Statistical Report: Risdiplam for Adults with Spinal Muscular Atrophy

April 2025 Version 1.1

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1. Background

‘‘There are currently two disease-modifying treatment (DMT) options approved for SMA in the UK. Nusinersen (Spinraza®) is recommended as an option for treating 5q SMA only if: people have pre-symptomatic SMA, or SMA types 1, 2 or 3, and the conditions in the MAA are followed.3 Onasemnogene abeparvovec (Zolgensma®) is an approved gene therapy for type 1 SMA. Of particular note, onasemnogene abeparvovec is recommended as an option for treating pre-symptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies, only if the conditions in the MAA are followed.4 While Nusinersen is administered through intrathecal injection and onasemnogene abeparvovec is administered intravenously, risdiplam is the first orally administered small molecule to be approved for SMA treatment.‘‘ – as stated in an earlier MAA submission for Risdiplam in December 2023 (version 1.1).

This report aims to provide the most recent evidence for the ongoing appraisal of Risdiplam, 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 report functions as an addition to the final report submitted for the Risdiplam appraisal in December 2023 and the reader is encouraged to reference it for additional questions and further background on SMA disease, Adult SMA REACH and the data collection.

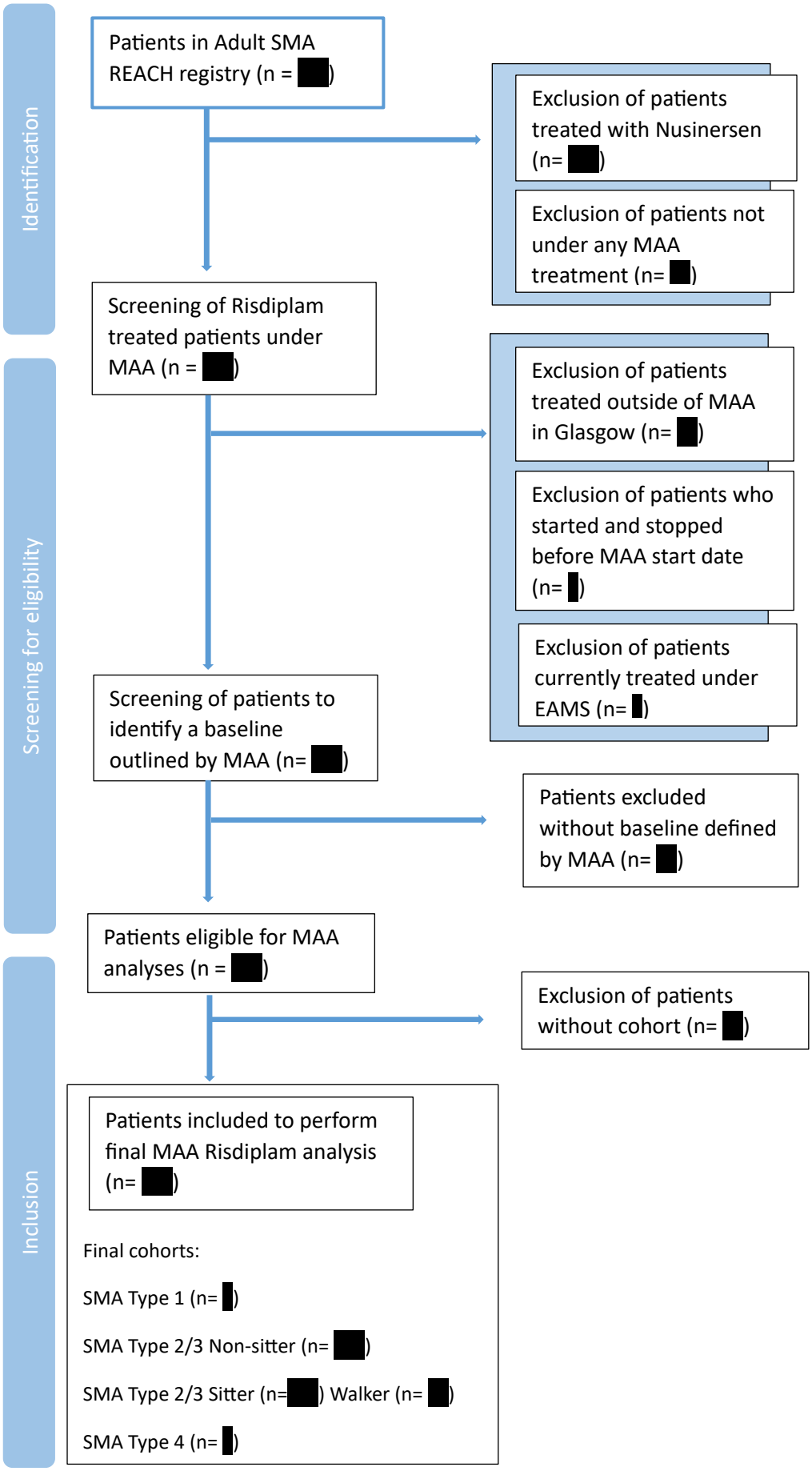
2. Data

Data used for this report was collected within the Adult SMA REACH registry and the data cut was completed on 10th March 2025. “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 UK to Adult SMA REACH at this age.’’ – as stated in the previous report from December 2023. For this updated report, no PROMs or adult outcome measures have been requested from the EAG. PROMs provide valuable insights for patients treated with DMT that may not otherwise be captured by the variables requested and should be used for decision making.

2.1 Analytic adult SMA population

Further details on inclusion and exclusion criteria can be found from the Report submitted in December 2023. For the present report, an updated illustration of the application of the exclusion and inclusion criteria can be viewed from Figure 1.

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



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

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

Additionally in section 3.1 of this report the non-ambulant patient population at baseline were stratified to sitters and walkers to provide the following cohorts for WHO motor milestones by follow up for granularity:

- 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)
- WHO motor milestones categories by follow-up (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)

3. Results

