

Nusinersen blocks an intronic splicing silencer that prevents skipping of exon 7 in SMN2, resulting in increased full-length SMN protein production [10]. Nusinersen is administered intrathecally every 4 months after a loading period of 2 months [11–14]. Nusinersen is the first disease-modifying treatment for SMA approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for all ages, type 1–3 and disease stages. In Switzerland, an early access program was initiated in June 2017 for SMA type 1 patients, and by April 2018, nusinersen became available to SMA patients with type 1–3 under the age of 20 years and 2 or more copies of SMN2. Reimbursement stopping criteria are: loss of motor function in more than 2 scales of more than 4 or 3 points in the CHOP-intend or HFMSE, respectively, in two consecutive assessments or if permanent ventilation is necessary and motor functions worsens and there is no medical explanations (e.g. scoliosis surgery). In adults, reimbursement was based on individual decisions until 2020. Since 2018, most children and some adults with SMA have received treatment with nusinersen in Switzerland. Some parents opted to not start treatment and chose palliative care, or wanted to wait if their children were stable.

The trials leading to approval and registry data focused on motor outcomes of children with SMA type 1 and 2 treated with nusinersen [11,15]. Little is known regarding motor outcomes of older patients and patients with milder phenotypes and even less about the need for tube feeding, ventilation and language development of children with SMA type 1 treated with nusinersen.

This study uses real-life outcome data and describes the development of motor function of patients with SMA type 1–3 treated with nusinersen over a follow-up period of up

to 42 months in Switzerland. In addition, we analyzed the need for feeding and ventilatory support as well as the language development of treated patients with SMA type 1. We also investigated whether changes in motor function during treatment correlated with the age at treatment start or with SMN2 copy numbers.

## 2. Material and methods

This study uses data collected by the Swiss Registry for Neuromuscular Disorders (Swiss-Reg-NMD). The registry was created in 2008; it has been hosted since 2017 at the Institute of Social and Preventive Medicine (ISPM) in Bern and it is approved by the Cantonal Ethics Committee of Bern (20.06.2018, KEK Bern, 2018-00289). It prospectively collects data of patients of all ages diagnosed with SMA, Duchenne and Becker dystrophinopathies, LAMA2-related muscular dystrophy or Collagen 6-related muscle diseases in Switzerland. Patients are identified in regional neuromuscular centres. When consent is obtained, physicians of these centres report the patient's baseline data to the Swiss-Reg-NMD and regularly provide follow-up data on the clinical status and treatment. Initially this was done via semi-structured reports; since 2018 we use pre-defined case report forms. The data for the registry is collected during routine patient visits. Information is entered into a secured database using REDCap electronic data capture tools [16,17].

This study used data collected until August 31, 2020. All subjects treated with nusinersen for at least 6 months were included. An exclusion criterion was participation in a clinical trial with nusinersen. We collected data from before the start of treatment, at completion of the loading phase (day 63) and every four months thereafter. In the case of treatment discontinuation, data were only included until 4 months after the last nusinersen administration.

Motor function was assessed with standardised clinical assessments that are also used by the global TREAT-NMD registry (<https://treat-nmd.org>), other SMA registries [18,19] and previous clinical trials in SMA. Motor assessments are performed by physiotherapists and occupational therapists who were specifically trained for these tests. For patients younger than 2 years of age and all “non-sitters” we used the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND, total score from 0 to 64) [20–22] or the Hammersmith Infant Neurological Examination (HINE, total score from 0 to 26) [23]. For older patients we used the Revised Upper Limb Module (RULM, score from 0 to 37) to investigate the upper limb function [24] and the Hammersmith Functional Motor Scale (HFMS, score from 0 to 40, and for patients with better motor functions the expanded version HFMSE, score from 0 to 66) [25]. HFMS and HFMSE were combined for analysis. For walkers, we performed the 6-Minute Walk Test (6MWT) [26]. Qualitative motor abilities were recorded following the ‘TREAT-NMD SMA Patient Registry Dataset, Version 2’ (<https://sma.treat-nmd.org/items/Motor%20function>): Holding head up without support; rolling onto the side; sitting

without support; crawling on hands and knees; standing with assistance; standing without support; walking with assistance; walking without support; walk 10 metres unaided; climbing stairs; useful function of hands (e.g. hold a pen, pick coins from a table); reaching overhead in a sitting position; raising hands to mouth in a sitting position.

