Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study

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Summary

Background Nusinersen is approved for the treatment of 5q spinal muscular atrophy of all types and stages in patients of all ages. Although clinical trials have shown improvements in motor function in infants and children treated with the drug, data for adults are scarce. We aimed to assess the safety and efficacy of nusinersen in adults with 5q spinal muscular atrophy.

Methods We did an observational cohort study at ten academic clinical sites in Germany. Patients with genetically confirmed 5q spinal muscular atrophy (age 16–65 years) with a homozygous deletion of exons 7, 8, or both, or with compound heterozygous mutations were eligible for inclusion and received nusinersen treatment in accordance with the label for a minimum treatment time of 6 months to a follow-up of up to 14 months. The primary outcome was the change in the total Hammersmith Functional Motor Scale Expanded (HFMSE) score, assessed at months 6, 10, and 14, and based on pre–post comparisons. This study is registered with the German Clinical Trials Register (number DRKS00015702).

Findings Between July 13, 2017, and May 1, 2019, 173 patients were screened, of whom 139 (80%) were eligible for data analysis. Of these, 124 (89%) were included in the 6-month analysis, 92 (66%) in the 10-month analysis, and 57 (41%) in the 14-month analysis; patients with missing baseline HFMSE scores were excluded from these analyses. Mean HFMSE scores were significantly increased compared with baseline at 6 months (mean difference 1·73 [95% CI 1·05–2·41], p<0·0001), 10 months (2·58 [1·76–3·39], p<0·0001), and 14 months (3·12 [2·06–4·19], p<0·0001). Clinically meaningful improvements (≥3 points increase) in HFMSE scores were seen in 35 (28%) of 124 patients at 6 months, 33 (35%) of 92 at 10 months, and 23 (40%) of 57 at 14 months. To 14-month follow-up, the most frequent adverse effects among 173 patients were headache (61 [35%] patients), back pain (38 [22%]), and nausea (19 [11%]). No serious adverse events were reported.

Interpretation Despite the limitations of the observational study design and a slow functional decline throughout the natural disease course, our data provide evidence for the safety and efficacy of nusinersen in the treatment of adults with 5q spinal muscular atrophy, with clinically meaningful improvements in motor function in a real-world cohort.

Funding None.

Introduction

5q spinal muscular atrophy, an autosomal-recessive inherited neuromuscular disorder, leads to progressive muscle atrophy and weakness. It is caused by degeneration of anterior horn cells in the spinal cord, which results in tetraparesis and paralysis of the respiratory muscles. Around 1 in 11 000 people are affected by the disorder, and it is a common genetic cause of early infant mortality.[1,2] The classification of spinal muscular atrophy is based on the achievement of motor milestones and age of symptom onset. 5q spinal muscular atrophy is caused by a homozygous deletion or mutation in the survival motor neuron 1 *(SMN1)* gene, which is one of two genes encoding the SMN protein, located on chromosome 5q13.2.[3,4]

Nusinersen is an antisense oligonucleotide capable of modifying the expression of the *SMN2* gene, thus increasing production of SMN protein and improving motor function. On the basis of the results of two pivotal studies,[5,6] nusinersen was approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) as the first drug treatment option for 5q spinal muscular atrophy in patients of all ages, types, and disease stages.[5–8]

However, very few data on nusinersen treatment in adults with spinal muscular atrophy are available. An observational study of 19 adult patients with spinal muscular atrophy type 3 showed a significant increase in motor function after 300 days of treatment.[9] However,

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See **Comment** page 283

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Research in context

Evidence before this study

We searched PubMed, MEDLINE, and the Cochrane Database of Systematic Reviews for English-language articles published up to Oct 29, 2019, using the search terms "spinal muscular atrophy" OR "SMA" AND "treatment" OR "nusinersen" AND "adults". Two large randomised phase 3 trials, ENDEAR (2017) and CHERISH-Study (2018), showed nusinersen at a dose of 12 mg per intrathecal injection to be an efficacious treatment for spinal muscular atrophy in infants and children, leading to improved survival in children with spinal muscular atrophy type 1 and improved motor function in children with spinal muscular atrophy type 2 or 3. Although nusinersen was the first available medical treatment for spinal muscular atrophy, to date only one prospective study on the efficacy of nusinersen in adult patients with 5q spinal muscular atrophy has been done. In this single-centre study, a group of 17 adult patients with 5q spinal muscular atrophy type 3 were observed over 1 year, and showed significant increases in 6-minute walk test distances, Revised Upper Limb Module scores, and peak cough flow with nusinersen, while scores on the Hammersmith Functional Motor Scale Expanded and Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised were not significantly altered.

Added value of this study

Patients with spinal muscular atrophy type 2 or 3 reach adulthood with varying states of motor dysfunction and with slow but ongoing disease progression. Therefore, evidence for the efficacy of current and future therapies in this patient population is warranted. This observational study provides evidence for the safety and efficacy of nusinersen in a large real-world cohort of adult patients with 5q spinal muscular atrophy. In this study, numerous patients showed clinically meaningful improvements in motor function or showed stabilisation of the disease, independent of age.