3.1 Baseline Descriptives

This section provides descriptive analysis of each cohort at the start of treatment. Baseline is identified as patients with clinical assessment +/-6 months from date of first dose, or 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]
1	n= (%)	[redacted]
2	n= (%)	[redacted]
3	n= (%)	[redacted]
4	n= (%)	[redacted]
Over 4	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	n= (%)	[redacted]
Over 4	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 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)	
	Median	
	Range	
Disease duration at start of treatment (years)	mean (SD)	
	Median	
	Range	
Sex		
female	n= (%)	
male	n= (%)	
SMN2 copy numbers		
2	n= (%)	
3	n= (%)	
4	n= (%)	
Over 4	n= (%)	
unknown	n= (%)	
SMA type		
type 2	n= (%)	
type 3	n= (%)	
Scoliosis = yes	n= (%)	
Scoliosis = no	n= (%)	
RULM performed = yes	n= (%)	
RULM Total score	mean (SD)	
	Median	
	Range	
ATEND performed = no	n= (%)	
EK2 performed = yes	n= (%)	
EK2 total score	mean (SD)	
	Median	
	Range	
VIGNOS performed = yes	n= (%)	
VIGNOS score	mean (SD)	
	Median	
	Range	
6MWT performed = yes	n= (%)	
	mean (SD)	
	Median	
	Range	

3.2 WHO motor milestone categories by follow-up

The WHO motor milestones were analysed as per statistical analysis plan section 2.9 – descriptive analysis for all available timepoints. For granularity non-ambulant (Table 6 – Appendix 3) patients were stratified to sitters and walkers (Tables 7 and 8, respectively) cohorts for this analysis.

Descriptive statistics of longitudinal WHO motor function:

- Table 4: Type 1
- Table 5: Type 2/3 Non-sitter
- Table 6: Type 2/3 Sitter and walker (see Appendix 3)
- Table 7: Type 2/3 Sitter
- Table 8: Type 2/3 Walker

Based on motor function at baseline the patient populations were analysed descriptively for each timepoint. In each table of results 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 in each motor function category (non-sitter; sitter; walker).

When interpreting the WHO motor score from a clinical perspective, it's important to avoid reading reported changes without proper clinical context. The definitions of the WHO motor milestones had been used to standardise the traditional classification for SMA in the functional status (Non-sitter, Sitter, Walker). These 3 categories offer an indication of gross motor function, stability on this scale is often a positive sign, especially in phases where natural history would predict decline. Any observed gains should be interpreted cautiously, as the score is not designed to capture subtle functional improvements. Comparing results against expected natural history is essential to avoid assumptions about treatment effects or disease progression that the score has no capacity to capture. The score can also point out how well over time most patients sustain baseline functional status, indication of stabilisation.