Language development was tested using the speech part of the Griffiths Mental Development Scale [27] in children under two years of age; in the older children, we used the language scale of the Bayley III test [28]. For articulation we used a 5-point scale adapted from other dysarthria scales [29,30]. We also recorded the type and hours/day of ventilation and the main route of nutrition.

Statistical analyses were done using R version 3.6.2 (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.r-project.org/>). Categorical variables were summarized with absolute and relative frequencies, continuous variables with median, minimum and maximum (in the text: min-max; median). For the median score at start and last assessment, only patients with data at treatment start and at least one follow-up assessment was considered for each score. Correlation between absolute changes of motor scores from treatment start to the last assessment and age at start of treatment, disease duration before treatment starts and SMN2 copy number was assessed using Spearman's correlation coefficient with asymptotic 95% confidence intervals (CI) based on Fisher's Z transformation (Fig. 2). The difference in motor score absolute changes between the groups of patients with and without ventilatory and nutritional support, respectively, was quantified using the Mann-Whitney statistic (the probability of having a higher score upon ventilation or tube feeding) with 95% CI and the *p*-value from a Mann-Whitney-Wilcoxon test. A *p*-value < 0.05 was considered as statistically significant.

### 3. Results

#### 3.1. Demographics

On 31st August 2020, 93 patients with SMA were included in the Swiss-Reg-NMD. By that time, 48 patients had been treated with nusinersen; all were alive. Four patients were excluded from the analysis, two because they had been treated for less than 6 months and two because they had been included in a clinical trial with nusinersen (Table 1).

Three patients (two SMA type 1 and one SMA type 2) have stopped nusinersen treatment during the observation period. Reasons for stopping treatment were: inclusion in a clinical trial with another disease-modifying drug; increasing difficulties with performing a lumbar puncture due to scoliosis; increased opening pressure at lumbar puncture. Discontinuation occurred after an average of 22 months of treatment. All three patients who discontinued treatment switched to another disease modifying therapy.

Table 1

Characteristics of patients with SMA in Switzerland treated with nusinersen included in the analysis. Categorical data are presented as number of patients and continuous data as median [minimum - maximum].

Characteristics of patients	N = 44
Gender	
Male	21
Female	23
Spinal muscular atrophy type	
SMA type 1	11
SMA type 2	21
SMA type 3	12
SMN2 copy number	
2 all	7
SMA type 1	5
SMA type 2	1
SMA type 3	1
3 all	23
SMA type 1	4
SMA type 2	16
SMA type 3	3
≥4 all	9
SMA type 1	0
SMA type 2	3
SMA type 3	6
Age at start treatment with nusinersen (years)	9.4 [0.1–44.6]
SMA type 1	1.4 [0.1–16.1]
SMA type 2	7.8 [1.2–31.4]
SMA type 3	16.6 [2.5–44.6]
Duration of treatment with nusinersen (years)	1.9 [0.5–3.4]
SMA type 1	2.1 [0.8–3.4]
SMA type 2	1.8 [0.5–2.9]
SMA type 3	1.9 [0.6–2.6]

#### 3.2. Adverse events of the treatment with nusinersen

15 patients (34%) had at least one adverse event other than complications due to lumbar puncture. These side effects include proteinuria, thrombocytosis, thrombocytopenia, coagulation disorder (low prothrombin) and ECG changes (mild repolarisation abnormalities and transient prolonged QT measures). Proteinuria, low prothrombin, thrombocytosis and thrombocytopenia were asymptomatic, mild and transient in all. The findings were not explained by concomitant medication or infection. Two patients had transient elevated opening pressure without clinical signs or ophthalmological findings of elevated pressure. Six patients had side effects caused by lumbar puncture like headache and lumbar pain. See Table 2 for the number and proportion of patients with adverse events.

#### 3.3. Motor function

We evaluated the motor function of these SMA patients with validated motor assessments (CHOP-INTEND, HINE, HFMSE, RULM, and 6MWT), and by recording the ability of patients to perform 13 different qualitative motor function, referred to as abilities in the following (e.g. holding head up without support, walking with assistance, raising hands to mouth in a sitting position).

Table 2  
Number and proportion of patients with adverse events and number and incidence of adverse events during treatment with Nusinersen.

