Effect of nusinersen on motor, respiratory and bulbar function in early-onset spinal muscular atrophy

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5q-associated spinal muscular atrophy is a rare neuromuscular disorder with the leading symptom of a proximal muscle weakness. Three different drugs have been approved by the European Medicines Agency and Food and Drug Administration for the treatment of spinal muscular atrophy patients, however, long-term experience is still scarce. In contrast to clinical trial data with restricted patient populations and short observation periods, we report here real-world evidence on a broad spectrum of patients with early-onset spinal muscular atrophy treated with nusinersen focusing on effects regarding motor milestones, and respiratory and bulbar insufficiency during the first years of treatment.

Within the SMArtCARE registry, all patients under treatment with nusinersen who never had the ability to sit independently before the start of treatment were identified for data analysis. The primary outcome of this analysis was the change in motor function evaluated with the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders and motor milestones considering World Health Organization criteria. Further, we evaluated data on the need for ventilator support and tube feeding, and mortality.

In total, 143 patients with early-onset spinal muscular atrophy were included in the data analysis with a follow-up period of up to 38 months. We observed major improvements in motor function evaluated with the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. Improvements were greater in children >2 years of age at start of treatment than in older children. 24.5% of children gained the ability to sit independently. Major improvements were observed during the first 14 months of treatment. The need for intermittent ventilator support and tube feeding increased despite treatment with nusinersen.

Our findings confirm the increasing real-world evidence that treatment with nusinersen has a dramatic influence on disease progression and survival in patients with early-onset spinal muscular atrophy. Major improvements in motor function are seen in children younger than 2 years at the start of treatment. Bulbar and respiratory function needs to be closely monitored, as these functions do not improve equivalent to motor function.

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Introduction

5q-associated spinal muscular atrophy (SMA) is a rare neuromuscular disorder with the leading symptom of a proximal muscle weakness. In most cases, SMA is caused by a homozygous deletion in the *survival motor neuron 1* (*SMN1*) gene on chromosome 5.[1] More than half of the patients suffer from the most severe phenotype—SMA type 1—that is characterized by marked muscle weakness also affecting bulbar and respiratory function in infancy. These children never gain the ability to sit independently. Life expectancy is below 2 years without disease-specific drug treatment or ventilator support.[2,3]

In Europe, three different disease-modifying drugs (nusinersen, risdiplam and onasemnogene abeparvovec) are now available for the treatment of SMA patients with a dramatic influence on the course of the disease.[4,5] Nusinersen was the first drug to be approved in Europe in 2017 for the treatment of all SMA patients irrespective of age, *SMN2* copy number and disease severity. As an antisense oligonucleotide, nusinersen acts as splicing modifier targeting the intronic splicing silencer N1 in *SMN2*.[6,7] Clinical trial data and real-world data from early access programmes have shown an improvement in motor function and event-free survival (defined as time to death or use of permanent assisted ventilation). An early start of treatment was observed to be crucial for the response to treatment and thus the prognosis and survival of children with SMA type 1.[8–13] Particularly when treatment is started presymptomatically, even children with the most severe type of SMA have the potential of an approximately age-appropriate motor development.[14,15] Data on respiratory and bulbar function are diverse and less promising when treatment is started in symptomatic patients.[16–18]

Approval of orphan drugs often occurs with limited evidence. In particular, data on the long-term effects of the drugs in a broad spectrum of patients are scarce. SMArtCARE was established in 2017 as disease-specific registry in Germany, Austria and Switzerland to collect real-world data on all available SMA patients.[19] We here report data on patients with early-onset SMA treated with nusinersen regarding effects on motor milestones, and respiratory and bulbar insufficiency during the first years of treatment.

Material and methods

SMArtCARE registry and study design

SMArtCARE is a disease-specific registry to collect longitudinal data on all available SMA patients with 49 participating adult and paediatric centres in Germany, Austria and Switzerland.[12,19] The registry encompassed a total number of 897 patients at the time of data analysis. Inclusion criterion for patients to be enrolled in SMArtCARE is a genetically confirmed 5q SMA. Genetic test results including *SMN2* copy number were reported by the centres using their local genetic testing providers; they were not confirmed by central genetic retesting within the SMArtCARE registry. Data are collected prospectively during routine patient visits as real-life outcome data supported by standardized case report forms that are aligned with the international consensus for SMA registries.[20,21] To evaluate motor function of patients, standardized physiotherapeutic assessments are recommended to be performed every 4 months. These physiotherapeutic assessments are not mandatory within the SMArtCARE data collection und thus not available for all patients at all time points. Follow-up time was set to a maximum of 38 months—the last available visit was evaluated for each patient. Central ethics approval was obtained by the ethics committee of the University of Freiburg (EK-Freiburg 56/18), and local ethics approvals were obtained from all participating centres. SMArtCARE is registered in the German Clinical Trials Registry (DRKS00012699).