Table 4. Descriptive statistics for WHO motor function [SMA Type I]

Parameter	**Category/ Statistic**	***Adult*** **(N = [redacted])**
WHO baseline	N	[redacted]
Non sitter	n (%)	[redacted]
WHO 6 month	N	[redacted]
Non sitter	n (%)	[redacted]
Unknown		[redacted]
WHO 12 month	N	[redacted]
Non sitter	n (%)	[redacted]
WHO 18 month	N	[redacted]
Non sitter	n (%)	[redacted]
WHO 24 month	N	[redacted]
Non sitter	n (%)	[redacted]
WHO 30 month	N	[redacted]
Non sitter	n (%)	[redacted]
WHO 36 month	N	[redacted]
Non sitter	n (%)	[redacted]

Overall: [redacted] Type 1 patients [redacted] a non-sitter from baseline, throughout the available data timepoints.

Table 5. Descriptive statistics for WHO motor function [SMA Type II and Type III: non-sitter]		
Parameter	**Category/ Statistic**	***Adult*** **(N = [redacted])**
WHO baseline	N	[redacted]
Non sitter	n (%)	[redacted]
WHO 6 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
WHO 12 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
WHO 18 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Unknown		[redacted]
WHO 24 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
WHO 30 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
WHO 36 month	N	[redacted]
Non sitter	n (%)	[redacted]
WHO 42 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
WHO 54 month	N	[redacted]
Non sitter	n (%)	[redacted]

Overall: [redacted] ([redacted]%) patients gained motor function status, throughout the available data timepoints. [redacted] ([redacted]) patients remained a non-sitter throughout the available data timepoints/visits. See Appendix 1 for illustration of patients with observed changes in motor function from baseline.

Table 6. Descriptive Statistics for WHO motor milestone: [SMA Type II and Type III: sitter]		
Parameter	**Category/ Statistic**	***Adult*** **(N =[redacted])**
WHO baseline	N	[redacted]
Sitter	n (%)	[redacted]
WHO 6 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
Unknown		[redacted]
WHO 12 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
WHO 18 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Unknown		[redacted]
WHO 24 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
WHO 30 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Unknown		[redacted]
WHO 36 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
WHO 42 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]

Overall: [redacted] ([redacted]) patients with sitter status at baseline lost motor function status and remained a non-sitter apart from [redacted] patients who returned to sitter status, at any point throughout the available data timepoints. [redacted] ([redacted]) sitter patients gained a walker status temporarily, at any point of the available data timepoints. [redacted] ([redacted]) sitter patients at baseline remained stable or gained motor

function throughout the available data timepoints. See Appendix 2 for illustration of patients with observed changes in motor function from baseline.

Table 7. Descriptive Statistics for WHO motor milestone: [SMA Type II and Type III: walker]

Parameter	**Category/ Statistic**	***Adult*** **(N = [redacted])**
WHO baseline	N	[redacted]
Walker	n (%)	[redacted]
WHO 6 month	N	[redacted]
Walker	n (%)	[redacted]
WHO 12 month	N	[redacted]
Walker	n (%)	[redacted]
WHO 18 month	N	[redacted]
Walker	n (%)	[redacted]
WHO 24 month	N	[redacted]
Sitter	n (%)	[redacted]
Walker		[redacted]
WHO 30 month	N	[redacted]
Walker	n (%)	[redacted]
WHO 36 month	N	[redacted]
Walker	n (%)	[redacted]
WHO 42 month	N	[redacted]

Overall: [redacted] walker patient lost motor function status to sitter at month 24. [redacted] patients with walker status at baseline remained a walker throughout the available data timepoints.

3.3 Time to permanent ventilation

Permanent ventilation (PV) is defined as: any ventilation required for ≥16 hours/day for 21 consecutive days in the absence of acute reversible infection or tracheostomy. The time to permanent ventilation was analysed as per the SAP and no patients had events of PV since commencing Risdiplam treatment, thus no results to display.

3.4 Overall survival

Occurrence of death after commencing Risdiplam was [redacted] ([redacted]) of the total population for Risdiplam analysis. [redacted] of the patients reported [redacted] as primary cause of death, and [redacted] reported [redacted], [redacted] had [redacted] for cause of death. These [redacted] patients were on treatment (to the time of event) for [redacted] (mean), [redacted] (range), years.

3.5 Discontinuation and reasons for discontinuation

The below results (Tables 8 and 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 Risdiplam treatment) have a record of reason for discontinuation of treatment specified in tables 8 and 9 below. SMA Type 1 cohort was too small to provide results. Time on treatment is calculated based on latest data timepoint/visit date and date of first dose.