Adverse events	Number of patients with adverse events (N=44)	Number and incidence of adverse events (79 person-years of treatment)
Proteinuria	6 (14%)	11 (0.14 per person-year)
Thrombocytosis	7 (16%)	22 (0.28 per person-year)
Thrombocytopenia	1 (2%)	1 (0.01 per person-year)
Coagulation disorder	2 (5%)	4 (0.05 per person-year)
ECG changes	2 (5%)	2 (0.03 per person-year)
Lumbar puncture	6 (14%)	9 (0.1 per person-year)
Other adverse events (elevated opening pressure)	2 (5%)	2 (0.03 per person-year)

Table 3  
Acquisition ('gain') and loss of motor abilities during treatment (n/non-missing).

	SMA type 1 0–18 months old at treatment start			SMA type 1 >18 months old at treatment start			SMA type 2			SMA type 3 Ambulatory			SMA type 3 Non- ambulatory		
	6			5			21			6			6		
Number of patients	6			5			21			6			6		
Months treated, median [min - max]	25.5 [9.7–41.3]			30.1 [21.6–34.7]			21.8 [6.2–35.1]			22.8 [13.6–27.7]			18.5 [6.9–30.8]		
Age (years), median [min - max] at treatment start	0.2 [0.1–1.4]			13.1 [5.4–16.1]			7.8 [1.2–31.4]			15.4 [4–29.3]			18.5 [2.5–44.6]		
Age (years), median [min - max] at last assessment	2.5 [1.0–3.6]			15.9 [7.4–17.9]			9.7 [1.7–33.3]			17.3 [6.25–31.3]			19.8 [5.1–47]		
	Start	Gain	Loss	Start	Gain	Loss	Start	Gain	Loss	Start	Gain	Loss	Start	Gain	Loss
Holding head up without support	0/6	5/6	0/6	1/5	1/5	0/5	18/21	0/21	1/21	6/6	0/6	0/6	6/6	0/6	0/6
Rolling onto the side	0/6	6/6	0/6	1/5	1/5	0/5	13/21	2/21	0/21	6/6	0/6	0/6	5/6	0/6	0/6
Sitting without support	0/6	4/6	0/6	0/5	1/5	0/5	15/21	3/21	0/21	6/6	0/6	0/6	6/6	0/6	0/6
Crawling on hands and knees	0/6	0/6	0/6	0/5	0/5	0/5	0/21	2/21	0/21	5/6	1/6	0/6	3/6	0/6	1/6
Standing with assistance	0/6	3/6	0/6	0/5	0/5	0/5	0/21	5/21	0/21	6/6	0/6	0/6	3/6	0/6	0/6
Standing alone*	0/6	0/6	0/6	0/5	0/5	0/5	0/21	1/21	0/21	6/6	0/6	0/6	2/6	0/6	0/6
Walking with assistance	0/6	0/6	0/6	0/5	0/5	0/5	0/21	2/21	0/21	6/6	0/6	0/6	2/6	0/6	0/6
Walking alone*	0/6	0/6	0/6	0/5	0/5	0/5	0/21	1/21	0/21	6/6	0/6	0/6	1/6	1/6	0/6
Able to walk 10 metres unaided	0/6	0/6	0/6	0/5	0/5	0/5	0/21	0/21	0/21	6/6	0/6	0/6	0/6	2/6	0/6
Climbing stairs	0/6	0/6	0/6	0/5	0/5	0/5	0/21	0/21	0/21	5/6	1/6	0/6	0/6	2/6	0/6
Useful function of hands	1/6	5/6	0/6	3/5	0/5	0/5	19/20	0/20	0/20	6/6	0/6	0/6	6/6	0/6	0/6
Reaching overhead in a sitting position	0/6	3/6	0/6	0/5	0/5	0/5	3/19	3/19	0/19	6/6	0/6	0/6	3/6	1/6	0/6
Raising hands to mouth in a sitting position	1/6	5/6	0/6	2/5	0/5	1/5	18/21	1/21	1/21	6/6	0/6	0/6	6/6	0/6	0/6

\* Without assistance.

### 3.3.1. Motor function and assessments of SMA type 1 patients

Motor abilities were assessed in all 11 SMA type 1 patients (Table 3). Six patients were <18 months old at treatment initiation (5 patients <4 months old, type 1b and one 1.45 years old, type 1c) and 5 patients were 5.4–16.1 years old (one type 1b, 4 type 1c). At treatment start, one individual was able to hold their head unsupported, one was able to roll onto their side, and three could raise their hands to mouth in a sitting position. During nusinersen treatment, 8 of 11 patients acquired between 1 and 7 motor abilities (median 4) and one patient lost a motor ability (“raising hands to mouth in a sitting position”). The highest motor ability, which three children achieved, was standing with assistance. The children aged <18 months at treatment start acquired the most motor abilities. At the last assessment all 6 patients were able to roll onto the side, 4/6 were able to sit without support (at age

of 11–46 months, one type 1c >12 months old at treatment start), all were able to raise their hands to mouth in a sitting position, and three were able to reach overhead in a sitting position.