Implications of all the available evidence

In line with a previous observational study, there is increasing evidence for the efficacy of nusinersen in adult patients with 5q spinal muscular atrophy, to a similar extent as has been shown for infants and children in randomised controlled trials, suggesting that age might not be a predictor for treatment efficacy in spinal muscular atrophy.

because of the small sample size and the non-inclusion of adult patients with 5q spinal muscular atrophy type 2, additional studies in these patients are needed. We aimed to investigate the safety and efficacy of nusinersen in adult patients with 5q spinal muscular atrophy.

Methods

Study design and participants

In this prospective, multicentre, observational study, we included adult patients with 5q spinal muscular atrophy from ten German neurological centres (Departments of Neurology in Essen, Ulm, Dresden, Hanover, Munich, Cologne, Heidelberg, Rostock, Halle, and Göttingen). Inclusion criteria were a genetically confirmed 5q spinal muscular atrophy with a homozygous deletion of exons 7, 8, or both, or with compound heterozygous mutations, and nusinersen treatment administered continuously according to the official prescribing information with a minimum treatment time of 6 months. All patients treated with nusinersen at each centre were included. No other selection criteria were defined. Study approval was obtained from the local ethics committees of all participating sites (approval numbers 18-8285-BO [Essen], 19/12 [Ulm], EK393122012 [Dresden], 6269 [Hanover], 16/14 [Munich], 14-305 [Cologne], S-554/2018 [Heidelberg], A 2019-0054 [Rostock], 2013-19 [Halle], and 10/2/17 [Göttingen]). All patients gave written informed consent.

Procedures

In all patients, 12 mg nusinersen was administered intrathecally on days 1, 14, 28, and 63, with repeated maintenance injections every 4 months in accordance with the label. Intrathecal injections by a trained neurologist or neuroradiologist were given via conventional, fluoroscopy-guided or CT-guided lumbar puncture. Patients were then observed for at least 3 h after each procedure for possible adverse events. Assessments were done on each injection day.

Evaluations were done according to the recommendations of the SMArtCARE real-world data collection initiative.[10] Patients were evaluated at baseline, at the completion of the loading phase (day 63), and every 4 months thereafter for a maximum of 14 months in total. Evaluators were trained by experienced physiotherapists from the SMArtCARE initiative from Freiburg University (Freiburg, Germany).

Outcomes

The primary endpoint was the change from baseline in the total Hammersmith Functional Motor Scale Expanded (HFMSE) score at months 6, 10, and 14. The HFMSE consists of 33 itemised motor functions to assess activities of daily living. Each item is scored on a scale from 0 to 2, with higher scores indicating better motor function, up to a maximum of 66 points. A score change of at least 3 points is considered to be a clinically meaningful improvement.[11]

Secondary endpoints were the change from baseline to months 6, 10, and 14 in the Revised Upper Limb Module (RULM) score (20 items with a maximum of 37 points, with higher scores indicating better arm function, and a score change of at least 2 points considered to be clinically meaningful), and the 6-minute walk test (6MWT; measuring the distance a patient is able to walk within 6 min).

Adverse drug reactions were evaluated and reported according to MedDRA (version 21.1).

Statistical analysis

Statistical analyses were based on pre–post comparisons from baseline to months 6, 10, and 14. In a pre–post comparison, a difference of 0·31 or greater in an effect size can be detected with a power of 80% and with a two-sided α of 0·05. This estimation is suitable for the primary endpoint and for the descriptive analysis of the secondary endpoints. Statistical analyses were done using the estimates of the pre–post differences for primary and secondary endpoints together with the corresponding 95% CIs and by using the Wilcoxon signed-rank test. Correlations were analysed by Spearman's rank correlation coefficient with α set to 0·05.

Several preplanned subgroup analyses were done with patients grouped on the basis of HFMSE baseline score (≥35 *vs* <35) or previous spondylodesis (yes *vs* no). Post hoc, we also did subgroup analyses based on ambulant versus non-ambulant status and on spinal muscular atrophy type (2 *vs* 3). Subgroup analyses were done by Mann-Whitney U test.

A mixed model was used to estimate the effect on the HFMSE score. The model was set up with sex, time, age, spondylodesis, and HFMSE baseline score as fixed effects and patient as a random effect. Outliers were not removed because there were no indications of incorrect measurements. No imputation of missing data was done for the 6-month, 10-month, or 14-month analyses. As no α adjustment was done for the secondary endpoints, the p values presented are to be interpreted on a descriptive basis only. All statistical analyses were done with SAS, version 9.4. The study is registered with the German Clinical Trials Register (number DRKS00015702).

