Statistical Report: Nusinersen for Adults with Spinal Muscular Atrophy

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1. Background

Prior to Nusinersen, treatment options were limited to multidisciplinary symptom management which included respiratory management (e.g. airway clearance, antibiotics, ventilation), nutritional and gastrointestinal support (e.g. dietician assessment, changing food consistency, tube feeding), and overall conservative symptom management interventions (e.g. exercise, postural and pain management, scoliosis surgery). Nusinersen represents a shift in the paradigm by changing the natural course of disease progression and is potentially beneficial for all types of SMA, although earlier treatment may lead to better outcomes.

In July 2019, Nusinersen was recommended within the conditions of the managed access agreement for people with 5q SMA Type I (also referred to as infantile-onset SMA), Types II, III (also referred as later-onset SMA), and presymptomatic (homozygous gene deletion or homozygous mutation, or compound heterozygous mutation detected in 5q SMA and have up to 4 SMN2 copies).

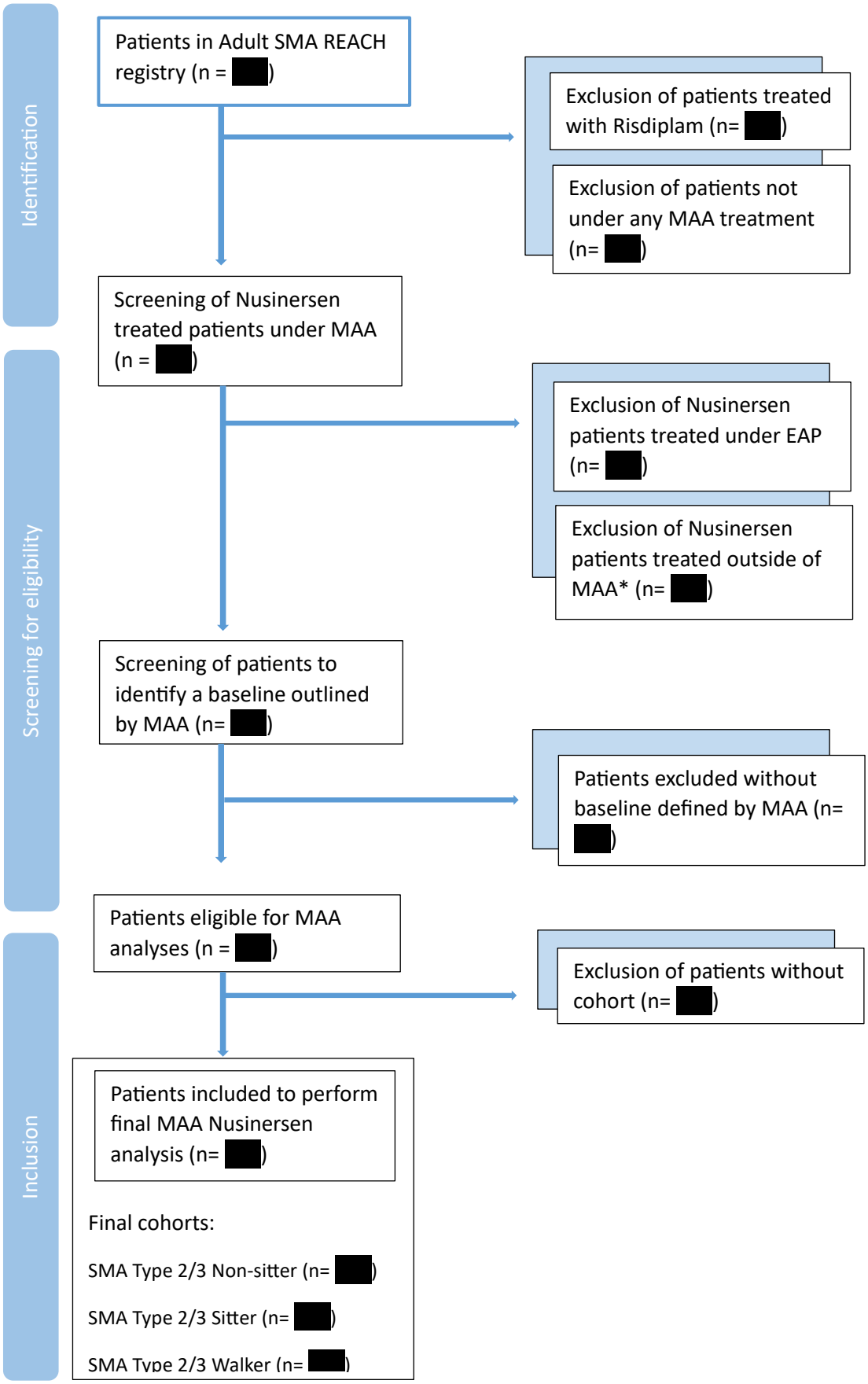
This report aims to provide the most recent evidence for the ongoing appraisal of Nusinersen, by utilising a new data cut from the Adult SMA REACH registry. The benefit of providing a new data cut at this stage is an increase in patient numbers in addition to an increased number of longitudinal patient visits captured within Adult SMA REACH data collection study. This is highly valuable in the analysis and appraisals of new treatments/disease modifying therapies (DMTs) in rare diseases like SMA due to limited patient numbers.

