GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

SMA REACH UK

Great Ormond Street Hospital for Children NHS Foundation Trust

Managed Access Agreement

Nusinersen for treating Spinal Muscular Atrophy in children and adults

Report to NICE MAOG / EAG

April, 2025

Paediatric Report

30/04/2025

Contents

NB: This report was prepared in relation to specific requests from the EAG. Details of definitions and methodology for the full analysis of the SAP can be found in the main December 2023/February 2024 report

Section numbers, table numbers and appendix numbers correspond to those used in main December 2023/February 2024 report for cross referencing.

Tables and Figures

NB: Table numbers have been maintained to align with those of the original report submission in December 2023. The following tables were included in the December 2023 report but not in the April 2025 report: Table 2, Table 3, Table 6, Table 7, Table 9, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, Table 17 and Table 18.

Table 1, Table 4, Table 5, Table 8 and Table 10 were included in December 2023 report

Appendices

NB: Appendix numbers have been maintained to align with those of the original report submission in December 2023. The following appendices were included in the December 2023 report but not in the April 2025 report: Appendix 1-9

Abbreviations

SMA: Spinal Muscular Atrophy

SMA REACH UK: Spinal Muscular Atrophy Research And Clinical Hub UK

MAA: Managed Access Agreement

SAP: Statistical Analysis Plan

EAG: External Academic Group

ISMAC: International SMA Consortium

EAP: Early Access Programme

MMRM: Mixed model repeated measures

Pre-symp: Pre-symptomatic SMA

SMA1-E: SMA Type I patients previously enrolled in Early Access Programme

SMA1-nE: SMA Type I patients not previously enrolled in Early Access Programme

SMA2/3-nS: SMA Type II or III patients, non-sitters at baseline (WHO total score = 0)

SMA2/3-S: SMA Type II or III patients, sitters at baseline (WHO total score = 1-5)

SMA2/3-W: SMA Type II or III patients, walkers at baseline (WHO total score = 6)

RHS: Revised Hammersmith Scale

RULM: Revised Upper Limb Module

WHO: World Health Organisation Developmental Milestones

HINE: Hammersmith Infant Neurological Assessment

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder

PROMS: Patient/Parent reported outcome measures

Consolidation of patient numbers in SMA REACH database with NHS Blueteq numbers

(February 2025)

	SMA Reach Database	Blueteq	Difference
Birmingham/Oswestry	[redacted]	[redacted]	[redacted]
Bristol	[redacted]	[redacted]	[redacted]
Cambridge	[redacted]	[redacted]	[redacted]
Cardiff	[redacted]	[redacted]	[redacted]
Evelina/St Georges	[redacted]	[redacted]	[redacted]
GOSH	[redacted]	[redacted]	[redacted]
Leeds	[redacted]	[redacted]	[redacted]
Leicester	[redacted]	[redacted]	[redacted]
Liverpool/Preston	[redacted]	[redacted]	[redacted]
Manchester	[redacted]	[redacted]	[redacted]
Newcastle	[redacted]	[redacted]	[redacted]
Nottingham	[redacted]	[redacted]	[redacted]
Oxford	[redacted]	[redacted]	[redacted]
Sheffield	[redacted]	[redacted]	[redacted]
Southampton	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Differences in the Blueteq numbers have been seen throughout the MAA; these are mostly due to the lag of data in the database; additionally, some patients might have been issued a Blueteq number when briefly on nusinersen treatment (there are a few instances of patients completing only the loading doses and then being switched to a different treatment).

A few patients have moved site.

4. Derivation of final cohort for analysis

Patients identified initially as receiving nusinersen in England and Wales through the MAA (N=307)

4.1 Exclusions

- Not eligible (n=[redacted])
- No first dose data ([redacted])
- Incorrect age at baseline ([redacted])
- Over 18 years at baseline ([redacted])
- No physio visit within baseline window ([redacted])
- Started treatment abroad ([redacted])

*[redacted] injection failures[redacted] compassionate use / EAP, [redacted] received nusinersen as part of a trial only

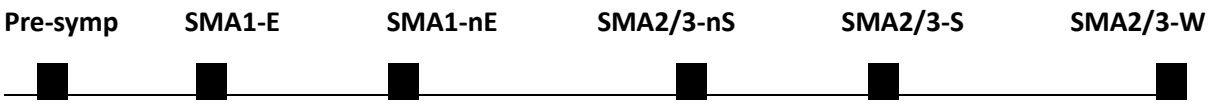
There are [redacted] patients eligible who fit the inclusion criteria.

