GREAT ORMOND STREET
INSTITUTE OF CHILD HEALTH

# Managed Access Agreement

# Risdiplam 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/March 2024 report

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

**Tables:**

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 5, Table 7, Table 8_A5, Table 8_A6, Table 9_A6, Table 10_A6

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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 2 – 7, Appendix 9-14.

**Appendix 8**: Summaries of WHO motor milestone categories by follow-up visit for each group

**New Appendices (2025)**

**Appendix 15**: Additional items requested by NICE / EAG: 26/02/2025

**Appendix 16**: Additional information on EK2 scale

**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

EAMS: Early Access to Medicines Scheme

MMRM: Mixed model repeated measures

Pre-symp: Pre-symptomatic SMA

SMA1: SMA Type I patients

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-SW: SMA Type II or III patients, sitters or walkers at baseline (WHO total score = 1-6)

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

3. **Consolidation of MAA Patient numbers in SMA REACH database with NHS Blueteq numbers**

Cohort was finalised and data cut February 2025

| | SMA Reach Database MAA Patients | Blueteq | Difference |
|---|---|---|---|
| **Birmingham** | [redacted] | [redacted] | [redacted] |
| **Bristol** | [redacted] | [redacted] | [redacted] |
| **Cambridge** | [redacted] | [redacted] | [redacted] |
| **Cardiff** | [redacted] | [redacted] | [redacted] |
| **Evelina** | [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] |
| **Oswestry** | [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 risdiplam treatment prior to switch to a different disease modifying therapy.

A few patients have moved site.

**4. Derivation of MAA analysis cohort (as per MAA inclusion criteria)**

Patients identified in February 2025 as receiving Risdiplam in England and Wales through the MAA (N=239)

**4.1 Exclusions**

- Not eligible (n=[redacted]$) N=[redacted]
- No first dose date (n=[redacted]) N=[redacted]
- Over 18 years at baseline (n=[redacted]) N=[redacted]
- No physio visit within baseline window (n=[redacted]) N=[redacted]
- Started treatment abroad (n=[redacted]^) N=[redacted]

$ Of [redacted], [redacted]on compassionate use, [redacted]transitioned to adult care before first dose and [redacted]switched to onasemnogene abeparvovec (zolgensma) prior to first dose.

^ [redacted]patients who enrolled into the MAA started treatment abroad. These patients were excluded from the eligible cohort, as no data was available consistently from outside the UK, and treatment may be given under a different protocol. [redacted]patients were SMA I and [redacted]in the SMA II/III sitters/walkers cohort.

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

Of [redacted]patients, [redacted]had a baseline measurement only and no follow-up visit available in the database as of February 2025.

Therefore, there are N=[redacted]patients with at least 1 follow-up physiotherapy visit, [redacted]of whom were diagnosed pre-symptomatically. For [redacted]patients we had no WHO motor milestone information at baseline, so could not classify them according to sitters/non-sitters/walkers.

| **Pre-symp** | **SMA Type I** | **SMA Type II/III non sitters** | **SMA Type II/III sitters/walkers** |
|---|---|---|---|
| (n=[redacted]) | (n=[redacted]) | (n=[redacted]) | (n=[redacted]) |

**Final Cohort**

**N=[redacted]patients**

Table 13: **Description of All Risdiplam Patients and MAA Eligible Patients**

| | All Risdiplam Patients N= | MAA cohort Patients N= |
|---|---|---|
| **Number stopped treatment** | | |
| **Reasons for stopping**<br>**Switched to Zolgensma^**<br>**Side effects**<br>**Adverse events**<br>**Moved away** | | |
| | | |
| **Number lost to follow-up** | | |
| **Reasons for lost to follow-up**<br>**Transitioned to adult care**<br>**Death** | | |
| | | |
| **Previous treatment** | | |
| **Details of previous treatment**<br>**Nusinersen**<br>**Nusinersen (SHINE trial)**<br>**Risdiplam (SUNFISH trial)**<br>**Risdiplam (Jewelfish)**<br>**Risdiplam (Manatee)**<br>**Risdiplam abroad**<br>**Zolgensma US** | | |
| | | |
| **EAMS patients** | | |
| | | |
| **Compassionate use** | | |

$ of started trial abroad

^ The use of Risdiplam as a bridging treatment was agreed nationally. Of the patients who switched to Zolgensma, none are included in the MAA cohort, received Risdiplam as a bridging treatment for less than 6 months, received treatment abroad and for the date of first dose was not available.

**Table 14: Description of numbers of patients included in the cohort and numbers of visits at previous datacuts**

| Date of reporting | Total Number of Patients$ |
|---|---|
| **December 2023 'Final' Report** | [redacted] |
| **June 2024 Interim Report** | [redacted] |
| **November 2024** | [redacted] |
| **February 2025** | [redacted] |

$ after all exclusions as outlined in previous reports

**December 2023 patient visits (Table 5 in report for NICE MAOG)**

| | Cohorts | | | |
|---|---|---|---|---|
| | Type I | Type II/III- Non-Sitters | Type II/III-Sitters/Walkers | All SMA types |
| **Baseline** | [redacted] | [redacted] | [redacted] | [redacted] |
| **6 months** | [redacted] | [redacted] | [redacted] | [redacted] |
| **1 year** | [redacted] | [redacted] | [redacted] | [redacted] |
| **18 months** | [redacted] | [redacted] | [redacted] | [redacted] |
| **2 years** | [redacted] | [redacted] | [redacted] | [redacted] |