This reports functions as an addition to the final report submitted for the Nusinersen appraisal in February 2024 and the reader is encouraged to refer it for additional questions and further background on SMA disease, Adult SMA REACH and the data collection.

2. Data

Data used for this report was collected within the Adult SMA REACH registry and the data cut was completed on 10th March 2025. As stated in previous report from February 2024, this project is sponsored by Newcastle upon Tyne Hospital Foundation Trust and led by Newcastle University. The Adult SMA REACH network covers 17 centres in England and the database collects both natural history and treatment data, regardless of disease modifying therapy, and its focus is on the adult population. Patients are included in Adult SMA REACH from the age of 16 years; data collection is transitioned from Paediatric SMA REACH to Adult SMA REACH at this age.

Figure 1: Illustration of data processing in preparation for Managed Access Agreement Nusinersen Analysis. Data collected in Adult SMA Reach Registry and processed from data cut in 10.3.2025.



* patient may have started prior Nusinersen MAA (24th July 2019) and then had stopping date during MAA without appropriate visits to use for baseline definition nor follow up visits, or patient started and stopped before MAA start date.

2.1 Analytic adult SMA population

Further details on inclusion and exclusion criteria can be found from the Biogen MAA SAP. For the present report, an updated illustration of the application of the exclusion and inclusion criteria can be viewed from Figure 1. Patients without cohort were excluded from the analysis, as these patients had missing data for either baseline motor function and/or SMA type.

The following three cohorts were identified in the data based on SMA type and WHO motor function status at baseline, and were analysed:

- Type II and Type III: non-sitter
- Type II and Type III: sitter
- Type II and Type III: walker

2.2 Analysis

This updated report will cover as specified in the statistical analysis plan:

- Baseline descriptives (see section 3.1)
- Attainment or maintenance of motor milestones (see section 3.2)
- Time to permanent ventilation (see section 3.3)
- Overall survival (see section 3.4)
- Discontinuation and reasons for discontinuation (see section 3.5)
- Change from baseline in outcome measures (see section 3.6)
- Descriptive longitudinal lung function (see section 3.7)
- PROMs (see section 3.8)

3. Results

3.1 Baseline descriptives

This section provides a descriptive analysis of each cohort at the start of treatment. Baseline is identified as patients with a clinical assessment -6/+3 months from the date of first dose, or for those patients transitioning from paediatric care, the first adult visit after the age of 16 was identified as baseline visit.