Table 8. [Type II and Type III: non-sitter] 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 (‘supply ran out while abroad’)	[redacted]
	Unknown	[redacted]

Table 9. [Type II and Type III: sitter/walker] 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	
	Stopping rule	
	Other (*)	
	Unknown	

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 deviation from SAP (statistical analysis plan) was the removal of requirements for a baseline score or at least one follow up score. Additionally, there were changes in the cohorts analysed. To ensure transparency, supplementary models including only patients with a baseline score—thus accounting for baseline score-by-visit interactions—were also run. However, using real-world data, these models resulted in fewer observations. Therefore, for transparency, models that included the baseline score-by-visit interaction are reported in the Appendix 4, while the main tables below present models without baseline score as a covariate.

Removing the requirement for baseline or follow-up scores 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.

The variation in cohorts was selected to maintain consistency with baseline descriptive statistics, to analyse appropriate functional patient populations, 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"). In previous models (2023), disease duration showed high collinearity; this issue was addressed by calculating treatment duration separately for each visit, thus avoiding redundancy.

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 or the overall observations from the patients.

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

Outcome measure	Cohort				
	T1	T2/3 non-sitter	T2/3 sitter	T2/3 walker	T4
6MWT	-	-	-	M (13)*	O (^)
ATEND LEFT	A (NA)	E (77)	I (76)	-	-
ATEND RIGHT	B (NA)	F (77)	J (76)	-	-
EK2	C (NA)	G (80)	K (94)	-	-
RULM	D (NA)	H (89)	-	-	-
RHS	-	-	L (26)	N (24)*	P (^)

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

^models failed to converge due to the limited data available

NA models not reported due to low patient numbers

Type 2/3 non-sitter mixed model results

Table E: ATEND LEFT mixed model [T2/3 non-sitter]

Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]

Table F: ATEND RIGHT mixed model [T2/3 non-sitter]

Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]

18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]

Table G: EK2 mixed model [T2/3 non-sitter]

Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]
48 months (8)	[redacted]	[redacted]	[redacted]

Table H: RULM(dominant hand) mixed model [T2/3 non-sitter]

Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]
48 months (8)	[redacted]	[redacted]	[redacted]

Type 2/3 Sitter mixed model results

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

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

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

Table K: EK2 mixed model [T2/3 sitter]

Visit	n=	LS Mean (SE)	Change from baseline (95% Cl)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]

Table L: RHS mixed model [T2/3 sitter]

Visit	n=	LS Mean (SE)	Change from baseline (95% Cl)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]

[redacted]

Type 2/3 walker mixed model results

Table M: 6MWT mixed model [T2/3 walker]			
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]

Table N: RHS mixed model [T2/3 walker]			
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]

[redacted]

3.7 PROMs

Results

PROMs comments from the SMA UK Patient Registry are reported in appendix 5.

4. Conclusions

Text

5. Software

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

6. Appendixes

Appendix 1: Cohort Non-sitter Type 2/3

0	6	12	18	24	30	36	42	months
NS	S	S	NS	S	-	-	-	
NS	S	S		S	S		S	
NS	S	S	-	-	-	-	-	
NS	NS	S	NS		NS	-	-	
NS	NS	S	S	S	S	-	-	
NS		NS	S	-	-	-	-	
NS	NS		S	S	S	-	-	
NS	NS	NS	NS	S	NS	-	-	
NS	NS		NS		S	-	-	
NS	NS	NS	NS	NS	S	-	-	
NS				NS		NS	S	

Appendix 1: Illustration of patients with any changes in motor function throughout the available data timepoints in cohort of patients with non-sitter functional status at baseline.

[illegible]

[illegible]

	[illegible]
	[illegible]
	[illegible]
[illegible]	[illegible]

Appendix 2: Cohort Sitter Type 2/3

0	6	12	18	24	30	36	42	months
S	NS	S	-	-	-	-	-	
S	NS	NS	-	-	-	-	-	
S	NS	NS	-	-	S	-	NS	
S	NS	-	S	-	-	-	-	
S	NS	-	-	-	-	-	-	