Patient cohort

We identified all patients under treatment with nusinersen in our database (data cut 15 February 2021). Inclusion criteria for this analysis were that children were younger than 18 years of age and never able to sit independently before start of treatment. As all patients were treatment naïve at inclusion, we only used motor function and not age of onset (e.g. <6 months of age) for SMA type classification. All patients were symptomatic at the start of treatment as assessed by the treating physicians. None of the patients was diagnosed by newborn screening programmes. Only patients were included with a documentation of baseline characteristics and motor function at the first visit, which corresponded to treatment initiation. If patients changed drug treatment, no further data were evaluated after discontinuation of nusinersen treatment. None of the patients received combination therapy with either onasemnogene abeparvovec or risdiplam. Patients were allocated to subgroups according to age at start of treatment: cohort 1a ≤2 years of age and cohort 1b >2 years of age. The definition of subgroups was based on previous results with different responses to treatment regarding motor function in children younger or older than 24 months.[9,22]

Outcomes

Primary outcome of this data analysis was the change in motor function evaluated with the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and motor milestones considering WHO criteria. Independent sitting was defined as sitting up straight with head erect for at least 10 seconds without using hands or arms to support position accordingly.[23] The CHOP INTEND consists of 16 items with a total score of 64 points with higher scores indicating better motor function.[24,25] Participating physiotherapists were regularly trained to ensure inter-rater reliability. Further, longitudinal data on the need for ventilator support with three categories (no ventilator support, non-invasive ventilation <16 h per day, non-invasive ventilation >16 h per day or invasive ventilation), the need for tube feeding (no tube feeding, supplementary tube feeding, exclusive tube feeding), and mortality were evaluated. Adverse events (AE) were recorded as AE with or without hospitalization and specified using the Medical Dictionary for Regulatory Activities code.[26]

Statistical analysis

Primary and secondary outcome measures and cohorts for subgroup analysis were defined in a statistical analysis plan before data were extracted from the database. Descriptive analyses were performed by calculation of absolute frequencies and percentages. Continuous data were analysed as mean ± standard deviation and median with range. Analyses were based on comparisons from baseline to month 14 (m14), month 26 (m26) and month 38 (m38). Inferential analyses were applied to evaluate the effect of age at diagnosis, age at start of treatment, *SMN2* copy number, gender, baseline CHOP INTEND score and elapsed time from baseline on changes in CHOP INTEND score. Further, logistic regression analyses were performed to evaluate the effect of age at start of

treatment, gender, *SMN2* copy number and changes ≥4 points in CHOP INTEND score on the need for ventilator support or tube feeding. For the time-to-event analyses, Kaplan–Meier curves were computed for the probabilities of gaining a motor milestone and the need for ventilation support or tube feeding. All curves are presented as cumulative incidence. Statistical analysis was performed using R statistical software (v.4.0.4).[27] A *P*-value of <0.01 was considered statistically significant.

Data availability

All data included in this analysis are recorded in the SMArtCARE registry. Data can be obtained anonymized and aggregated upon request and approval by the SMArtCARE steering committee.

Results

Within the SMArtCARE data collection, we identified 143 patients who met the inclusion criteria. Data were collected and documented at 28 neuropediatric departments in Germany and Austria. Baseline characteristics of all patients allocated to cohort 1a and 1b are summarized in Table 1. The number of patients per cohort and time points are listed in Table 2. Mean follow-up time was 23.3 ± 12.9 months in cohort 1a and 27.6 ± 11.0 in cohort 1b with a range of 0 to 38 months. 44.8% of patients completed the m38 follow-up. During the observation period, seven patients (4.9%) changed treatment to risdiplam. Three patients (2.1%) were lost to follow-up with no data entered >12 months.