Table 1: Type 2/3 Non-sitter N = [redacted]	Statistics	
Transition	n= (%)	[redacted]
Age of symptom onset (years)	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Age at start of treatment (years)	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Disease duration at start of treatment (years)	mean (SD)	[redacted]
	Median	[redacted]

	Range	[redacted]
Sex		[redacted]
female	n= (%)	[redacted]
male	n= (%)	[redacted]
SMN2 copy numbers		[redacted]
2	n= (%)	[redacted]
3	n= (%)	[redacted]
4 and over	n= (%)	[redacted]
unknown	n= (%)	[redacted]
SMA type		[redacted]
type 2	n= (%)	[redacted]
type 3	n= (%)	[redacted]
Scoliosis = yes	n= (%)	[redacted]
Scoliosis = no	n= (%)	[redacted]
RULM performed = yes	n= (%)	[redacted]
RULM Total score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
ATEND performed = yes	n= (%)	[redacted]
ATEND total left	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
ATEND total right	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
EK2 performed = yes	n= (%)	[redacted]
EK2 total score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
VIGNOS performed = yes	n= (%)	[redacted]
VIGNOS score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
6MWT performed = no	n= (%)	[redacted]

Table 2: Type 2/3 Sitter N= [redacted]	Statistics	
Transition	n= (%)	[redacted]
Age of symptom onset (years)	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Age at start of treatment (years)	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Disease duration at start of treatment (years)	mean (SD)	[redacted]

	Median	[redacted]
	Range	[redacted]
Sex		[redacted]
female	n=(%)	[redacted]
male	n=(%)	[redacted]
SMN2 copy numbers		[redacted]
2	n=(%)	[redacted]
3	n=(%)	[redacted]
4 and over	n=(%)	[redacted]
unknown	n=(%)	[redacted]
SMA type		[redacted]
type 2	n=(%)	[redacted]
type 3	n=(%)	[redacted]
Scoliosis = yes	n=(%)	[redacted]
Scoliosis = no	n=(%)	[redacted]
Scoliosis = unknown	n=(%)	[redacted]
RULM performed = yes	n=(%)	[redacted]
RULM Total score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
ATEND performed = yes	n=(%)	[redacted]
ATEND total left	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
ATEND total right	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
EK2 performed = yes	n=(%)	[redacted]
EK2 total score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
VIGNOS performed = yes	n=(%)	[redacted]
VIGNOS score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
6MWT performed = no	n=(%)	[redacted]

Table 3: Type 2/3 Walker N = [redacted]	Statistics	
Transition	n=(%)	[redacted]
Age of symptom onset (years)	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Age at start of treatment (years)	mean (SD)	[redacted]
	Median	[redacted]

	Range	[redacted]
Disease duration at start of treatment (years)	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Sex		[redacted]
female	n= (%)	[redacted]
male	n= (%)	[redacted]
SMN2 copy numbers		[redacted]
2	n= (%)	[redacted]
3	n= (%)	[redacted]
4 and over	n= (%)	[redacted]
unknown	n= (%)	[redacted]
SMA type		[redacted]
type 2	n= (%)	[redacted]
type 3	n= (%)	[redacted]
Scoliosis = yes	n= (%)	[redacted]
Scoliosis = no	n= (%)	[redacted]
Scoliosis =unknown	n= (%)	[redacted]
RULM performed = yes	n= (%)	[redacted]
RULM Total score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
ATEND performed = no	n= (%)	[redacted]
EK2 performed = yes	n= (%)	[redacted]
EK2 total score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
VIGNOS performed = yes	n= (%)	[redacted]
VIGNOS score	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
6MWT performed = yes	n= (%)	[redacted]
6MWT total score (meters)	mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]

3.2 Attainment or maintenance of motor milestones

As stated in February 2024 report, the same has been provided in this report: “Within each cohort as outlined in Section 3.1, the number and proportion of patients who fall into each of the following categories were presented with 95% Clopper-Pearson confidence intervals (CIs):

- Net attainment of a new motor milestone
- Either net attainment of a new motor milestone or remained in the same motor milestone category

This was assessed using the WHO motor milestones (‘a three-point scale’ of non-sitter, sitter and walker), at every 6 months (± 3 months), following baseline where data are available. Descriptive analysis included paired observations for subjects with baseline and follow-up measurements.”