CHOP-INTEND was reported for all 11 SMA type 1 patients. At treatment initiation, patients achieved a median total score of 25 (range 2–29). All achieved higher total scores at the last assessments than at treatment initiation (increase of 2–42 points; median 25). The patients treated earlier (treatment start <18 months of age) achieved larger improvements (increase of 25–42 points; median 29.5; Fig. 1A) than patients treated later (increase of 2–8 points; median 5; Fig. 1B). Of the three patients with a CHOP INTEND of <10 at start of treatment, only the child with treatment start at an age of <18 months gained motor functions. One of two patients with CHOP INTEND between 10 and 20 at treatment start, gained motor functions (both treated at <18 months of

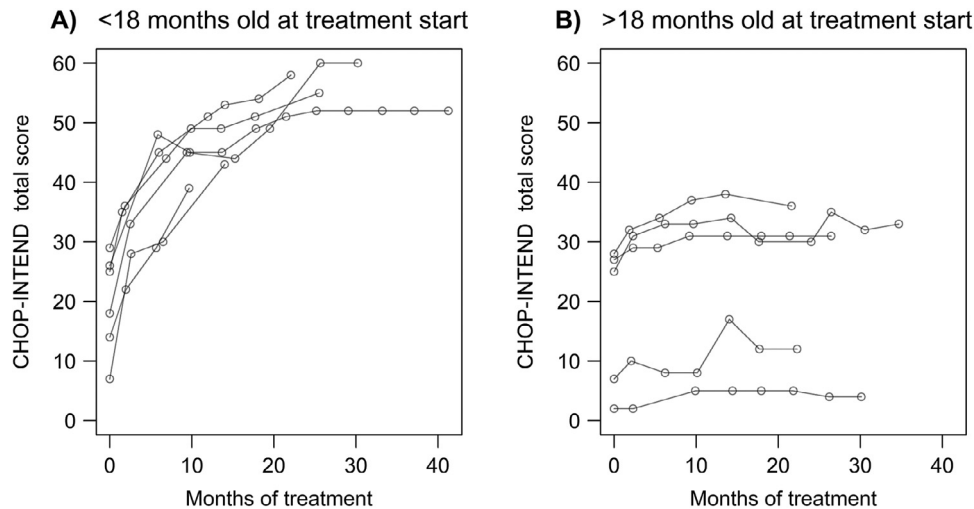


Fig. 1. CHOP-INTEND after treatment start (baseline) assessed every 4 months for SMA type 1 patients. A) treatment start at <18 months of age; B) treatment start at >18 months of age.

age). Five of six patients with CHOP INTEND of >20 at treatment start gained motor functions, including two patients treated late in the disease.

We found a correlation between the age at treatment initiation and the degree of motor improvement measured by the change in CHOP-INTEND (Fig. 2A). Likewise, the disease duration before treatment initiation (defined as the time between the onset of first symptoms and treatment start) correlated with the change in CHOP-INTEND ( $r_s = -0.85$  (95% CI:  $-0.96$  to  $-0.48$ ;  $p = 0.002$ )). There was no correlation between SMN2 copy number and motor improvement (Fig. 2B, Spearman correlation coefficient (95% CI):  $p = 0.57$ ,  $-0.22$  ( $-0.77$  to  $0.52$ )).

### 3.3.2. Motor function and assessments of SMA type 2 patients

Motor abilities were assessed in 21 SMA type 2 patients (Table 3). At treatment start, most patients could hold their head unsupported, sit without support, raise hands to mouth in a sitting position and had useful function of their hands. By definition, no patient was able to walk. During nusinersen treatment, 8 of 21 patients acquired between 1 and 5 motor abilities and one patient lost 2 motor abilities. Five patients gained the motor ability standing with assistance, two achieved walking with assistance and one could walk without assistance.