S	NS	NS		NS	NS	-	-
S	NS	NS	NS	NS	-	-	-
S	NS	-	-	-	-	-	-
S	W	W	S	-	-	-	-
S	W	S	S	-	-	-	-
S		NS	NS	NS	NS	-	-
S		NS		NS	-	-	-
S	S	NS	-	-	-	-	-
S	S	NS	-	-	-	-	-
S	S	W	-	-	-	-	-
S	S	W	-	S	-	-	-
S	S	S	NS	NS	NS	-	-
S	S	S	NS	NS	NS	-	-
S	S	S	NS	NS	NS		NS
S	S	S	NS	-	-	-	-
S	S	S		NS		NS	NS
S				NS	-	-	-
S	S	S		NS	-	-	-
S		S	S	W	S	-	-
S		S	S	-	-	NS	-
S	S		S		S	NS	-
S	S	S	S		S	NS	-
S		S	S	S	S	NS	-

Appendix 2: Illustration of patients with any changes in motor function throughout the available data timepoints in cohort of patients with sitter functional status at baseline.

Appendix 3: Cohort sitter/walker Type 2/3

Table 6. Descriptive Statistics for WHO motor milestone: [SMA Type II and Type III: sitter/walker]		
Parameter	**Category/ Statistic**	***Adult*** **(N =153)**
WHO baseline	N	[redacted]
Sitter	n (%)	[redacted]
Walker		[redacted]
WHO 6 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
Unknown		[redacted]
WHO 12 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
WHO 18 month	N	[redacted]

Table 6. Descriptive Statistics for WHO motor milestone: [SMA Type II and Type III: sitter/walker]		
Parameter	**Category/ Statistic**	***Adult*** **(N =153)**
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
Unknown		[redacted]
WHO 24 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
WHO 30 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
Unknown		[redacted]
WHO 36 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]
Walker		[redacted]
WHO 42 month	N	[redacted]
Non sitter	n (%)	[redacted]
Sitter		[redacted]

Appendix 4: Mixed models with baseline as a covariate

This section is reported for transparency, where models include a smaller number of patients, thus observations in the model as not all patients with longitudinal scores had a baseline score, due to missing data. Table 10 works as a reference for results in this section like section 3.6.

Table 10. Summary of models/outcome measures fitted for each cohort. Letters A-P indicate corresponding table and figure number.

Outcome measure	Cohort				
	T1	T2/3 non-sitter	T2/3 sitter	T2/3 walker	T4
6MWT	-	-	-	M (9)	O (NA)
ATEND LEFT	A (NA)	E (48)	I (61)	-	-
ATEND RIGHT	B (NA)	F (48)	J (61)	-	-
EK2	C (NA)	G (81)	K (85)	-	-
RULM	D (NA)	H (70)	-	-	-
RHS	-	-	L (19)	N (24)	P (NA)

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

^models failed to converge due to the limited data available
NA models not reported due to low patient numbers

Type 2/3 non-sitter mixed model results (with baseline-score-by-visit interaction)

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

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

Table G: EK2 mixed model [T2/3 non-sitter]			
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]
42 months (7)	[redacted]	[redacted]	[redacted]
48 months (8)	[redacted]	[redacted]	[redacted]

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

Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
24 months (4)	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]
30months (5)	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]
36 months (6)	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]
42 months (7)	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]
48 months (8)	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]

[redacted]

Type 2/3 sitter mixed model results (with baseline-score-by-visit interaction)

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

Table J: ATEND RIGHT mixed model [T2/3 sitter]			
Visit	n=	LS Mean (SE)	Change from baseline (95% Cl)
Baseline (0)	[redacted]	[redacted] [redacted] [redacted] [redacted]	
6 months (1)	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]
12 months (2)	[redacted]	[redacted] [redacted] [redacted] [redacted]	[redacted] [redacted]

18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]

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

Table L: RHS mixed model [T2/3 sitter]			
Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]

Type 2/3 walker mixed model results (with baseline-score-by-visit interaction)

Table M: 6MWT mixed model [T2/3 walker]

Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]
24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]

Table N: RHS mixed model [T2/3 walker]

Visit	n=	LS Mean (SE)	Change from baseline (95% CI)
Baseline (0)	[redacted]	[redacted]	
6 months (1)	[redacted]	[redacted]	[redacted]
12 months (2)	[redacted]	[redacted]	[redacted]
18 months (3)	[redacted]	[redacted]	[redacted]

24 months (4)	[redacted]	[redacted]	[redacted]
30months (5)	[redacted]	[redacted]	[redacted]
36 months (6)	[redacted]	[redacted]	[redacted]

[redacted]

Appendix 5: Patient comments

Patient ID	Comment # (per patient)	Age at time of Comment	Years on treatment at time of Comment	Comment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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