In the following tables, based on motor function at baseline the patient populations were analysed for net attainment or stabilisation of motor function status. In each table N= indicates the number of patients in each cohort and n= indicates the number of patients available at each timepoint from the cohort, and the number of patients that fall into the categories specified above.

Table 4. Attainment or Maintenance of Motor Milestones: [Type II and III: non-sitter] **Parameter**	**Adult Cohort**
6 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
12 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
18 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
24 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
30 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
36 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
42 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
48 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
54 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]

Overall: [redacted] gained a motor function status and remained a sitter, throughout the available data timepoints (from month 18 to month 36). [redacted]

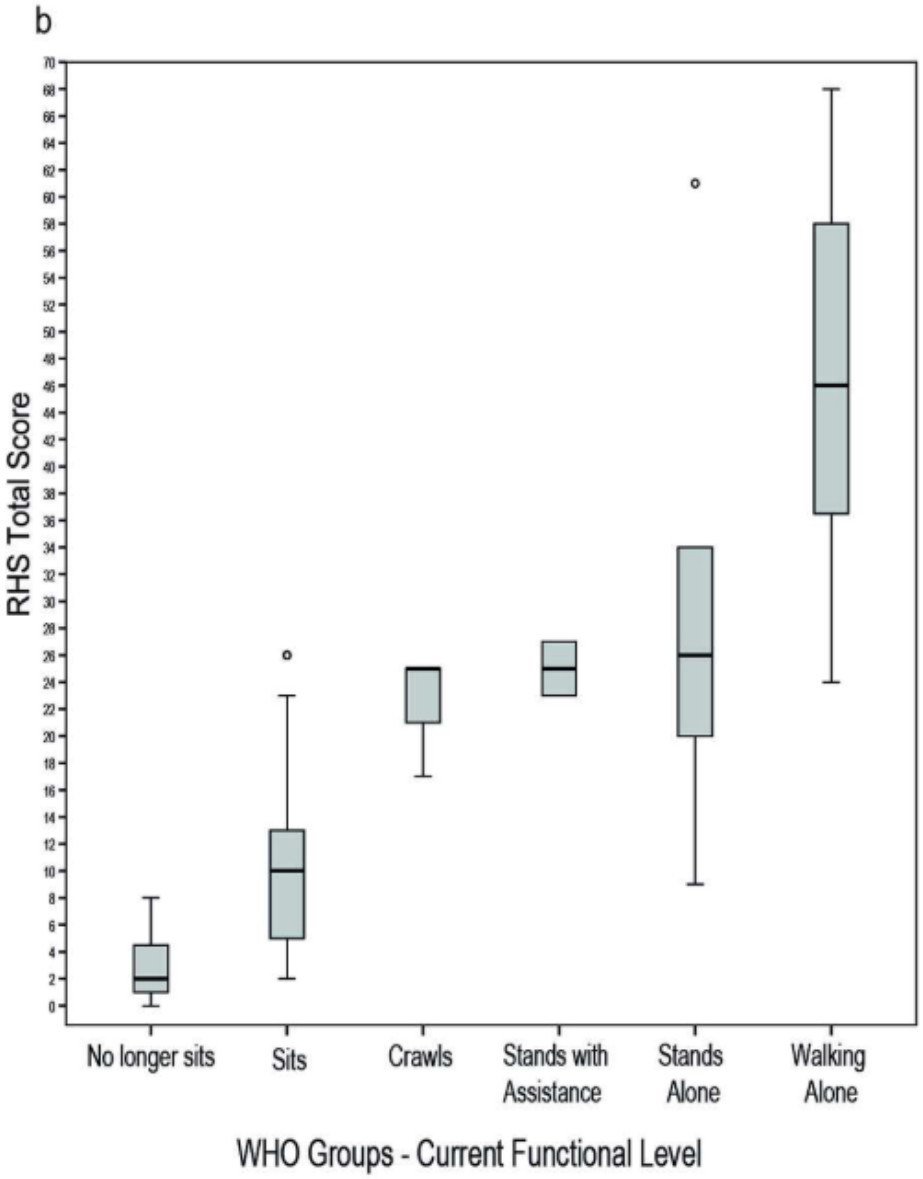
Table 5. Attainment or Maintenance of Motor Milestones: [Type II and III: sitter] **Parameter**	**Adult Cohort**
6 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
12 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
18 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
24 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
30 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
36 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
42 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]
48 months (± 3 months) following baseline: n	[redacted]
Net attainment of a motor milestone: n (%), 95% CI	[redacted]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	[redacted]