RULM was reported for 12 patients. At treatment start, patients obtained a median total score of 14 (range 0–24). Five patients reached higher total scores at the last assessment than at the initiation of treatment (increase of 1–5 points) and 5 patients lost 1–3 points. In two patients, the achieved scores remained unchanged. HFMSE was reported for 16 SMA type 2 patients. At treatment start, patients achieved a median total score of 5.5 (range 0–25). Five patients achieved higher total scores at the last assessment than at the treatment start (increase of 1–15 points; time of follow-up: median 23 months, range 6.4–29.7; 3 patients gained >2 points)

and 4 patients lost 1–5 points, of those, 2 patients lost >2 points. Seven patients maintained the same scores. Age at treatment initiation was not correlated with the degree of motor improvement by HFMSE (Fig. 2C). However, there was some evidence for a correlation between the SMN2 copy number and motor improvement (Fig. 2D).

A similar diverse picture was obtained for the CHOP-INTEND (3 patients gained 2–14 points, 1 patient obtained the same score, and 2 patients lost 1 to 4 points). Taken together, 12 of 19 patients showed an improvement in at least one of the three assessments, noticeable usually after 2 to 6 months of treatment, with 4 of these 12 patients also showing in at least one assessment a decrease in the score.

### 3.3.3. Motor function and assessments of SMA type 3 patients

Motor abilities were assessed in 12 SMA type 3 patients (Table 3). Of those, all could sit without support, 8 could stand and 7 walk at treatment start. During nusinersen treatment, 3 of 12 patients acquired between 2 and 4 motor abilities and one patient lost a motor ability (crawling on hands and knees). Three patients gained the ability to climb stairs and 2 of those the ability to walk 10 metres unaided. One of these three patients had never been able to walk 10 m unaided and climb chairs, while the other two had first gained but then lost one or both abilities before the start of treatment.

RULM was reported for 5 patients. At treatment start, patients obtained a median total score of 31 (range 18–37). Two patients reached higher total scores at the last assessment than at the initiation of treatment (increase of 4–6 points), two patients obtained the same scores and one patients lost 2 points. 6MWT was reported for five SMA type 3 patients. At treatment start, patients achieved a median score of 387 m (range 169–576 m). All reached longer distances at the last assessments than at treatment start (increase of 72–146 m; median score of 466 m). Age at treatment start and change in