Motor milestones

During the observation period of up to 38 months of treatment with nusinersen, 29 children in cohort 1a (33.0%) and six children in cohort 1b (10.9%) gained the ability to sit independently, a milestone that is usually not reached in SMA type 1 patients without disease-modifying treatment.[28] In cohort 1a, four children (4.5%) gained the ability to stand and two children (2.3%) gained the ability to walk. Details on patients who gained new motor milestones under treatment with nusinersen are summarized in Table 3. The probability to gain the ability to sit increased to 44.8% in cohort 1a and 12.9% in cohort 1b at last observation. Figure 1 demonstrates the probability to gain the ability to sit in both cohorts. In both cohorts, no motor milestones were lost under treatment with nusinersen. The greatest improvements were observed within the first 14 months: of all children in cohort 1a who gained the ability to sit, 23 patients (79.3%) achieved the motor milestone between baseline and m14, four (13.8%) between m14 and m26, and only two children (3.4%) between m26 and m38.

CHOP INTEND

CHOP INTEND scores improved in both cohorts under treatment with nusinersen, whereas improvements in cohort 1a were greater than in cohort 1b. Only including patients with CHOP INTEND scores at baseline and m38, in cohort 1a improvements in CHOP INTEND score were mean 12.8 points ($n = 14$), and in cohort 1b mean 3.3 points ($n = 8$). In untreated children with SMA type 1, CHOP INTEND score is expected to decrease within the first 12 months after diagnosis.[29] Figure 2 displays the difference of the longitudinal progression of all patients in both cohorts.

Again, main improvements were observed in both cohorts between baseline and m14: Between baseline and m14, 32 children (43.8%) in cohort 1a and seven children (14.0%) in cohort 1b experienced an improvement in CHOP INTEND score >4 points. Between m14 and m26, eight children (14.3%) in cohort 1a and four children (9.5%) in cohort 1b, and between m26 and m38 four children (11.8%) in cohort 1a and two children in cohort 1b (6.7%) showed greater improvements than four points in CHOP INTEND score, respectively (Fig. 3 and Supplementary Fig. 1). In natural history, mean decrease in CHOP INTEND score is expected to be >10 points within the first 12 months.[29]

Inferential analysis revealed the following covariates to have a significant influence on changes in CHOP INTEND score: improvements in CHOP INTEND score were significantly smaller in time-period m26—m38 compared with the time-period baseline—m14.

Table 1 Baseline characteristics of all patients

	Cohort 1a ($n = 88$)	Cohort 1b ($n = 55$)
Age at symptom onset, months	2.8 ± 2.5, 2 [0–10]	6.2 ± 7.8, 5 [0–56]
Age at start of treatment, months	8.4 ± 6.0, 7 [0–24]	89.8 ± 58.4, 68 [24–207]
SMN2 copy number		
1 *SMN2*	1 (1.1%)	1 (1.8%)
2 *SMN2*	64 (72.7%)	18 (32.7%)
3 *SMN2*	17 (19.3%)	20 (36.3%)
≥4 *SMN2*	1 (1.1%)	3 (5.5%)
Unknown	5 (5.7%)	13 (23.6%)
Ventilator support		
No ventilator support	60 (68.1%)	16 (29.1%)
Ventilator support during intercurrent illness only	0 (0%)	2 (3.6%)
Ventilator support <16 h per day	14 (15.9%)	20 (36.4%)
Ventilator support ≥16 h per day	13 (14.8%)	16 (29.1%)
Unknown	1 (1.1%)	1 (1.8%)
Nutrition		
No tube feeding	62 (70.5%)	34 (61.8%)
Tube feeding supplementary	17 (19.3%)	14 (25.5%)
Tube feeding exclusively	9 (10.2%)	7 (12.7%)
Unknown	0 (0%)	0 (0%)
CHOP INTEND score (*n*)	27.9 ± 14.6 (70), 25 [1–62]	20.1 ± 14.7 (30), 20 [1–57]

Baseline characteristics of all patients allocated to cohort 1a and 1b. Data are listed as mean ± standard deviation and median [range] or *n* (%).

Table 2 Number of patients per cohort and time point

Cohort	Baseline	m14	m26	m38
1a	88	73	56	34
1b	55	50	42	30

Further, children with higher baseline CHOP INTEND score showed significant smaller improvements than children with lower CHOP INTEND scores—most likely due to a ceiling effect of the CHOP INTEND. Younger age at start of treatment was associated with larger improvement in CHOP INTEND score. *SMN2* copy number was not revealed to have a significant influence on changes in CHOP INTEND. Thus, the better outcome in cohort 1a can be explained by earlier treatment initiation (Table 4).