Overall: [redacted] lost motor function status and remained a non-sitter, and [redacted] patients gained WHO motor function status and remained a walker, throughout the available data timepoints. Therefore, [redacted] sitter patients at baseline remained a sitter. For granularity, patients who lost WHO motor function ([redacted]), scored 1 on WHO scale and dropped to WHO score 0 at the time of loss of motor function, or had missing data. Patients who gained WHO walker motor function ([redacted]), were observed to score 3-5 on previous visits as a sitter before gaining walker status (Score 6).

Table 6. Attainment or Maintenance of Motor Milestones: [Type II and III: walker] **Parameter**	Adult Cohort
6 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
12 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
18 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
24 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
30 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
36 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
42 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
48 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]
54 months (± 3 months) following baseline: n	[redacted]
remained in the same motor milestone category: n (%), 95% CI	[redacted]

Overall: [redacted] patients lost a motor function status and remained a sitter, throughout the available data timepoints. Therefore, [redacted] walker patients at baseline remained a walker.

In summary, WHO motor milestones showed stability with limited transition to a different functional group, similar to what is observed in natural history of SMA in adult population. The aggregate figures report [redacted] patients gaining a motor milestone whilst [redacted] lost one, the remaining [redacted] were stable throughout the whole period. This highlights the known stability of the adult SMA population with WHO motor scale, but also the lack of sensitivity that WHO motor milestones can capture more subtle changes. This is particularly clear in the sitter's group being a broader term referring to patients scoring 1-5 in WHO motor scale. A change from sitter to walker will therefore imply a significant change in their motor function (PMID: 28222119).



PMID: 28222119

3.3 Time to permanent ventilation

Permanent ventilation (PV) is defined as: any ventilation type for > 16 hours/day for 21 consecutive days or tracheostomy requirement. The time to PV was analysed as per the SAP and no patients had events of PV since commencing Nusinersen treatment, thus no results to display.

3.4 Overall survival

Occurrence of death after commencing Nusinersen was zero.

3.5 Discontinuation and reasons for discontinuation

The below results (Tables 7-9) present the number of patients that continued or discontinued treatment at the time of the data cut. For patients who stopped treatment (and are currently not on

Nusinersen treatment) have a record of reason for discontinuation of treatment specified in tables 7-9 below. Time on treatment is calculated based on the latest timepoint/visit date and date of first dose.

Table 7. Discontinuation and continuation of treatment: [Type II and III: non-sitter] N=		
Status		
	Ongoing n= (%)	
	Discontinued n= (%)	
Time on treatment (years)		
	Ongoing mean (range)	
	Discontinuation mean (range)	
Reason for discontinuation		
	Side effects from procedure	
	Side effects from drug	
	Lack of apparent benefit	
	Elective choice no treatment	
	Stopping rule	
	Other - free text	
	Unknown	

Table 8. Discontinuation and continuation of treatment: [Type II and III: sitter] N=		
Status		
	Ongoing n= (%)	
	Discontinued n= (%)	
Time on treatment (years)		
	Ongoing mean (range)	
	Discontinuation mean (range)	
Reason for discontinuation		
	Side effects from procedure	
	Side effects from drug	
	Elective choice/patient's choice	

	Stopping rule	[redacted]
	Other – free text ([redacted])	[redacted]
	Unknown	[redacted]

*time on treatment range could not be calculated due to small patient population

Other – free text 'Lack of apparent benefit' was not recorded as clinical stopping criteria for discontinuation.