N=[redacted] patients with physio data, however[redacted] patient did not have WHO motor milestone recorded at baseline, therefore we were not able to assess motor function and hence assign patient to a group. This patient was removed from the final cohort.

N=243

Of [redacted] patients, [redacted] had a baseline measurement only and no follow-up – see Appendix 3 for description.

Therefore, there are N=[redacted] patients with at least 1 follow-up physio visit (see SAP 3.1.1), 5 of whom were diagnosed pre-symptomatically. The pre-symptomatic group are not included in the SAP.



4.2 Final Analysis Cohort

N=[redacted] patients

Table 19: Description of All Nusinersen Patients and MAA Eligible Patients

	All Nusinersen Patients [redacted]	MAA cohort Patients [redacted]
Number lost to follow-up	[redacted]	[redacted]
Reasons for lost to follow-up **Transitioned to adult care** **Death** **Moved away** **Withdraw consent**	[redacted]	[redacted]
Number stopped treatment	[redacted]	[redacted]
Reasons for stopping **Switched to Zolgensma** **Switched to Risdiplam** **Side effects** **Spinal surg** **Unknown**	[redacted]	[redacted]
Previous treatment	[redacted]	[redacted]
Details of previous treatment **Resilience trial** **EAP abroad** **STRIVE trial** **Nusinersen abroad** **RESPOND trial** **Nusinersen trial** **Zolgensma abroad** **Unknown**	[redacted]	[redacted]
EAPS patients	[redacted]	[redacted]
Compassionate use	[redacted]	[redacted]

Explanation on patients on compassionate use: Most patients who initiated Nusinersen under the EAP were chronic patients and were older; a proportion were permanently ventilated (>16 hours/day) when starting treatment under the EAP, this would have prevented their inclusion in the MAA.

Table 20: Description of numbers of patients included in the cohort and number of visits at previous data-cuts

Date of reporting	Total Number of Patients$
December 2023 'Final' Report	[redacted]
February 2025	[redacted]

$ after all exclusions as outlined in previous reports

December 2023 patient visits

	Cohorts					
	Type I- EAP	Type I- Non-EAP	Type II/III- Non-Sitters	Type II/III- Sitters	Type II/III- Walkers	All SMA types
Baseline	[redacted]					
6 months	[redacted]					
1 year	[redacted]					
18 months	[redacted]					
2 years	[redacted]					
30 months	[redacted]					
3 years	[redacted]					
3.5 years	[redacted]					
4 years	[redacted]					

February 2025 patient visits

	Cohorts					
	Type I- EAP	Type I- Non-EAP	Type II/III- Non-Sitters	Type II/III- Sitters	Type II/III- Walkers	All SMA types
Baseline	[redacted]					
6 months	[redacted]					
1 year	[redacted]					
18 months	[redacted]					
2 years	[redacted]					
30 months	[redacted]					
3 years	[redacted]					
3.5 years	[redacted]					
4 years	[redacted]					

Latest Follow-up February 2025

	Cohorts					
	Type I- EAP	Type I- Non-EAP	Type II/III- Non-Sitters	Type II/III- Sitters	Type II/III- Walkers	All SMA types
6 months	[redacted]					
1 year	[redacted]					
18 months	[redacted]					
2 years	[redacted]					
30 months	[redacted]					
3 years	[redacted]					
3.5 years	[redacted]					
4 years	[redacted]					

Table 1: Baseline Demographics and Clinical Characteristics

	Cohorts					
	Type I- EAP	Type I-Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers	All SMA types
Number of Patients						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMA Type						
Type I						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type II						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type III						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at Symptom Onset (months)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at First Nusinersen (years)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base Age						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender						
Male						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of SMN2 copies						
1						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scoliosis						

No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP-Intend						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP-Intend (Rescale)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HINE-2						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HINE-2 (Imputed)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RHS						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RHS (Imputed)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RULM						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RULM (Imputed)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