Need for ventilator support and tube feeding

During the observation period, the probability of the need for any ventilator support increased from 29.5% at baseline to 59.7% at m38 and from 70.9 to 79.0% in cohorts 1a and 1b, respectively. Five children (3.5%) [three children in cohort 1a (3.4%) and two children in cohort 1b (3.6%)] became additionally dependent on invasive ventilation. Of these, two children required permanent ventilation (>16 h/day). The probability of the need for tube feeding increased from 23.9% at baseline to 52.5% at m38 in cohort 1a and from 43.6% at baseline to 51.4% in cohort 1b at last observation. Figure 4 demonstrates the probability of the need for ventilator support or tube feeding in both cohorts. Logistic regression analysis resulted in *SMN2* copy number having a significant effect on the need for tube feeding and tends to have an effect on the need for ventilator support. Patients with three *SMN2* copies had a lower probability to start ventilator support or tube feeding under treatment with nusinersen than patients with two *SMN2* copies. Conversely, positive changes in CHOP INTEND score ≥4 points had no influence on the need for ventilator support or tube feeding (see Supplementary Table 1).

Mortality

In addition to the five children who became dependent on invasive or permanent ventilation, three children (2.1%) died during the observation period (two children in cohort 1b and one child in cohort 1a): mean age at death was 46.3 months (rage 13–74 months) and mean treatment duration was 24.3 months (range 11–36 months). Cause of death was acute respiratory tract infection in one child and clinical deterioration due to previous respiratory tract infections in the remaining children.

Adverse events

In total, 239 AEs among 74 patients were reported during the observation period: 173 AEs in cohort 1a and 66 AEs in cohort 1b. Of all AEs, 179 (74.9%) were AEs with hospitalization and 58 (24.3%) without hospitalization. The most common type of AE were respiratory tract infections (64.9%), followed by acute respiratory failure (5.9%), gastroenteritis (6.3%), abdominal symptoms including constipation, abdominal pain and gastritis (5.4%), epileptic seizures (3.3%) or febrile seizures (3.3%), other type of infections (2.9%), post-lumbar puncture syndrome (2.1%), aspiration (1.3%), nephrocalcinosis (0.8%) and others (3.3%).

Table 3 Motor milestones

	Cohort 1a	Cohort 1b
Gaining the ability to sit		
SMN2 copy number		
1 *SMN2*	1 (3.4%)	0 (0%)
2 *SMN2*	14 (48.3%)	0 (0%)
3 *SMN2*	12 (41.4%)	3 (50%)
≥4 *SMN2*	0 (0%)	1 (16.6%)
Unknown	2 (6.9%)	2 (33.3%)
Age at start of treatment	9.7 ± 6.0, 8 [0–24]	63.3 ± 39.7, 52 [26–117]
Gaining the ability to stand		
SMN2 copy number		
1 *SMN2*	0 (0%)	
2 *SMN2*	2 (50%)	
3 *SMN2*	2 (50%)	
≥4 *SMN2*	0 (0%)	
Unknown	0 (0%)	
Age at start of treatment	7.3 ± 7.9, 7 [0–15]	
Gaining the ability to walk		
SMN2 copy number		
1 *SMN2*	0 (0%)	
2 *SMN2*	1 (50%)	
3 *SMN2*	1 (50%)	
≥4 *SMN2*	0 (0%)	
Unknown	0 (0%)	
Age at start of treatment	5.5 ± 7.8, 5.5 [0–11]	

Details on patients who gained motor milestones with *SMN2* copy number and age at start of treatment. Data are listed as mean ± standard deviation and median [range] or *n* (%).

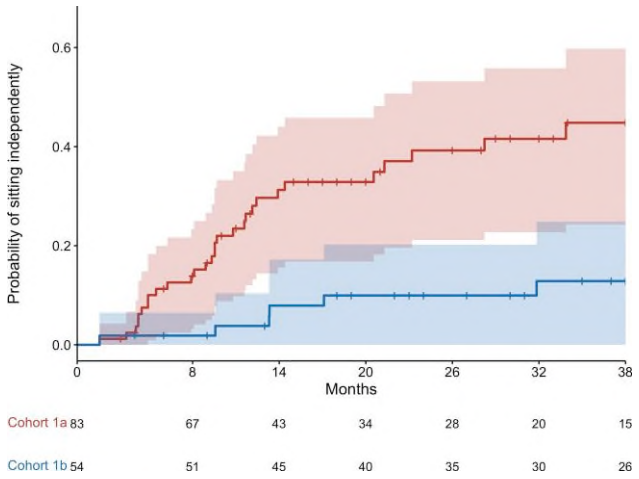

Figure 1 Probability to gain the ability to sit independently. The probability to gain the ability to sit independently under treatment with nusinersen in cohort 1a (red) and 1b (blue), respectively. Numbers at risk are listed for dedicated time points. Coloured areas indicate 99% confidence intervals.