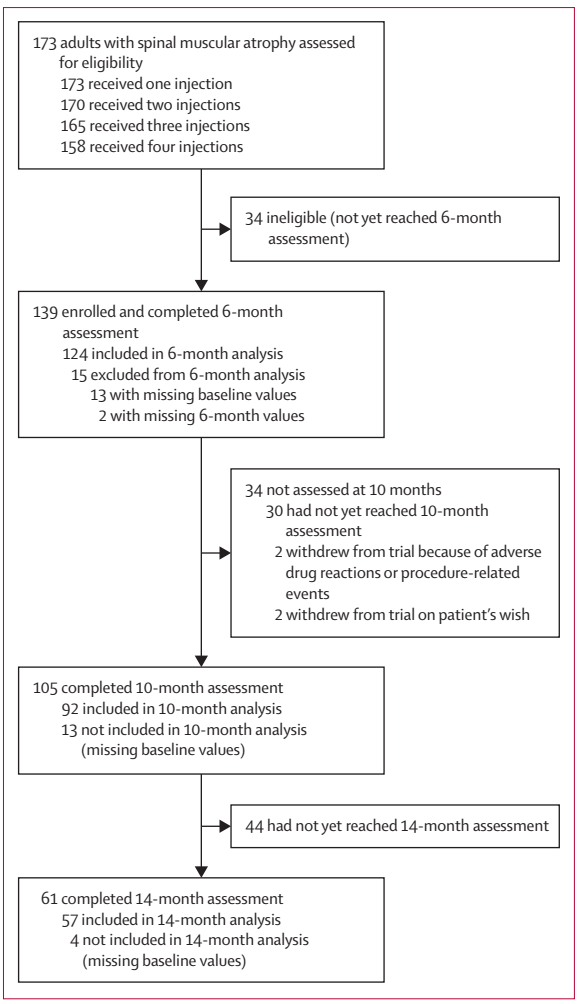

Figure 1: **Study profile**

Role of the funding source

There was no funding source for this study.

Results

Between July 13, 2017, and May 1, 2019, 173 patients were assessed for eligibility for this study, of which 139 (80%) patients completed the 6-month assessment, 105 (61%) completed the 10-month assessment, and 61 (35%) completed the 14-month assessment at the time of analysis. For the 6-month analyses, 15 patients were excluded because 13 patients had missing baseline values (eg, because the patient declined functional testing, there was a competing disease due to bone fracture, or no scoring was done at baseline) and two patients had missing data at 6 months. Two patients withdrew from the treatment because of adverse drug reactions, and two withdrew on the patient's wishes before the 10-month assessment. 30 patients had not yet reached the 10-month assessment and 44 had not reached the 14-month assessment at the time of analysis. The primary endpoint analysis included 124 (89%) patients with a treatment period of at least 6 months, 92 (66%) patients with a treatment period of 10 months, and 57 (41%) patients with a treatment period of 14 months (figure 1). The demographic and clinical baseline data of these patients are presented in table 1.

Mean HFMSE scores were significantly increased compared with baseline at 6 months (mean difference 1·73 [95% CI 1·05–2·41]), 10 months (2·58 [1·76–3·39]), and 14 months (3·12 [2·06–4·19]) after initiation of treatment with nusinersen (figure 2, table 2). Clinically meaningful improvements (≥3 points) in HFMSE score were seen in 35 (28%) of 124 patients at 6 months, 33 (35%) of 92 at 10 months, and 23 (40%) of 57 at 14 months. Except for two patients, all patients with an increase of 3 points or more (ie, clinically meaningful improvement) at 10 months maintained the improvement up to and after 14 months of treatment (figure 2; appendix p 1). Five patients showed an increase in HFMSE score of more than 10 points (three women and two men, three ambulant and two non-ambulant, age range 48–59 years; all with spinal muscular atrophy type 3

See Online for appendix

	Included in 6-month analysis (n=124)	Included in 10-month analysis (n=92)	Included in 14-month analysis (n=57)
Sex			
Female	57 (46%)	39 (42%)	20 (35%)
Male	67 (54%)	53 (58%)	37 (65%)
Age at treatment, years	36 (12; 16–65)	37 (12; 16–65)	33 (11; 16–59)
SMN2 copy number			
2	7 (6%)	7 (8%)	4 (7%)
3	48 (39%)	33 (36%)	21 (37%)
4	41 (33%)	31 (34%)	21 (37%)
5	2 (2%)	1 (1%)	0
6	2 (2%)	0	0
Unknown	24 (19%)	20 (22%)	11 (19%)
Spinal muscular atrophy type			
1	2 (2%)	1 (1%)	0
2	45 (36%)	30 (33%)	20 (35%)
3	77 (62%)	60 (65%)	37 (65%)
4	0	1 (1%)	0
Ambulant	46 (37%)	35 (38%)	23 (40%)
Previous spondylodesis	28 (23%)	18 (20%)	14 (25%)
Baseline HFMSE score (out of 66)	20·74 (21·39)	22·95 (21·66)	24·65 (21·83)
High (≥35 points)	39 (31%)	33 (36%)	22 (39%)
Low (<35 points)	85 (69%)	59 (64%)	35 (61%)
Baseline RULM score (out of 37)	20·87 (13·27)	23·00 (12·80)	23·85 (12·16)
Baseline 6-minute walk test distance, m	321·76 (217·66)	353·03 (218·46)	371·43 (210·34)

Data are n (%), or mean (SD; range). HFMSE=Hammersmith Functional Motor Scale Expanded. RULM=Revised Upper Limb Module.