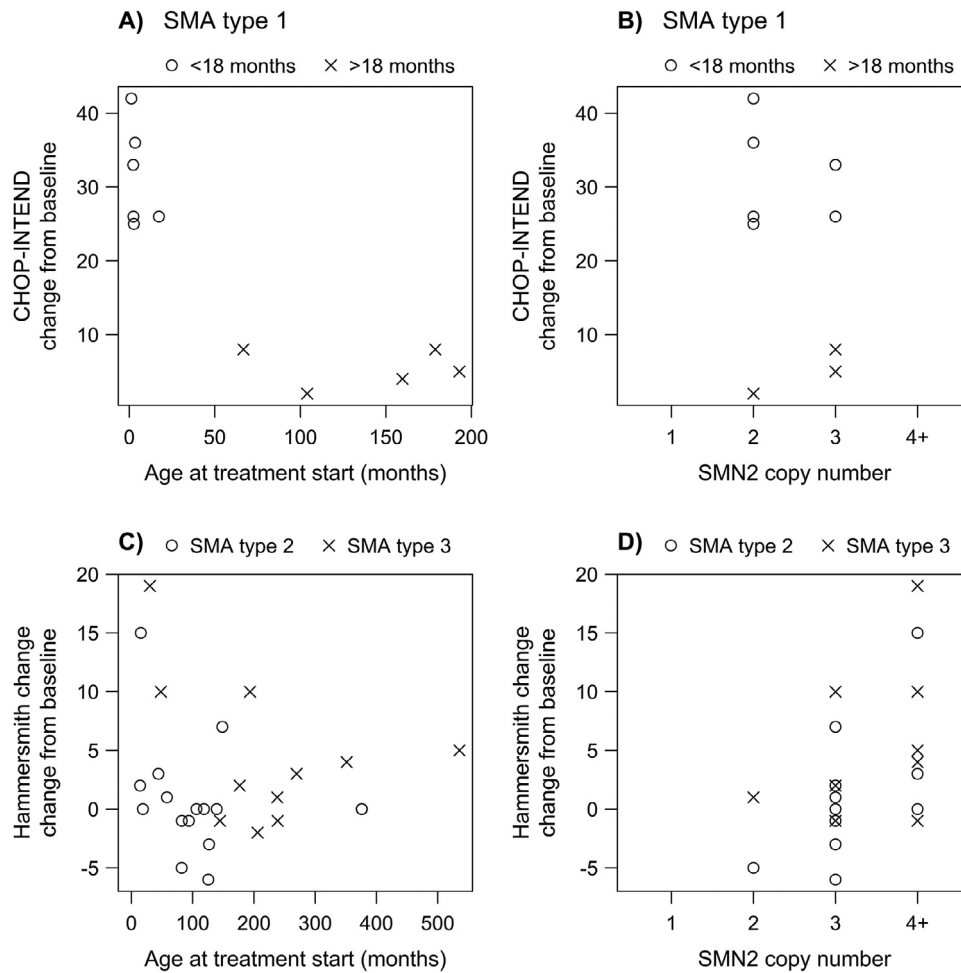


Fig. 2. Change in CHOP-INTEND from treatment start to last assessment in SMA type 1 patients by age at treatment start (A) and SMN2 copy number (B). Change of HFMSE from treatment start to last assessment for SMA type 2 and type 3 patients by age at treatment start (C) and SMN2 copy number (D). A, SMA type 1:  $r_s = -0.82$  (95% CI:  $-0.95$  to  $-0.44$ ;  $p = 0.002$ ); B, SMA type 1;  $r_s = -0.22$  (95% CI:  $-0.77$  to  $0.52$ ;  $p = 0.57$ ); C, SMA type 2  $r_s = -0.29$  (95% CI:  $-0.69$  to  $0.24$ ;  $p = 0.27$ ) and SMA type 3:  $r_s = -0.23$  (95% CI:  $-0.73$  to  $0.43$ ;  $p = 0.50$ ); D, SMA type 2:  $r_s = 0.55$  (95% CI:  $0.06$  to  $0.83$ ;  $p = 0.032$ ) and SMA type 3:  $r_s = 0.38$  (95% CI:  $-0.38$  to  $0.83$ ;  $p = 0.32$ ). Remark: under C, two circles of patients with almost the same age at treatment start are overlapping.

6MWT showed a rank correlation ( $r_s = -1$ ;  $p = 0.017$ , suppl. Fig.).

HFMSE was reported for 11 SMA type 3 patients. At treatment start, patients achieved a median score of 41 (range 6–62) and 53 (range 6–64) at the last assessment. Eight patients achieved higher total scores at the last assessments (increase of 1–19 points, 6 patients gained >2 points) than at treatment start and three patients lower total scores (loss of 1–2 points). The three patients who lost points in the HFMSE reached longer distances in the 6MWT.

### 3.3.4. Motor function in older patients

16 patients were at least 14 years old at treatment start (SMA type 1:  $n = 2$ ; SMA type 2:  $n = 4$ ; SMA type 3:  $n = 10$ ). Their median age at start of treatment was 19.8 years (range 14.7–44.6) and median treatment duration was 1.9 years (range 0.5–2.9). One patient lost a motor ability (raise hand to mouth) during nusinersen treatment while two

gained at least one motor ability (roll onto the side, sit without support and climb stairs).

Motor assessments (CHOP-INTEND, RULM, HFSME or 6MWT) were reported for 14 patients. Twelve patients achieved at least one motor assessment higher total score at the last assessments (increase of 1–19 points) than at treatment start. Two patients had a lower score in the HFMSE (decrease of 1–2 points).

### 3.4. Ventilatory support and swallowing abilities in SMA type 1

Of the 6 SMA type 1 patients aged <18 months at treatment start (five type 1b and one type 1c), none required non-invasive ventilation (NIV) or tube feeding at treatment initiation. After 8–30 months of treatment, 4/6 patients needed tube feeding. Three of these four also started NIV <16h/day (nocturnal NIV), almost at the same time as the tube feeding. In all cases, tube feeding and ventilation became

necessary during or after a respiratory infection at the age of 12–23 months. Swallowing was regained, but gastrostomy feeding became necessary. Two of the patients with treatment start <18 months of age required neither ventilation nor tube feeding at the last assessment. We investigated the relationship between changes in motor function and the need for ventilation or tube feeding, at the last assessment. We found no statistically significant difference between patients with or without the need for ventilation, or tube feeding, at the last assessment and the change in CHOP-INTEND under treatment (SMA type 1, <18 months old at treatment start; ventilation:  $N=6$ ,  $U=0.72$ , 95% CI=0.22–0.99,  $p=0.5$ ; nutrition:  $N=6$ ,  $U=0.44$ , 95% CI=0.05–0.88,  $p=0.93$ ).