Discussion

Data from clinical trials and early access programmes have demonstrated nusinersen to be an effective and well-tolerated drug to significantly influence the course of the disease in SMA patients. Most data encompass smaller cohorts and an observation period of a maximum of 2 years.[8,9,22] We report our results here on longitudinal data from patients with early-onset SMA treated with nusinersen that were documented within the SMArtCARE registry with an observation period of up to 38 months.

In SMA type 1 patients, the age at start of treatment was shown to have a decisive influence on the response to treatment with nusinersen.[10,12,22] This finding is confirmed by our data analysis demonstrating a greater change in CHOP INTEND score and motor milestones in children younger than 2 years at start of treatment. We recently published a consensus statement on the indication of treatment with nusinersen in children with SMA type 1. Here, an observation period of 12–24 months was recommended to evaluate the response to treatment with the main limitation of a lack of long-term follow-up data.[30] Our data show that—especially in cohort 1a—major improvements in motor function were observed within the first 14 months of treatment followed by a plateau phase with stabilization of the course of the disease. Even in children older than 2 years at start of treatment, improvements >4 points in CHOP INTEND score were observed in a small percentage of children. Thus, nusinersen has the potential to improve or to stabilize disease progress in most patients with early-onset SMA. Larger and especially opposite fluctuations in the CHOP INTEND score over time, that were observed in a few children (see Fig. 3), may be caused by the compliance of the children in the test situations or e.g. by acute deteriorations in the context of infections. So far, it is not sufficiently understood how changes in the CHOP INTEND score affect everyday functions or motor milestones. In most of the children in cohort 1b, no improvements in motor milestones were observed. Therefore, especially in these children, the indication for the intrathecal treatment with nusinersen remains an individual shared-decision process balancing benefit and burden of the treatment.

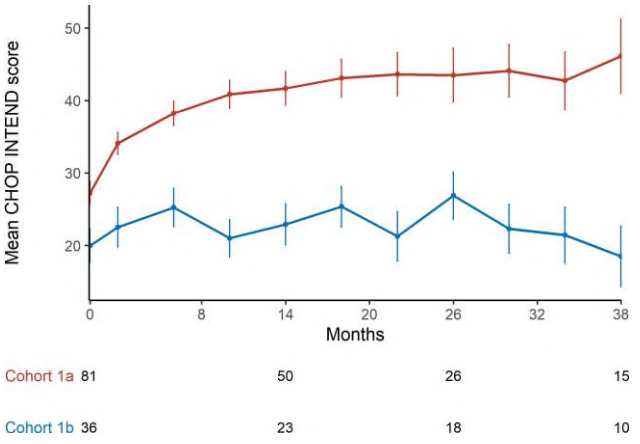

Figure 2 Longitudinal progression of CHOP INTEND score. CHOP INTEND score for cohort 1a (red) and 1b (blue). Data are listed as mean and standard error. Available patients at baseline, m14, m26 and m38 are added. For a group size <10 patients no data are depicted.

Focusing on motor milestones under treatment with nusinersen, 33.0% of children in cohort 1a gained the ability to sit independently within the first 38 months of treatment compared to 31.9% reported by Aragon-Gawinska *et al.*[8] and 30.9% reported by Pane *et al.*[22] In contrast to the natural course of SMA type 1 children, this is an exceeding success, but the results are inferior to data from presymptomatically treated infants that have the potential of an approximate age-appropriate motor development.[14,15] This finding again underlines the importance of an ubiquitous accessibility to newborn screening programmes [14,31] and drug treatment.

While motor function shows continuous improvements or stabilization following treatment with nusinersen, data on respiratory