Table 1: **Baseline characteristics and demographics of analysed patients**

and three or four copies of *SMN2*). 14 patients showed worsening motor function under treatment. A correlation analysis did not reveal any dependence of change in HFMSE score on patient age (6-month change r=–0·03; 10-month change 0·11; 14-month change 0·06; appendix p 8). The correlation coefficient between patient age and HFMSE score at baseline was 0·02 (p=0·7807).

Arm motor function, as measured by the RULM, also improved significantly compared with baseline at months 6, 10, and 14 after initiation of treatment with nusinersen (table 2). At 6 months, 28 (23%) of 120 patients showed an increase of at least 2 points in RULM score (ie, clinically meaningful improvement), whereas 74 (61%) showed no meaningful change, 18 (15%) showed a decline of 1 point or more, and ten (8%) showed a decline of 2 points or more. 28 (23%) patients maintained full functionality according to RULM score (37 of 37 points) 6 months after treatment initiation (appendix p 2). Mean RULM scores were also increased significantly at 10 months (appendix p 3) and 14 months (appendix p 4). 21 (75%) of the 28 patients who showed a clinically meaningful increase in RULM score at 6 months remained stable after 14 months of treatment (appendix pp 2–4). A correlation analysis showed no evidence of dependency of the RULM score at 6 months (r=–0·08, p=0·4000) or 14 months of treatment (r=–0·06, p=0·6478) on the patient's age (appendix p 9). However, age was negatively correlated with change in RULM score after 10 months of treatment (r=–0·23, p=0·0303; appendix p 9).

Mean walking distances on the 6MWT significantly increased at 6 months, 10 months, and 14 months after initiation of treatment with nusinersen (table 2; appendix pp 5–7). HFMSE, RULM, and 6MWT values at baseline, and months 6, 10, and 14, as well as changes between timepoints, are summarised in the appendix (p 13).

The frequency of adverse drug reactions or procedure-related complications was documented for all 173 who received at least one injection. Adverse events occurred in 82 (47%) patients throughout the 14-month period, with headache (61 [35%] patients), back pain (38 [22%]), and nausea (19 [11%]) reported most frequently (table 3).

Exploratory subgroup analyses are summarised in table 4. Exploratory subgroup analysis between the spinal muscular atrophy type subgroups showed that the mean HFMSE scores were significantly increased at months 6, 10, and 14 versus baseline in the spinal muscular atrophy type 2 and type 3 subgroups (table 4). Clinically meaningful improvements (≥3 points increase) in HFMSE scores were seen in 23 (30%) of 77 patients at 6 months, 19 (32%) of 60 at 10 months, and 15 (41%) of 37 at 14 months in the spinal muscular atrophy type 3 subgroup, and in one (2%) of 45 patients at 6 months, two (7%) of 30 at 10 months, and one (5%) of 20 at 14 months in the type 2 subgroup. Mean RULM scores were also significantly increased at all three timepoints in the spinal muscular atrophy type 2 subgroup and at month 14 in the type 3 subgroup, whereas increases at months 6 and 10 in the type 3 subgroup were non-significant (table 4).

Exploratory subgroup analysis between ambulant and non-ambulant patients showed that the mean HFMSE score was significantly increased at months 6, 10, and 14 in both subgroups versus baseline, with significantly larger increases in the ambulant than in the non-ambulant subgroup at all three timepoints (p=0·0007 at 6 months, p=0·0009 at 10 months, and p=0·0127 at 14 months; table 4; appendix p 10).

Mean changes in HFMSE score versus baseline were also analysed in the subgroups of patients with high (≥35 points; n=39 [32%]) or low (<35 points; n=85 [68%]) HFMSE scores at baseline. Significant increases were seen at all three timepoints, with greater improvements seen at months 6 (p=0·0221), 10 (p=0·0143), and 14 (p=0·0036) in patients with high baseline HFMSE scores than in those with low baseline HFMSE scores (table 4; appendix p 10). HFMSE scores at baseline were positively correlated with improvements in the HFMSE score after 6 months (r=0·3, p=0·0006; appendix p 10).

Mean HFMSE scores increased in patients with spondylodesis (n=28) and without spondylodesis (n=96), with no significant differences in improvement between these two subgroups at months 6 (p=0·2900), 10 (p=0·2543), or