WHO Motor Achievement						
Non-sitters						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting Without Support						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crawling						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with Assistance						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with Assistance						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing Alone						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking Alone						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Feeding problems						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TLSO Brace use						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least one fracture						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Upper limb contractures						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower limb contractures						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal surgery						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Salbutamol Use						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other treatments						
No						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Feeding problems: includes G tube, fundoplication, nasogastric tube, PEG, gastrojejunal
Fracture is any fracture requiring surgery
Other treatments: other medications of note, such as: Azithromycin, Multivitamins, Omeprazole, Movicol, Cetirizine

4.4 Nusinersen Treatment (SAP 4.2)

Table 4: Nusinersen Treatment (at latest visit)

	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Enrolled on the EAP					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Previously Received Treatment					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on Nusinersen at Last Visit					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Discontinued Nusinersen Treatment					
No					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reason for Discontinuing Nusinersen					
Moved Away					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam/Scoliosis					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal Surgery/Scoliosis					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zolgensma					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown					

N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Information about number of doses and actual dose are not included in above table, as data for this is poorly captured in the database. This has been discussed with Biogen and it was decided that treatment duration is a preferable description, and this has been described, as in previous reports.

The main reason for nusinersen discontinuation is related to the lumbar puncture (LP) procedure. Patients who over time developed scoliosis or had their scoliosis progressing, found it increasingly difficult to tolerate repeated LPs. Even after treating SMA symptomatic patients with any disease modifying treatment, we see early development of scoliosis in SMA type 1 and scoliosis development in SMA type II and III; this is considered part of the progressive nature of the condition and could be modified only with very early treatment (i.e. pre-symptomatic patients). Additionally, once patients have spinal surgery, then LP accessibility might change and, although there has been an effort to leave a lumbar space for LP, this is not always possible. Some centres will be able to perform LP through interventional radiology guidance and therefore patients will be able to remain on nusinersen even with progressed scoliosis of after spinal surgery. None of the cases discontinued nusinersen for lack of efficacy. SMA II and III mainly have discontinued switching to Risdiplam as orally available.

Those with SMA 1 who discontinued in favour of receiving gene therapy, were mostly driven by the possibility of receiving a “one-off” treatment. The one-off treatment was also appealing to families as concerns on treatment accessibility post MAA have raised over time.

4.5 Attainment or Maintenance of Motor Milestones (SAP 4.3.1.1)

Two definitions of attainment, based on the WHO motor milestone scale, were defined in the SAP:

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

For patients with missing WHO information at the timepoint of interest for whom data is available at flanking visits, linear interpolation was applied based on the patient's observed data at the flanking visits with the result rounded to the nearest integer score. If the missing value is the last visit, no imputation was applied, and the patient was not included in the denominator.

The number and proportion of patients who fall into each of the above categories are presented with 95% Clopper-Pearson confidence intervals (CIs) in Table 5. Note that confidence intervals are presented on a proportion scale rather than percentage scale.

Table 5: Attainment or Maintenance of WHO Motor Milestones

Time Since Baseline = 6 months					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of					

a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 1 year					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Net Attainment of Motor Milestone or Stayed the Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 18 months					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the					

Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 2 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 2.5 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 3 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers

Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 3.5 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Net Attainment of a Motor Milestone [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 4 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Non-Sitters	Type II/III-Sitters	Type II/III-Walkers
Number of Patients [Non-flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Non-Flanked]					

Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Non-Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients [Flanked]					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of a Motor Milestone [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Attainment of Motor Milestone or Stayed the Same [Flanked]					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

It is noticeable with longer follow-up that maintenance and improvement are documented, confirming long lasting treatment effect, even with expected disease progression (i.e. increased contractures/scoliosis).

The natural history of SMA has been well described and is characterised by progressive deterioration in motor function as well as respiratory and bulbar function. This will be more rapid in SMA Type I but will inevitably happen in SMA Type II and III as well. Stabilisation needs therefore to be considered a treatment effect, leading to better long-term outcomes and quality of life. Even in this heterogenous cohort of real-world data, where patients started treatment when heavily symptomatic and chronically affected by the disease, there is an clear treatment effect resulting in stabilisation.