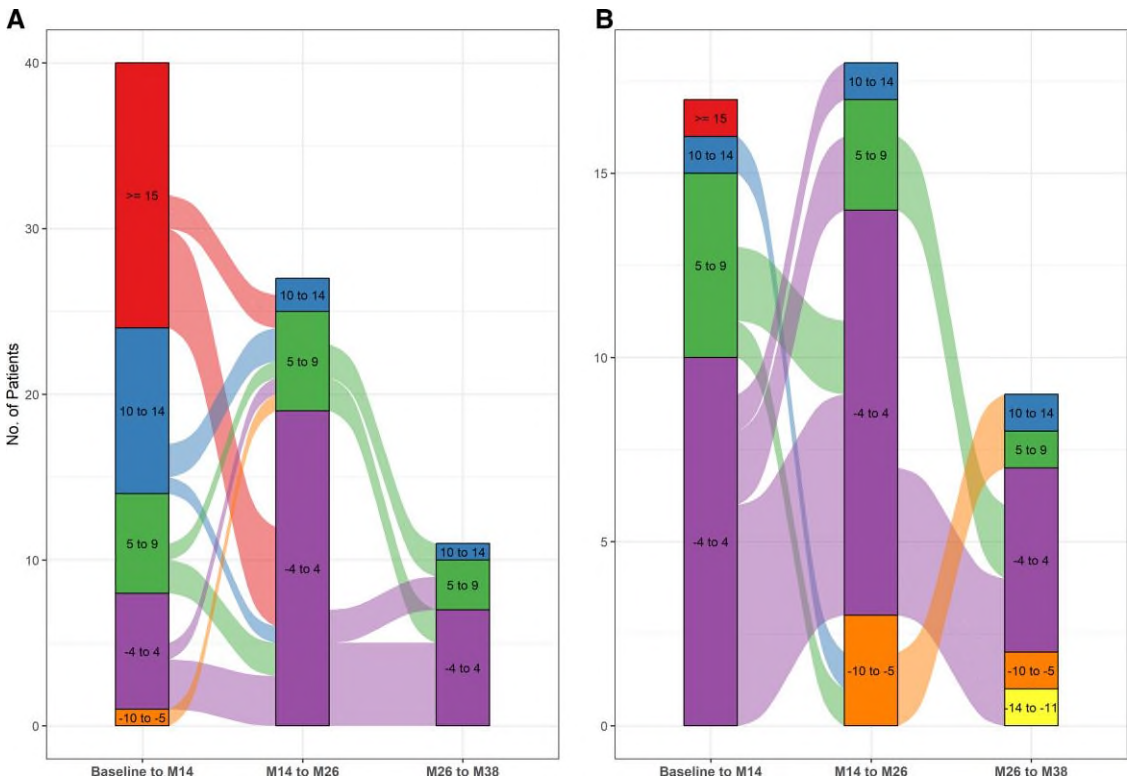

Figure 3 Responder analysis. Responder analysis for (**A**) cohort 1a and (**B**) cohort 1b. Different colours indicate response groups according to changes in CHOP INTEND score per time-period (baseline–m14, m14–m26, m26–m38). Lines between columns indicate the progression of patients over time with either gaining or losing points in CHOP INTEND score.

and bulbar insufficiency are less promising with an increasing need for intermittent ventilator support and tube feeding in symptomatic treated SMA type 1 patients.[16,17,18] Patients who had been using ventilator support since treatment initiation are reported to remain stable with less serious exacerbations due to respiratory infections. But most patients not using ventilator support at start of treatment required non-invasive ventilation during a 2-year follow-up.[16,17] Van der Heul *et al.* focused on bulbar function in treated and untreated SMA type 1 patients. Here, swallowing function deteriorated between the ages of 8 to 12 months under treatment with nusinersen.[18] In our cohort, the probability of the need for ventilator support and tube feeding also increased under treatment with nusinersen. Particularly in cohort 1a, the need for ventilator support and tube feeding increased despite great improvements in motor function during the first 14 months of treatment. However, only two patients became additionally dependent on permanent ventilation, which contrasts the natural course of untreated patients with a probability of permanent ventilator support of up to 80% within the first 2 years of age.[32] Thus, our data suggest that treatment with nusinersen can prevent the need for permanent ventilation in symptomatic treated patients, but a significant number of patients will still require intermittent ventilator support. Therefore, early informed consent discussions with parents before start of treatment remain decisive for symptomatic treated SMA type 1 patients. The DEVOTE study—an ongoing clinical trial—is currently investigating the efficacy and safety of a higher dosage of nusinersen. It is important to see whether respiratory and bulbar outcomes will improve under the higher dosage potentially through a better bioavailability in the bulbar or higher cervical motor nuclei. Further, research is needed on presymptomatically treated patients to evaluate whether respiratory and bulbar outcomes are as favourable as motor development. Here, standardized and detailed assessments to evaluate respiratory and bulbar function in infants need to be implemented in clinical routine.

Reported AEs were compatible with known side-effects of lumbar puncture, related to underlying disease or not observed with increased frequency compared to other infants of similar age. Thus, we did not detect any new safety signals concerning long-term treatment with nusinersen.