Of the 5 SMA type 1 patients with a disease duration of 5–16 years before the start of treatment, one patient required NIV, one patient needed tube feeding and three required both ventilation and tube feeding at treatment start. One of those with 23–24h/day NIV at treatment start was able to tolerate breaks of up to 2h under treatment and showed a marked reduction of respiratory infections. The other four patients had no change in ventilation support during the observation period.

### 3.5. Speech development in SMA type 1 patients with treatment start <18 months of age

We assessed language development using the speech part of the Griffiths Mental Development Scale (age <2 years) in 4 and language scale of the Bayley III (age >2 years) in 2 of the 6 SMA type 1 patients with treatment start at 18 months of age or younger. Three had age-appropriate language development, three patients showed a delay (one with a family history of marked language development delay). There was no relationship between the need for chronic tube feeding/part-time ventilation and language development.

Two patients did not speak any words at the time of the last assessment at age >16 months. Both were without ventilation and one needed feeding support at the time of last assessment. We assessed articulation in the four patients that were able to produce comprehensible words. Of those four, one patient had a normal articulation. This patient has a milder SMA-phenotype (type 1c) and has no need for ventilation or feeding support. Two had mild, one moderate dysarthria (defined by someone who sees the patient less than once a week and is able to understand the child only with difficulties). All three needed feeding and ventilation support.

## 4. Discussion

Our study of 44 patients with SMA type 1, 2 and 3 aged 0.1–44 years treated with nusinersen in Switzerland for 6–42 months confirms a positive treatment effect on motor function in all age groups and all forms of severity, as reported elsewhere. The therapeutic effect was most striking in type 1 patients who were treated before the age of 18 months. However, the older patients with longer disease duration and less severe phenotypes also showed

some positive effects on motor function. No patients died. Previously described side effects occurred in 35% of the patients. These side effects were generally mild and transient. Increased opening pressure at lumbar puncture was recently reported by Becker et al. [31]. In our cohort, it was not consistently measured but for two of our patients increased opening pressure was reported without simultaneous headache, atypical head circumference changes or pathological ophthalmologic findings. Three patients, including one with elevated pressure, stopped nusinersen and switched to another disease-modifying treatment.

In SMA type 1 the ENDEAR trial showed a response rate of 71% defined as improvement of >4 points on the CHOP-INTEND score after 13 months of treatment. A correlation between the age at treatment onset and the motor response thus favouring early treatment initiation was seen in the open label extension study (SHINE) and also in several early access programmes (EAP) [32–36]. In our cohort, an improvement of the CHOP-INTEND score in the SMA type 1 group of at least 4 points was observed in 100%, with a median increase of 25 points when treatment was started at 18 months of age or below. The correlation between age at treatment start and disease duration before treatment start and change in CHOP-INTEND was statistically significant. In line with the findings of Pane et al. [34] and Pechmann et al. [33], but contrary to the findings of Osredkar et al. [36], we did not find a correlation between the SMN2 copy number and motor improvement. Four of six SMA type 1 patients treated before the age of 18 months, including one patient with type 1c were able to sit unsupported at age of 11–46 months, and the highest reached motor ability was standing with assistance at the last assessment ( $n=3$ ). All SMA type 1 patients with treatment start <18 months of age were able to reach the mouth with their hands when sitting. For quality of life standards, the ability to sit unsupported and raise the hand to the mouth is extremely important [37]. Of the SMA type 1 patients treated later in the disease course (>18 months) the motor response was much less pronounced, (median CHOP INTEND gain 5); two patients with type 1c and a baseline CHOP-INTEND score >20 gained head control and sitting unsupported, respectively. This is in line with the findings of Pane et al. [34] that less severely affected type 1 patients improve more also when treated later than 7 months of age.

The effect of nusinersen on respiratory function and swallowing has been reported in less detail compared to the treatment effect on motor function. We did not find an improvement of respiratory status in most of the older, chronic patients, who were already dependant on respiratory support at treatment start, confirming recent reports from registries in other countries [38,39]. For the six SMA type 1 patients in whom treatment was started shortly after diagnosis, three were without ventilatory support at age 15–44 months, two of them without the need for tube feeding, one of them having a milder phenotype (type 1c) with head control before treatment start. Tube feeding and ventilatory support became necessary at age of 8–20 months, associated with a respiratory infection in all. In our cohort, we did not see a correlation

between motor response and the need for ventilatory or feeding support, which is in line with previous reports [38,40]. Patients continued to show improvements with acquisition of a stable sit or the ability to stand with assistance.