5.8 Proportion of Patients Who Achieve Important Improvement

A responder definition (RD) for 2 motor function scales was pre-defined and represents "a score change in a measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit" (US Department of Health and Human Services, 2019). Thus, the RD is the minimum amount of improvement that is important to the patient or caregiver. Change is measured at the individual level (what is an important change for patients/caregivers?) rather than at the group level (what is the minimum amount of change between groups that could be considered clinically meaningful?).

For HINE: RD = 1 point

For CHOP-INTEND : RD= 9 points

For patients with missing information at some timepoints, information was used from flanking visits as in summaries for Attainment or Maintenance of Motor Milestones above. The number and proportion of patients who fall into the responder category are presented with 95% Clopper-Pearson confidence intervals (CIs) in Table 8. Note that NB confidence intervals are presented on a proportion scale rather than percentage scale.

Table 8: Responders Analysis

Time Since Baseline = 6 months					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W
Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved					

important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 1 year					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W
Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 18 months					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W

Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	
Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 2 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W
Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	

Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 2.5 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W
Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	
Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time Since Baseline = 3 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W
Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	
Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	

Time Since Baseline = 3.5 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W
Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					

Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	
Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	

Time Since Baseline = 4 years					
	Cohorts				
	Type I- EAP	Type I- Non-EAP	Type II/III-Walkers	SMA2/3-S	SMA2/3-W
Number of Patients with Evaluable CHOP Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					
Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	
Number of Patients with Evaluable HINE-2 Data					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieved important improvement					

Yes					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binary Confidence Interval					
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HINE and CHOP are relevant for young patients and non-sitters, although the CHOP cannot be formally completed in heavier patients.

During the relatively extended period of the EAP when patients with SMA I were able to receive nusinersen, we observed an initial cohort of older and already heavily symptomatic patients treated in the EAP, some of whom are currently under compassionate use. Newly diagnosed patients in the EAP were symptomatic at treatment initiation but younger and therefore better responders to treatment. By the time these younger patients transitioned from the EAP to the MAA they had already improved CHOP and HINE scores, with a higher baseline at MAA initiation. After the initial more rapid response, with increased scores of the motor scales, a period of plateau or slow response is often observed, which coincides with being the next meaningful step change in motor milestone. A proportion of patients who had already a relatively high baseline score at the time of starting nusinersen under the MAA, have been already treated with nusinersen for some time, but gains in scores are missed. As expected, stabilization is observed in these patients.

5.9 Permanent Ventilation – no change since previous report

(Definition: Any ventilation type for ≥ 16 hours/day continuously for > 21 days or tracheostomy)

[redacted] SMA type I EAP patients in the final cohort are recorded at a particular visit as being on ventilation for > 16 hours per day. [redacted]

[redacted] SMA type I EAP patient was recorded as being on permanent ventilation, although was not included in the final cohort because no baseline physio assessment was available (one of those excluded for this reason).

It is noticeable that only patients in the EAP (which included the first and more chronic SMA type I patients) are recorded to have needed permanent ventilation (>16 hours); these [redacted] patients in total represent a very small number compared with the expected natural history of SMA type I where approximately 90% of children are either deceased or need permanent ventilation by the age of 2 years.

5.10 Tracheostomy – no change since previous report

[redacted] SMA type I-EAP patients had a tracheostomy at baseline.

No other patient was recorded as having a tracheostomy whilst in the MAA.

Table 10: Overall Survival (as outlined in the SAP)

There is insufficient data to run a time to event analysis and a narrative summary of the data is provided below. Available life status was recorded as available in data extract accessed February 2025

From our initial cohort of n= [redacted] patients, [redacted] patients are deceased.

[redacted] of these patients were not included in the analysis cohort, they were all Type I patients.

For the [redacted] patients included in the analysis cohort, [redacted] were Type I non-EAP patients and died after [redacted] months of nusinersen treatment, [redacted]

11. Additional Requests from EAG

1. **Mean (SE) HINE-2 scores at each follow-up point (Based on Section 5.4 and Table 6 in the ridisplam for SMA report)**

2. **Change mean (SE) in HINE-2 scores from baseline (Based on Section 5.4 and Table 6 in the ridisplam for SMA report)**

Observational summaries have been requested, however, it should be noted that there is sufficient data to run a MMRM longitudinal analysis (M8) from which we can obtained estimates of means and changes from baseline at each visit. Details are below.