The significance of real-world data and evidence for post-marketing surveillance compared to results from clinical trials is intensely discussed. Main limitations of real-world data were identified as absence of standards for defining content, completeness and quality of data, absence of standards for analysis and data linkage, and limited access to data for all stakeholders.[33,34] Nevertheless, real-world data play an increasing role in regulatory processes especially in rare diseases.[35,36] Within the SMArtCARE registry, we use standardized case report forms and outcome measures for data collection. Physiotherapists are regularly trained to ensure inter-rater reliability. Data are reviewed for completeness,

Table 4 Inferential analysis

	Estimate	Confidence interval[a]		d.f.	P-value
		0.5%	99.5%		
(Intercept)	7.500	4.16	10.84	581	<0.001
baseline_m14 versus m14_m26	−0.587	−2.42	1.25	581	0.41
baseline_m14 versus m26_m38	**−3.127**	**−6.15**	**−0.11**	**581**	**0.008**
Age at diagnosis	0.012	−0.22	0.25	112	0.9
Age at start of treatment	−0.033	−0.07	−0.00	112	0.01
SMN2 copy number	0.787	−2.57	4.15	112	0.55
Gender (male)	−0.377	−2.93	2.18	112	0.70
CHOP INTEND score at baseline	**−0.129**	**−0.23**	**−0.03**	**112**	**<0.001**

Inferential analysis evaluates the effect of age at diagnosis, age at start of treatment, *SMN2* copy number (2 *SMN2* copies versus ≥3 *SMN2* copies), gender, baseline CHOP INTEND score and past time from baseline on changes in CHOP INTEND score. d.f. = degree of freedom.

[a]Lower bound confidence interval = 0.5%; upper bound confidence interval = 99.5%.

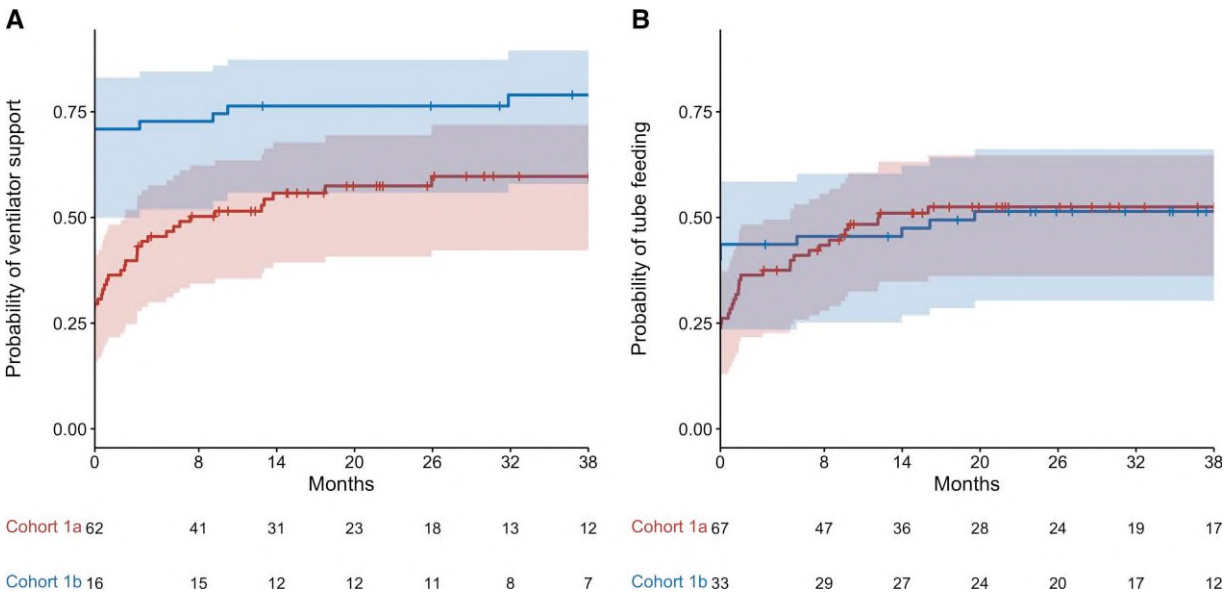

Figure 4 Probability of ventilator support and tube feeding. The probability for the need of ventilator support (**A**) or tube feeding (**B**) under treatment with nusinersen in cohort 1a (red) and 1b (blue), respectively. Events are defined as new need for ventilator support or tube feeding independent of type of ventilator support or tube feeding. Numbers at risk are listed for dedicated time points. Coloured areas indicate 99% confidence interval.