Table 9. Discontinuation and continuation of treatment: [Type II and III: walker] N=[redacted]		
Status		
	Ongoing n= (%)	[redacted]
	Discontinued n= (%)	[redacted]
Time on treatment (years)		
	Ongoing mean (range)	[redacted]
	Discontinuation mean (range)	[redacted]
Reason for discontinuation		
	Side effects from procedure	[redacted]
	Side effects from drug	[redacted]
	Lack of apparent benefit	[redacted]
	Elective choice no treatment	[redacted]
	Stopping rule	[redacted]
	Other – free text ([redacted]')	[redacted]
	Unknown	[redacted]

3.6 Change from baseline in outcome measures

The mixed-effects repeated measures models were fitted for each cohort as described in Table 10. The mixed-effects models were used to provide summary statistical estimates of longitudinal mean scores and change from baseline.

The primary deviations from SAP (statistical analysis plan) was the removal of requirements for at least one follow-up score and weight as a covariate. Removing the requirement for at least one follow-up score increased both the number of patients and the volume of data (i.e., scores) contributing to the models. This decision was necessary due to the nature of real-world data, which often includes missing values, particularly in adult cohorts where patient numbers are typically lower - agreed with NICE in 2023. Weight was not used as parameter in the model due to missing data. Additionally, there were changes in the cohorts analysed. The variation in cohorts was selected to maintain consistency with

baseline descriptive statistics, to analyse appropriate functional assessments, and to represent real-world SMA settings, as outlined in Table 10.

Each mixed-effects model included a random effect for patient and fixed covariates for age at symptom onset, age at treatment initiation, SMA type, treatment duration at time of visit, and disease duration (calculated as "age at treatment start" minus "age at symptom onset").

Repeated measures over time were accommodated using an unstructured covariance matrix. Least-squares (LS) estimated mean scores and changes from baseline were provided at 6-month intervals. All models were fitted using the restricted maximum likelihood (REML) method to produce unbiased estimates of variance and covariance parameters.

In each model: N= number of patients contributing to the model; n= number of observations contributing to the model at all longitudinal timepoints. Models with not enough patients (n=) have been marked as NA, and results not displayed at various longitudinal visit timepoints.

Table 10. Summary of models/outcome measures fitted for each cohort. Letters A-J indicate corresponding table and figure number and (N=) the number of patients contributing to the overall model.

Outcome measure	Cohort		
	T2/3 non-sitter	T2/3 sitter	T2/3 walker
ATEND LEFT	[redacted]	[redacted]	[redacted]
ATEND RIGHT	[redacted]	[redacted]	[redacted]
EK2	[redacted]	[redacted]	[redacted]
RULM	[redacted]	[redacted]	[redacted]
RHS	[redacted]	[redacted]	[redacted]
6MWT	[redacted]	[redacted]	[redacted]

*SMA type not used as covariate – did not fit the model

Type 2/3 non-sitter mixed model results

Table A: ATEND LEFT mixed model [T2/3 non-sitter]												
Visit	n=	LS Mean (SE)					Change from baseline (95% CI)					P-value
Baseline (0)	[redacted]	[redacted]					[redacted]					[redacted]
6 months (1)	[redacted]	[redacted]					[redacted]					[redacted]
12 months (2)	[redacted]	[redacted]					[redacted]					[redacted]
18 months (3)	[redacted]	[redacted]					[redacted]					[redacted]
24 months (4)	[redacted]	[redacted]					[redacted]					[redacted]
30 months (5)	[redacted]	[redacted]					[redacted]					[redacted]

Table B: ATEND RIGHT mixed model [T2/3 non-sitter]												
Visit	n=	LS Mean (SE)					Change from baseline (95% CI)					P-value
Baseline (0)	[redacted]	[redacted]					[redacted]					[redacted]
6 months (1)	[redacted]	[redacted]					[redacted]					[redacted]
12 months (2)	[redacted]	[redacted]					[redacted]					[redacted]
18 months (3)	[redacted]	[redacted]					[redacted]					[redacted]
24 months (4)	[redacted]	[redacted]					[redacted]					[redacted]
30 months (5)	[redacted]	[redacted]					[redacted]					[redacted]