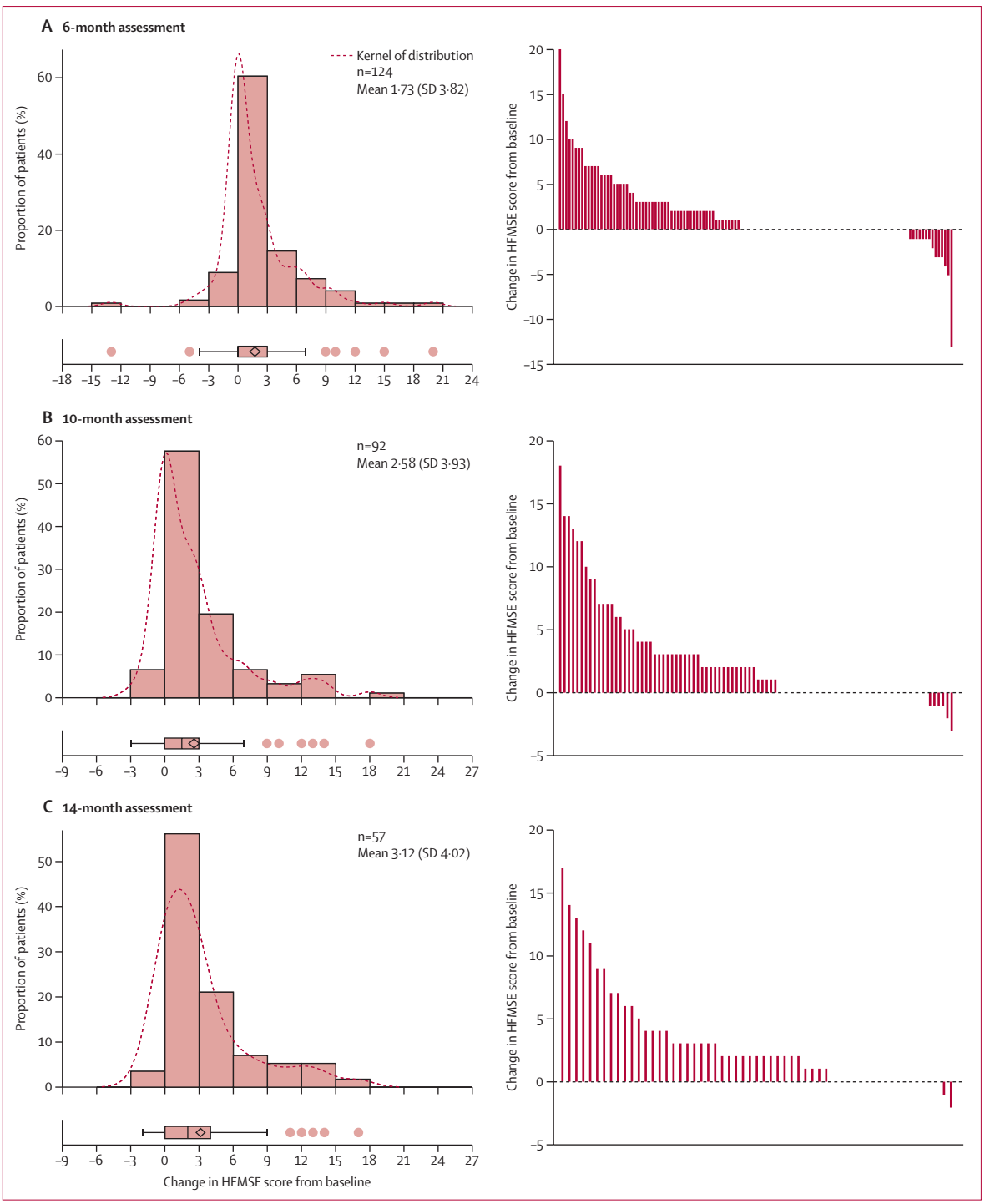

Figure 2: **Changes in HFMSE score from baseline to 6 months (A), 10 months (B), and 14 months (C)**
Panels on the left show mean changes in HFMSE score from baseline to 6 months, 10 months, and 14 months, with each bar representing the proportion of patients who had improved to this extent. Box and whisker plots show median (central line), IQR (boxes), and 1·5 × IQR (whiskers), with individual points representing outliers (those outside of 1·5 × IQR from the median). Diamonds indicate the mean values. Panels on the right show improvements in HFMSE in individual patients from baseline. Each bar represents a single patient. HFMSE=Hammersmith Functional Motor Scale Expanded.

14 (p=0·1104; table 4; appendix p 10). Although the effects of nusinersen in patients with spondylodesis appear to be slightly lower than in those without spondylodesis, these effects depend on the underlying disease severity, as reflected by the lower mean HFMSE scores at baseline in patients with spondylodesis (4·48 points [SD 7·1]) than

	6-month analysis				10-month analysis				14-month analysis			
	n	Mean score (SD)	Mean difference versus baseline (95% CI)	p value	n	Mean score (SD)	Mean difference versus baseline (95% CI)	p value	n	Mean score (SD)	Mean difference versus baseline (95% CI)	p value
HFMSE score	124	22·47 (22·41)	1·73 (1·05–2·41)	<0·0001	92	25·52 (22·97)	2·58 (1·76–3·39)	<0·0001	57	27·77 (23·47)	3·12 (2·06–4·19)	<0·0001
RULM score	120	21·53 (13·28)	0·66 (0·26–1·05)	0·0007	90	23·27 (12·46)	0·59 (0·15–1·03)	0·0014	58	23·95 (12·42)	1·09 (0·62–1·55)	<0·0001
6-minute walk test distance, m	47	366·8 (200·8)	22·1 (8·7–35·6)	0·0022	37	363·2 (224·2)	31·1 (15·2–47·1)	<0·0001	25	403·0 (225·7)	46·0 (25·4–66·6)	<0·0001

HFMSE=Hammersmith Functional Motor Scale Expanded. RULM=Revised Upper Limb Module.