For the full model, [redacted]. Weight was not a mandated field and as it contributed to the most missing data, we ran a sensitivity analysis of a model without weight which included [redacted]. The results were very similar, and we present results from the model excluding weight below, as it included more data. We show both models in the plots below for completeness. The interaction between visit and baseline HINE score was significant (P<0.001) and we represent this graphically.

Table 21: M8: HINE-2 for SMA Type I patients (EAP and non-EAP)

Visit	Number of patients with HINE-2 score per visit	Estimated CHOP-INTEND score^	SE	Predicted change in HINE-2 from baseline	95% CI	P value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1: Model M8: Results from MMRM model for SMA Type I patients: HINE outcome

The 3 profiles in above figure represent different baseline HINE scores: Blue is lower tertile score = [redacted], Red is median score = [redacted] and Green is upper tertile score = [redacted]

M8A: SMA Type I HINE – considering non-EAP v EAP patients

This was not a pre-specified comparison and was not part of original SAP. For exploration we have added a term for **non-EAP v EAP** and its interaction with visit to model M8 above. The interaction between visit and non-EAP/EAP group was significant (P<0.001) and we show estimates in the plots below, as well as coefficients.

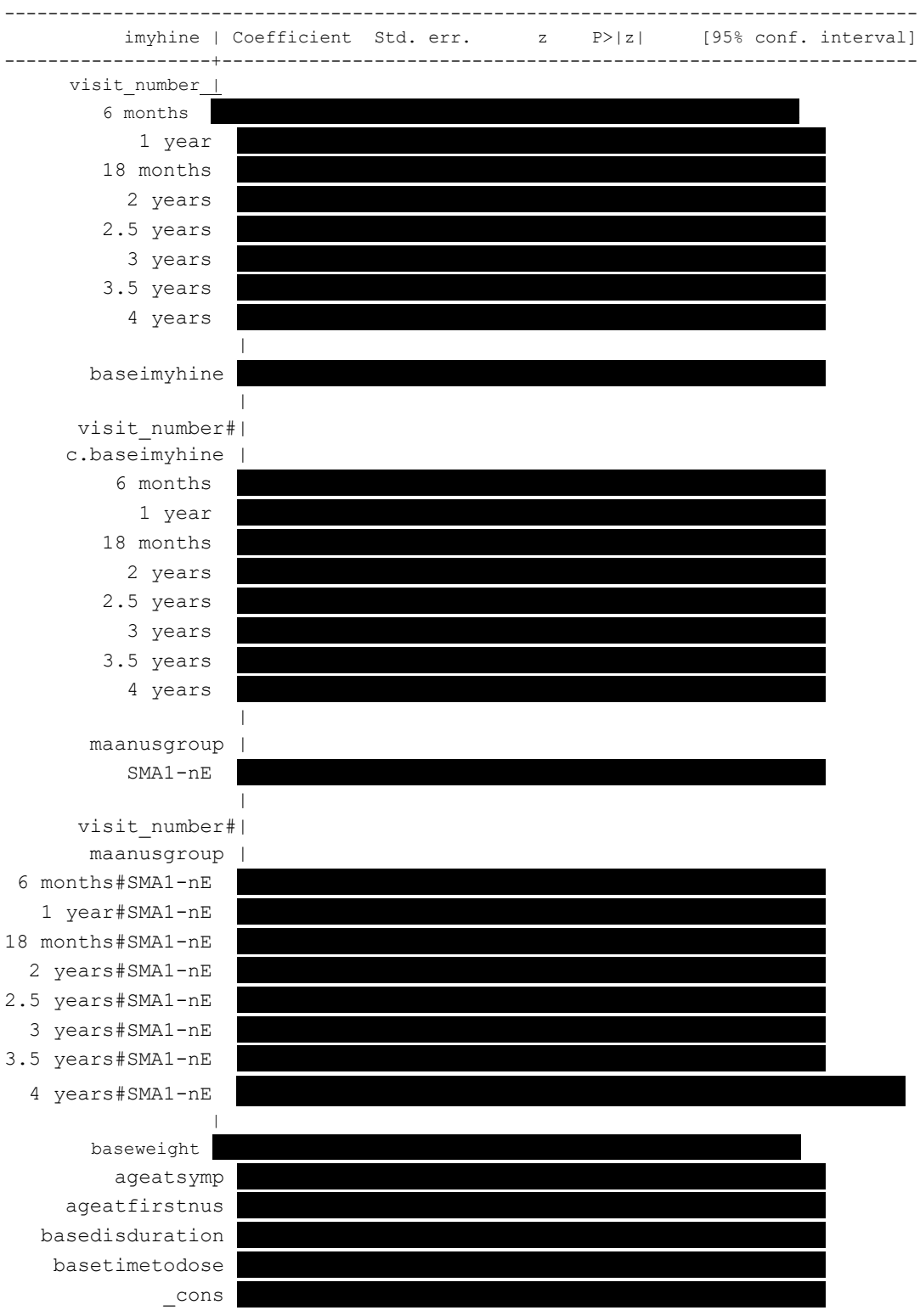
Figure 2: Model M8A Results from MMRM model for SMA Type I patients – considering non-EAP / EAP groups