Table C: EK2 mixed model [T2/3 non-sitter]				
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)	P-value
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
6 months (1)	[redacted]	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]	[redacted]
30 months (5)	[redacted]	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]	[redacted]

Table D: RULM dominant hand mixed model [T2/3 non-sitter]				
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)	P-value
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
6 months (1)	[redacted]	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]	[redacted]
30 months (5)	[redacted]	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]	[redacted]

Overall, the non-sitter population has been positively influenced by treatment which is observed when assessing motor function with traditional (RULM) and novel (ATEND) outcome measures. EK2 scores include aspects beyond motor function which is the likely explanation for the different trend compared to the rest of outcomes (EK2 score are reversed, increment in the score implies poorer disease status).

Type 2/3 sitter mixed model results

Table E: ATEND LEFT mixed model [T2/3 sitter]				
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)	P-value
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
6 months (1)	[redacted]	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]	[redacted]
30 months (5)	[redacted]	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]	[redacted]

Table F: ATEND RIGHT mixed model [T2/3 sitter]				
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)	P-value
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
6 months (1)	[redacted]	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]	[redacted]
30 months (5)	[redacted]	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]	[redacted]

Table G: EK2 mixed model [T2/3 sitter]				
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)	P-value
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
6 months (1)	[redacted]	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]	[redacted]
30 months (5)	[redacted]	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]	[redacted]

Table H: RULM dominant hand mixed model [T2/3 sitter]				
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)	P-value
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
6 months (1)	[redacted]	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]	[redacted]
30 months (5)	[redacted]	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]	[redacted]

42 months (7)	[redacted]	[redacted]	[redacted]	[redacted]

Table I: RHS mixed model [T2/3 sitter]				
Visit	n=	LS Mean (SE)	Change from baseline (95% Cl)	P-value
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
6 months (1)	[redacted]	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]	[redacted]
30 months (5)	[redacted]	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]	[redacted]
48 months (8)	[redacted]	[redacted]	[redacted]	[redacted]

In the sitters' groups, motor function was assessed with RHS and RULM for the more functional individuals showing a clear improvement for overall function and moderate improvement for upper limb function. The less functional patients (Score <6 for RHS) were assessed with ATEND that is showing an unusual degree of asymmetric progressions. This is highly linked to the limited sample

[redacted]

size as it has not been observed in previous preliminary studies. In this functional group, EK2 score show an overall picture of stability.

Type 2/3 walker mixed model results

[illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]

[illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]
[illegible]	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]	[redacted]

[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	

[redacted]

For the walkers group, motor function was assessed with the RHS which shows an overall picture of stability. 6MWT was used to capture performance fatigability and shows the benefit on this dimension of the disease that is hardly represented in other functional group.

3.7 Descriptive longitudinal lung function

Table 11: Non-sitter T2/3

	FVC (Liters)			FVC %		
visit timepoint (month)	Mean	Range	n=	Mean	Range	n=
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*data not displayed due to low patient numbers

Table 12: Sitter T2/3

	FVC (Liters)			FVC %		
visit timepoint (month)	Mean	Range	n=	Mean	Range	n=
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*data not displayed due to low patient numbers

Table 13: Walker T2/3

	FVC (Liters)			FVC %		
visit timepoint (month)	Mean	Range	n=	Mean	Range	n=
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*data not displayed due to low patient numbers

Respiratory function remains stable for all functional groups.

3.8 PROMs

Patient comments reported in Appendix 1.

4. Software

All data summarisation and analyses were performed using R Version 4.3.1 or later.