Table 2: **Changes in HFMSE, RULM, and 6-minute walk test scores versus baseline**

	Day 1 (injection 1; n=173)	Day 14 (injection 2; n=170)	Day 28 (injection 3; n=165)	Day 63 (injection 4; n=158)	Month 6 (injection 5; n=139)	Month 10 (injection 6; n=105)	Month 14 (injection 7; n=61)
Total adverse reactions	68	58	31	23	20	14	8
Total patients with adverse reactions	52 (30%)	40 (24%)	26 (16%)	20 (13%)	17 (12%)	13 (12%)	6 (10%)
Headache	35 (20%)	27 (16%)	19 (12%)	12 (8%)	7 (5%)	4 (4%)	4 (7%)
Back pain	16 (9%)	16 (9%)	7 (4%)	5 (3%)	7 (5%)	3 (3%)	2 (3%)
Nausea	12 (7%)	6 (4%)	3 (2%)	2 (1%)	3 (2%)	1 (1%)	1 (2%)
Vertigo	3 (2%)	5 (3%)	2 (1%)	0	1 (1%)	2 (2%)	0
Upper airway infection	1 (1%)	0	0	2 (1%)	0	2 (2%)	0
Constipation	1 (1%)	2 (1%)	0	1 (1%)	2 (1%)	0	1 (2%)
Diffuse pain	0	0	0	0	0	1 (1%)	0
Bladder disorder not otherwise specified	0	0	0	1 (1%)	0	0	0
Tinnitus aggravated	0	0	0	0	0	1 (1%)	0
Infection	0	1 (1%)	0	0	0	0	0
Meningitis aseptic	0	1 (1%)	0	0	0	0	0

Data are n (%).

Table 3: **Adverse drug reactions and procedure-related complications recorded in participants (n=173), classified according to MedDRA version 21.1**

in those without spondylodesis (25·4 points [21·8]; see mixed-model analysis, appendix p 11).

In the subgroup of patients who had not yet completed the 6-month course of nusinersen (n=34), there was a higher proportion of men and fewer cases of spinal muscular atrophy type 2 than in the subgroup who had completed the 6-month course (n=139). In the subgroup of patients who had completed 14 months of treatment (n=57), mean age was lower and there was a higher proportion of male patients compared with the subgroup who had completed the 6-month course (appendix p 12).

In a sensitivity analysis, missing baseline values were replaced in the primary outcome parameter by the existing values at later timepoints, such that these values were included in the analysis with a change from baseline of 0, and thus replaced conservatively. In a further sensitivity analysis, we also considered worst case scenarios by replacing missing baseline values with values 5 points higher than the values at later timepoints. In both scenarios, the results remained consistent and significant with the results of the primary analysis (data not shown).

Discussion

Our data show the safety and efficacy of nusinersen treatment in adult patients with 5q spinal muscular atrophy, with statistically significant improvements in motor function observed at all timepoints. Greater improvement of motor function was correlated with lower severity of disease at baseline, as shown by a positive correlation between HMFSE scores at baseline and improvement in HMFSE score after 6 months. This finding was supported by a subgroup analysis, which showed higher proportions of patients with clinically meaningful improvements in motor function (HFMSE score) at all timepoints in the spinal muscular atrophy type 3 subgroup than in the type 2 subgroup. No correlation was found between improvement in motor function and age. Furthermore, no new safety concerns were identified. After lumbar puncture, back pain and post-puncture headaches occurred in up to a fifth of patients, similar to the rates reported for lumbar punctures in general (about 8–25%).[12–15]

In a prospective observational study, Walter and colleagues showed a statistically significant increase in motor function, as measured by RULM and 6MWT, after