For the plot in above right panel, red=non-EAP and blue=EAP

Table 22: M8A: HINE-2 for SMA Type I patients (EAP vs non-EAP)

Model M8A

For interpretation of interaction between non-EAP / EAP group and visit



3. **WHO motor milestone categories by follow-up (Based on Appendix 8 of the ridisplam SMA report): *Risdiplam Appendix 8***

***Risdiplam Table 12_A8*: Summaries of WHO motor milestone categories by follow-up visit for each group** as outlined in SAP 2.11.1.2

Table 23: Summaries of WHO motor milestone categories by follow-up visit for each group

SMA Type I - EAP

	Follow-up visits				
	Baseline	1 year	2 years	3 years	4 years
Number of Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHO Motor Achievement					
Non-sitters					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting Without Support					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crawling					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SMA Type I – Non-EAP

	Follow-up visits				
	Baseline	1 year	2 years	3 years	4 years

Number of Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHO Motor Achievement					
Non-sitters					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting Without Support					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crawling					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SMA Type II/III – Non-Sitters

	Follow-up visits				
	Baseline	1 year	2 years	3 years	4 years
Number of Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHO Motor Achievement					
Non-sitters					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting Without Support					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crawling					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Walking with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SMA Type II/III – Sitters

	Follow-up visits				
	Baseline	1 year	2 years	3 years	4 years
Number of Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHO Motor Achievement					
Non-sitters					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting Without Support					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crawling					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SMA Type II/III – Walkers

	Follow-up visits				
	Baseline	1 year	2 years	3 years	4 years
Number of Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHO Motor Achievement					
Non-sitters					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting Without Support					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crawling					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking with Assistance					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking Alone					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In the natural history, less than 10% of patients with Type I SMA would have survived beyond 2 years of age and skills attainment in this nusinersen treated SMA I group is noteworthy. For the Type II SMA groups, SMA-related co-morbidities such as scoliosis and contractures, as well as scoliosis surgery may have impacted on function. The Type III group are achieving a maximum score of 6 on the WHO and the scale is not sensitive enough to pick up small functional changes.

12. Additional information on EK2 scale

The EK2 (Egen Klassification 2) scale assesses activity and participation in individuals with non-ambulatory SMA. It is a composite scale and consists of 17 items, each scored from 0 to 3, with a maximum possible score of 51. The scale covers eight daily-life categories including wheelchair use and transfers, trunk mobility, eating, swallowing, breathing, coughing and fatigue. A higher EK2 score indicates a greater level of functional impairment.

Figure 3: Individual trajectory plots for observed EK2 data

The plots show most individuals maintain their level of function and some, particularly SMA Type I patients improve. A few patient decline; i.e. their score increases over time. No SMA Type I-Non-EAP patient had 2 EK2 measurements, hence no trajectory is available.

NB this data was not mandated, therefore has not been captured and cleaned to the same degree as mandated items.