5. Appendixes

Appendix 1: Patient comments from SMA patient Registry

Patient ID	Comment # (per patient)	Age at time of comment	Years on treatment at time of comment	Comments
NNA01	[redacted]	[redacted]	[redacted]	[redacted]
NNA02	[redacted]	[redacted]	[redacted]	[redacted]
NNA03	[redacted]	[redacted]	[redacted]	[redacted]
NNA03	[redacted]	[redacted]	[redacted]	[redacted]

NNA03	[redacted]	[redacted]	[redacted]	[redacted]
NNA03	[redacted]	[redacted]	[redacted]	[redacted]
NNA03	[redacted]	[redacted]	[redacted]	[redacted]
NNA04	[redacted]	[redacted]	[redacted]	[redacted]
NNA05	[redacted]	[redacted]	[redacted]	[redacted]
NNA05	[redacted]	[redacted]	[redacted]	[redacted]
NNA06	[redacted]	[redacted]	[redacted]	[redacted]
NNA07	[redacted]	[redacted]	[redacted]	[redacted]

NNA08	[redacted]	[redacted]	[redacted]	[redacted]
NNA08	[redacted]	[redacted]	[redacted]	[redacted]
NNA08	[redacted]	[redacted]	[redacted]	[redacted]
NNA08	[redacted]	[redacted]	[redacted]	[redacted]
NNA09	[redacted]	[redacted]	[redacted]	[redacted]
NNA10	[redacted]	[redacted]	[redacted]	[redacted]
NNA10	[redacted]	[redacted]	[redacted]	[redacted]
NNA11	[redacted]	[redacted]	[redacted]	[redacted]
NNA11	[redacted]	[redacted]	[redacted]	[redacted]
NNA11	[redacted]	[redacted]	[redacted]	[redacted]
NNA11	[redacted]	[redacted]	[redacted]	[redacted]
NNA11	[redacted]	[redacted]	[redacted]	[redacted]
NNA12	[redacted]	[redacted]	[redacted]	[redacted]
NNA12	[redacted]	[redacted]	[redacted]	[redacted]
NNA12	[redacted]	[redacted]	[redacted]	[redacted]
NNA12	[redacted]	[redacted]	[redacted]	[redacted]
NNA13	[redacted]	[redacted]	[redacted]	[redacted]
NNA13	[redacted]	[redacted]	[redacted]	[redacted]
NNA13	[redacted]	[redacted]	[redacted]	[redacted]
NNA13	[redacted]	[redacted]	[redacted]	[redacted]
NNA13	[redacted]	[redacted]	[redacted]	[redacted]
NNA13	[redacted]	[redacted]	[redacted]	[redacted]

NNA14	[redacted]	[redacted]	[redacted]	[redacted]
NNA14	[redacted]	[redacted]	[redacted]	[redacted]
NNA14	[redacted]	[redacted]	[redacted]	[redacted]
NNA15	[redacted]	[redacted]	[redacted]	[redacted]
NNA16	[redacted]	[redacted]	[redacted]	[redacted]
NNA17	[redacted]	[redacted]	[redacted]	[redacted]
NNA17	[redacted]	[redacted]	[redacted]	[redacted]
NNA17	[redacted]	[redacted]	[redacted]	[redacted]
NNA18	[redacted]	[redacted]	[redacted]	[redacted]
NNA18	[redacted]	[redacted]	[redacted]	[redacted]
NNA18	[redacted]	[redacted]	[redacted]	[redacted]
NNA19	[redacted]	[redacted]	[redacted]	[redacted]
NNA19	[redacted]	[redacted]	[redacted]	[redacted]
NNA19	[redacted]	[redacted]	[redacted]	[redacted]
NNA19	[redacted]	[redacted]	[redacted]	[redacted]
NNA20	[redacted]	[redacted]	[redacted]	[redacted]
NNA21	[redacted]	[redacted]	[redacted]	[redacted]
NNA21	[redacted]	[redacted]	[redacted]	[redacted]
NNA21	[redacted]	[redacted]	[redacted]	[redacted]
NNA22	[redacted]	[redacted]	[redacted]	[redacted]