	6-month analysis			10-month analysis			14-month analysis		
	n	Mean difference versus baseline*	p value†	n	Mean difference versus baseline*	p value†	n	Mean difference versus baseline*	p value†
HFMSE score									
Spinal muscular atrophy type									
2	45	0·6 (1·4; 0·2 to 1·1)	0·0010	30	0·8 (1·5; 0·2 to 1·4)	0·0054	20	1·1 (1·4; 0·4 to 1·7)	0·0059
3	77	2·4 (4·6; 1·4 to 3·5)	<0·0001	60	3·4 (4·4; 2·2 to 4·5)	<0·0001	37	4·2 (4·5; 2·7 to 5·7)	<0·0001
Ambulant									
Yes	46	3·0 (4·7)	<0·0001	35	4·3 (3·7)	<0·0001	23	4·6 (4·4)	<0·0001
No	78	1·0 (3·0)	0·0006	57	1·5 (3·0)	<0·0001	34	2·1 (3·4)	<0·0001
Baseline HFMSE score									
≥35	39	2·4 (4·5)	0·0002	33	3·6 (4·1)	<0·0001	22	4·6 (4·2)	<0·0001
<35	85	1·4 (3·5)	<0·0001	59	2·0 (3·7)	<0·0001	35	2·2 (3·7)	<0·0001
Spondylodesis									
Yes	28	0·8 (1·1)	0·0024	18	1·2 (1·6)	0·0059	14	1·4 (1·3)	0·0078
No	96	2·0 (4·3)	<0·0001	74	2·9 (4·3)	<0·0001	43	3·7 (4·4)	<0·0001
RULM score									
Spinal muscular atrophy type									
2	43	1·1 (2·4; 0·3 to 1·8)	0·0005	30	1·1 (1·7; 0·5 to 1·7)	0·0010	20	1·6 (2·0; 0·7 to 2·5)	0·0049
3	74	0·4 (2·1; –0·1 to 0·9)	0·1371	58	0·4 (2·0 (–0·1 to 0·9)	0·0702	38	0·7 (1·7; 0·2 to 1·3)	0·0100

HFMSE=Hammersmith Functional Motor Scale Expanded. RULM=Revised Upper Limb Module. *Data are mean difference (SD; 95% CI) or mean difference (SD). †For 6-month, 10-month, or 14-month values versus baseline.

Table 4: **Exploratory subgroup analysis of changes in HFMSE and RULM scores versus baseline**

treatment with nusinersen in a cohort of 19 adult patients with spinal muscular atrophy type 3.[9] Consistently, we found similar improvements in RULM and 6MWT scores in our cohort. However, we also found significant improvement in HFMSE scores, whereas Walter and colleagues did not. This difference might be related to the different sample sizes and the lack of inclusion of patients with type 2 disease in the earlier study. In concordance with Walter and colleagues findings, we also found the effects to be independent of age (ie, disease duration before treatment initiation).

The main limitation of our study was the absence of a control group and the observational design. Because nusinersen was approved for the treatment of a severe chronic progressive disease without limitations related to age or disease classification, these controls were not warranted. Inter-rater variability in the evaluation of motor function was another potential limitation in this study. To minimise this variability, all evaluators were trained and rating was done in accordance with standardised manuals. Furthermore, the natural disease course of spinal muscular atrophy might be influenced by the type and level of supportive care provided to the patient.[16,17] In this study, all patients had access to longstanding standard supportive care before and during nusinersen treatment. Nonetheless, this study cohort represents a multicentric real-world population of adult patients with 5q spinal muscular atrophy, including various spinal muscular atrophy types, ambulant and non-ambulant patients, and patients with or without a history of spondylodesis.

Although data on the natural history of 5q spinal muscular atrophy in the adult population are scarce, available evidence shows a decline in motor function over time in almost all adult patients, with an estimated decline of 0·5–1 points per year on the HFMSE.[18,19] However, inter-individual and intra-individual variations in disease progression are observed among adult patients, with phases of clinical worsening but also periods of stable disease course. Considering these data, we considered the clinically meaningful improvement of motor function to be a relevant drug effect, as concluded by Walter and colleagues in their study.[9] Based on natural history data in adult patients as well as findings from clinical trials in infants and children with 5q spinal muscular atrophy (ENDEAR and CHERISH),[5,6] placebo effects, even minor, are unlikely to explain improvements in motor function tests (appendix p 14). In patients who showed a stable disease course over 14-months of nusinersen treatment without clinically meaningful changes in this study, it should be discussed whether the drug had the effect of preventing disease progression that would otherwise have occurred, or whether a longer observation period is required.

In our cohort, motor improvement was not correlated with age; however, this finding might be related to the small number of patients included. All five patients who showed an increase in HFMSE score of more than 10 points had spinal muscular atrophy type 3 and three or four copies of *SMN2*. Of these five patients, three were female and two were male, age ranged from 48 years to 59 years, and two patients were non-ambulant. Of the

14 patients who showed worsening motor function under treatment, two were siblings who were both non-ambulant and had spinal muscular atrophy type 3. Other genetic SMN-modifying proteins are known in patients with spinal muscular atrophy, and might be linked to either worsening function or a super-response to nusinersen treatment.[20] Our data suggest a higher efficacy of nusinersen in patients with a baseline HFMSE score of more than 35. This is further supported by the subgroup analysis of spinal muscular atrophy types, which showed a clinically meaningful improvement in the HFMSE scores of patients with spinal muscular atrophy type 3, who usually have less severe symptoms than those with type 2 disease. However, the HFMSE has some limitations, having been evaluated predominantly in children, and to a lesser extent in adults with spinal muscular atrophy. Especially in mildly or severely affected patients, floor and ceiling effects, which restrict the validity of the measured effects in these subpopulations, must be considered. The 6MWT for less affected patients and the RULM for severely affected patients complement the HFMSE score.