consistency and plausibility. We further follow the FAIR principles[37] having aligned the items for data collection with other international SMA registries.[19] In addition, analyses have to be adapted to remaining inconsistencies and incompleteness of data. In our cohort, age at symptom onset was documented as later than 6 months in 25% of children, and later than 12 months in 3% of children, which is not consistent with the classical definition of SMA type 1. We only considered motor function for SMA type classification to ensure comparability of patients, as the information of age at symptom onset is assessed retrospectively in symptomatic patients and might differ in parents' perception. Further, 4.2% of patients of our cohort had either one or four *SMN2* copies, which is rather unusual but not unreported for a phenotype of SMA type 1.[38,39] However, the number of patients with one or four *SMN2* copies in the total cohort was too small so that they were analysed collectively as ≤2 SMN2 copies or ≥3 SMN2 copies rather than separately. Further research is needed to implement standards for analysis and data linkage to increase the real-world evidence for decision-making processes in clinical routine but also for regulatory purposes.

All neuromuscular centres in Germany, Austria and Switzerland are invited to participate in the SMArtCARE data collection without any selection criteria. We included data from centres that were initiated at the time of data analysis (February 2021). Centres were geographically distributed across Germany and Austria. Therefore, we consider our cohort to be representative for these countries in the follow-up period.

In conclusion, our findings add to the increasing real-world evidence that nusinersen is an effective treatment in patients with early-onset SMA leading to major improvements in motor function in children <2 years of age at start of treatment. Main changes in motor function were observed within the first 14 months of treatment. In symptomatic treated SMA type 1 patients, bulbar and respiratory function need to be closely monitored as these functions do not improve equivalent to motor function.

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Competing interests

A.P. received compensation for advisory boards, training activities and research grants from Novartis and Biogen. S.V. received compensation for advisory boards and training activities from Biogen. S.St. received compensation for advisory boards and training activities from Roche and Biogen. G.B. received compensation for advisory boards from Biogen, Novartis and Roche. T.H. received compensation for advisory boards, lectures from Biogen, Roche, Novartis GeneTherapies, Sanofi-Genzyme, Hormosan, Alnylam and Alexion and research support from Biogen, Roche and Novartis GeneTherapies. U.S. received honoraria for adboards, invited talks and scientific counselling from Novartis, Biogen and Roche. M.D. received personal fees as speaker/consultant from Biogen, Roche, Sanofi-Genzyme and Alnylam. A.E. received honoraria for adboards and invited talks from Roche, Novartis, Sarepta and Biogen. M.F.B. received honoraria for participation in advisory boards and consultancy fees from Biogen, Roche and Novartis. V.H. participated in workshops and received compensation for advisory boards from Novartis and Biogen. R.A.H. received compensation for advisory board participation and personal fees from Novartis and received consulting fees and honoraria for lectures support from Biogen. S.I. received compensation for advisory boards from Novartis. J.J. received advisory board and/or speaker honoraria and financial support for conference attendances from Avexis/Novartis, Biogen, Roche, PTC and Sarepta. M.M. received compensation for expert meetings, training activities and data collection from Novartis, Roche and Biogen. G.S. received payment for one presentation and one patient casuistic from Novartis. M.S. received compensation for participation in advisory boards by Biogen, in workshops by Roche and for presentations for Avexis/Novartis Gene Therapies. R.T. received compensation for advisory boards from Novartis and Biogen. K.V. has received travel expenses and speaker fees from Biogen. C.W. received compensation for advisory boards, presentations and publications from Novartis, Biogen and Roche. G.W. received compensation for advisory boards from Roche, EISAI and Desitin. A.Z. received compensation for advisory boards from Novartis gene Therapies, Biogen and Roche, personal fees for presentations from Novartis, Biogen and Roche and a research grant from Biogen. H.L. does consultancy and received financial support for research projects and clinical trials from Amplo Biotechnology, AMO Pharma, Biogen, Desitin, Fulcrum Therapeutics, GW Pharma, KYE Pharmaceuticals, Milo Biotechnology, Pfizer, PTC Therapeutics, Hoffman-La Roche Limited, Sanofi-Genzyme, Santhera, Sarepta, Satellos and Ultragenyx. H.L. is the Editor-in-Chief for the *Journal of Neuromuscular Diseases* (IOS Press). J.K. received compensation for research and/or educational and consultancy activities from Biogen, Avexis/Novartis, Roche and Scholar Rock.

Appendix 1

SMArtCARE study group

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