To our knowledge, communication skills and dysarthria have not been examined in SMA type 1 children with treatment start soon after diagnosis so far. Ball et al. [41] reviewed the published literature and parents' perspectives on quality of life regarding communication in untreated SMA type 1 children. According to these reports, most SMA type 1 patients showed an age-appropriate receptive language development, but severe impairment in expressive language production. Recently Van der Heul et al. [42] published a self-reported evaluation of bulbar problems in SMA patients not treated with nusinersen. Beside problems of mastication, choking and lack of intelligibility have been frequently reported. Our cohort is too small to make a statistical analysis of a possible correlation between ventilation support, motor response and language production. Of the six SMA type 1 children aged <18 months at treatment initiation, language development was normal in three. Articulation assessed in four patients was only normal in one child, with a milder phenotype (type 1c). Our data showed no clear correlation for these patients with a need for ventilation or tube feeding. It seems important to evaluate language and articulation early in nusinersen treated children, particularly for those who do not need tube feeding or ventilation to implement early intervention and communication aids.

The response to treatment for patients with SMA type 2, was more diverse in our cohort. Results of motor scores fluctuated between visits or showed gains in one motor score and loss in another measure, reflecting the limitations of the motor scores applied to show clinically meaningful changes in growing patients with contractures and scoliosis and the floor effect in weak patients with very low baseline values to show small, but for the patient meaningful changes when tested with RULM and HFMSE. Some patients gained up to 5 motor abilities or up to 15 points in the HFMSE. The minimal clinically important difference in the HFMSE was reported to be 2 points [43]. A change up to 2 points was also chosen as an indicator of stabilisation by a very recent report by Coratti G et al. about real world data of type 2 patients after 12 months of nusinersen treatment [44]. In this report, age and baseline score were found to be predictive of the treatment response. The therapeutic response in our small cohort was not correlated to age or baseline score, but showed some correlation with SMN2 copy numbers. When using the definition used by Coratti in our cohort of SMA type 2 patients, 11/16 showed a stabilisation ( $\pm 2$  points), three improvement ( $>2$  points), and two lost more than 2 points. In view of the natural history studies in SMA type 2 and 3 that show a loss of motor function over time, stabilisation of motor function represents a therapeutic response. This was also the view of a majority of patients with SMA type 2 and 3 and their parents in a large survey conducted in Europe [45,46]. Our SMA type 3 patients and all patients older than 14

years of age showed gain or stabilisation of motor function. In the SMA type 3 patients we saw a correlation with age at treatment start for the 6MWT. A limitation in describing motor function in high functioning type 3 patients with high baseline values is the ceiling effect of the RULM and HFMSE to document improvement.

For children there is evidence from the placebo controlled CHERISH trial [12] and the open label extension (SHINE) [47] that treatment with nusinersen improves motor function. The improvement in the HFMSE in our study for type 3 patients was more pronounced than in type 2 patients and contradicts the findings of Darras et al. [47] as well as real-life data by Szabo et al. [48] and Mendonca et al. [49]. However, our finding is in line with the data reported by Hagenacker et al. [50] and Maggi et al. [51], who showed a better nusinersen treatment response of adults with less severe forms of the disease. The improvement of our type 3 patients in the 6MWT corresponds with the findings previously reported by Darras et al. [47] and Hagenacker et al. [50].

## 5. Limitations

The heterogeneity and small number of our population as a reflection of the real-life situation in Switzerland can be seen as a limitation of this study. The low number of patients in each group is a further limitation and a longer follow-up study with larger numbers would be necessary to confirm our findings.

## 6. Conclusion

Nusinersen is an effective treatment of SMA in children and adults, especially in young children with SMA type 1. In our study, no patient died and side effects were mild and transient. Our data confirm that early initiation of treatment positively affects motor outcome in SMA type 1. Patients with SMA type 2 and 3 also gained or stabilised motor function in our cohort. Ventilation and tube feeding became necessary in SMA type 1 children before the age of 2 years, while good motor response was present. Language development and articulation difficulties in SMA type 1 children need to be closely monitored. In our cohort both were not correlated with the need of ventilation and feeding support.

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### Declaration of Competing Interest

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.nmd.2022.02.001](https://doi.org/10.1016/j.nmd.2022.02.001).

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