Improvements in respiration and swallowing during treatment with nusinersen were not reflected by changes in HFMSE scores in this study. Although there were minor differences (ie, age and sex distributions) in the characteristics of patients who had not yet completed the 6-month course of treatment, these characteristics had no influence on the overall improvement in HFMSE score in the multivariate model (appendix p 11). Similarly, improvement in HFMSE score did not differ substantially among patients who had completed the 14-month course, although higher baseline values at all endpoints were noticeable in this subgroup (appendix p 12). It cannot be ruled out that the patients who were started on nusinersen tended to be those clinically less severely affected, as some centres prefer to start treatment in patients less affected first because of technical aspects of the injection procedure. Identification of an ideal outcome parameter that reflects worsening or improvement in motor function at all grades of disease severity might be not feasible; therefore, future studies should consider the relevance of minimal function in severely affected patients and ceiling effects in patients with well preserved motor function. In the severely affected patients, rest functions might be highly relevant and closely linked to quality of life. For this purpose, patient-individualised scores such as Measure Yourself Medical Outcome Profile (MYMOP2) could be helpful.[21]

In summary, our data provide evidence for the safety and efficacy of nusinersen in the treatment of adult patients with 5q spinal muscular atrophy. Future studies should focus on the long-term effects of nusinersen, other motor or motor-related functions such as swallowing and ventilation, and possible individualisation of nusinersen treatment with respect to dosing regimen and application intervals.

Contributors

TH, CDW, and RG wrote the manuscript, planned the study, interpreted the data and coordinated the study, and were responsible for local data collection. MW planned the study, was involved in coordination of the study, was responsible for local data collection and contribution, and critically revised the manuscript. OS-K, AO, SP, JCK, IS, GW, HL, IC, MD, PL, CKa, LP, and HR were responsible for local data collection and contribution and critically revised the manuscript. AZ, JKu, NS, BS, KK, AT, and CM were responsible for local data collection and contribution. OvV and CO were responsible for data analysis, figure production, and writing of the statistical part of the manuscript. MF, AP, and JKi were involved in the study design, data interpretation, and critical revision of the manuscript. ACL and AH planned the study, were involved in coordination of the study and were responsible for local data collection and contribution. CKl was involved in study design, data interpretation, supervision, and writing of the manuscript.

Declaration of interests

TH has received grants and personal fees from Biogen, and personal fees from Roche and Novartis outside of the submitted work. CDW has received personal fees from Biogen and Hoffmann–La Roche outside of the submitted work. RG has received grants, personal fees, and non-financial support from Biogen during the conduct of the study, as well as receiving personal fees, non-financial support, and research support, and serving on the advisory board of Biogen, outside of the submitted work. OS-K has received grants from the German Neuromuscular Society and the Young Faculty Program of Hanover Medical School, and personal fees and travel costs from Biogen outside of the submitted work. AO, CKa, BS, and CKl have received personal fees from Biogen outside of the submitted work. SP has received grants from the German Neuromuscular Society, the Federal Ministry of Education and Research, the German Israeli Foundation for Scientific Research and Development, and the EU Joint Programme for Neurodegenerative Disease Research; and other support from Cytokinetics, Desitin Pharma, Biogen, Novartis, and Teva outside of the submitted work. MW has received personal fees from Biogen during the conduct of the study; and personal fees from Akcea Therapeutics, Alnylam Pharmaceuticals, Pfizer, and Roche outside of the submitted work. AZ has received personal fees from Biogen and Avexis outside of the submitted work. JCK has received compensation for a lecture from Biogen and fees for advisory board participation from Avexis outside of the submitted work. IS has received non-financial support from Biogen during the conduct of the study. HL has received grants and personal fees from Novartis, and personal fees from Biogen, CSL Behring, and Grifols outside of the submitted work. IC has received grants from Biogen outside of the submitted work. MD has received grants from SMArtCARE and personal fees from Biogen outside of the submitted work. PL has received support for symposium organisation from Biogen during the conduct of the study; as well as speaker honoraria from Desitin, BIAL, and AbbVie, and fees for advisory board participation from Novartis outside of the submitted work. KK has received grants from Biogen outside of the submitted work. CM has received personal fees from Bayer, Daiichi Sankyo, Teva, and National Cohort Study Germany outside of the submitted work. AP has received grants and personal fees from Biogen outside of the submitted work. JKi has received grants, personal fees, and non-financial support from Biogen during the conduct of the study; and grants, personal fees, and non-financial support from Roche, grants and personal fees from PTC Therapeutics, grants from Santhera, and personal fees and non-financial support from Avexis outside of the submitted work. ACL has received personal fees from AB Science, Biogen, Cytokinetics, GlaxoSmithKline, Orion Pharma, Novartis, Tau Rx Therapeutics, Teva, Mitsubishi, and Hoffmann–La Roche outside of the submitted work. AH has received personal fees and non-financial support from Biogen and DESITIN during the conduct of the study; and grants from the Helmholtz Foundation, the Federal Ministry of Education and Research, Innovationsausschuss des G-BA, the German Neuromuscular Society, and the Schilling-Stiftung outside of the submitted work. JKu, GW, NS, LP, AT, OvV, CO, HR, and MF declare no competing interests.

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