**February 2025 patient visits**

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

**Latest Follow-up February 2025**

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

**Table 1: Baseline Demographics and Clinical Characteristics**

| | Cohorts | | | |
|---|---|---|---|---|
| | Type I | Type II/III- Non-Sitters | Type II/III-Sitters/Walkers | All SMA types |
| **Number of Patients** | | | | |
| **N** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Age at Symptom Onset (months)** | | | | |
| **Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Median** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Range** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Age at First Risdiplam (years)** | | | | |
| **Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Median** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Range** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Base Age** | | | | |
| **Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Median** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Range** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Gender** | | | | |
| **Male** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Female** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Number of SMN2 copies** | | | | |
| **2** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **3** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **4** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scoliosis** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **CHOP-Intend** | | | | |
| **N** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Mean (SD)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Median** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Range** | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| **CHOP-Intend (Imputed)** | | | | |
| **N** | | | | |
| **Mean (SD)** | | | | |
| **Median** | | | | |
| **Range** | | | | |
| **HINE-2** | | | | |
| **N** | | | | |
| **Mean (SD)** | | | | |
| **Median** | | | | |
| **Range** | | | | |
| **HINE-2 (Imputed)** | | | | |
| **N** | | | | |
| **Mean (SD)** | | | | |
| **Median** | | | | |
| **Range** | | | | |
| **RHS** | | | | |
| **N** | | | | |
| **Mean (SD)** | | | | |
| **Median** | | | | |
| **Range** | | | | |
| **RHS (Imputed)** | | | | |
| **N** | | | | |
| **Mean (SD)** | | | | |
| **Median** | | | | |
| **Range** | | | | |
| **RULM** | | | | |
| **N** | | | | |
| **Mean (SD)** | | | | |
| **Median** | | | | |
| **Range** | | | | |
| **RULM (Imputed)** | | | | |
| **N** | | | | |
| **Mean (SD)** | | | | |
| **Median** | | | | |
| **Range** | | | | |
| **WHO Motor Achievement** | | | | |
| **Non-sitters** | | | | |
| **N (%)** | | | | |
| **Sitting Without Support** | | | | |
| **N (%)** | | | | |
| **Crawling** | | | | |
| **N (%)** | | | | |
| **Standing with Assistance** | | | | |
| **N (%)** | | | | |
| **Walking with Assistance** | | | | |

| | | | | |
|---|---|---|---|---|
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Standing Alone** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Walking Alone** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Feeding problems** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **TLSO Brace use** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **At least one fracture** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Upper limb contractures** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Lower limb contractures** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Spinal surgery** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |

| | | | | |
|---|---|---|---|---|
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Salbutamol Use** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Other treatments** | | | | |
| **No** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Yes** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Unknown** | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] |

As discussed and reported in previous 2023 report, the initial treated cohort was mainly older and more chronic than more recently treated patients, they had more 'difficult' spines which prevented nusinersen treatment. Once the Risdiplam drug approval was implemented and extended to babies younger than 6 weeks, the cohort of treated patients changed, becoming younger and therefore expected to have a better outcome.

**Table 4: Risdiplam Treatment (at latest visit)**

| | Cohorts | | |
|---|---|---|---|
| | Type I | Type II/III- Non-Sitters | Type II/III-Sitters/Walkers |
| **Number of Patients** | | | |
| **N** | [redacted] | [redacted] | [redacted] |
| **Patient Enrolled on the EAM** | | | |
| **Yes** | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] |
| **Patient Previously Received Treatment** | | | |
| **Yes** | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] |
| **Time on Risdiplam at Last Visit (months)** | | | |
| **Mean (SD)** | [redacted] | [redacted] | [redacted] |
| **Median** | [redacted] | [redacted] | [redacted] |
| **Range** | [redacted] | [redacted] | [redacted] |
| **Patient Discontinued Risdiplam Treatment** | | | |
| **No** | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] |
| **Yes** | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] |
| **Reason for Discontinuing Risdiplam** | | | |
| **Side Effects** | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] |

### 4.4 Models to describe estimated means and changes from baseline (SAP 2.9)

Models

- M1: SMA I CHOP-INTEND
- M2: SMA I RHS
- M3: SMA I RULM
- [redacted]
- M5: SMA II/III RHS
- M6: SMA II/III RULM

Adjusted for the following pre-defined baseline covariates listed in the SAP (2.9).

- Age at symptom onset
- Age at treatment initiation
- Time between diagnosis and treatment initiation
- Baseline motor function milestone categorised by walkers/sitters or non-sitters (for SMA Type II/III model only)
- Weight

[redacted]

For the full model, this analysis included [redacted] observations from [redacted] patients (i.e. only [redacted] patients had a baseline HINE score and a follow-up score). This is insufficient data to run a full MMRM, including multiple covariates. Observed cross-sectional summaries and changes from baseline are described in Table 6 below, although it should be noted that the small sample size makes interpretation difficult, so these should be considered with extreme caution.

**Table 6: Observed mean by visit and observed changes from baseline by visit for SMA Type I patients**

| Visit | Number of patients with HINE score per visit | HINE score<br><br>Mean (sd) | Change in HINE from baseline<br><br>Mean (sd) |
|---|---|---|---|
| **Baseline** | [redacted] | [redacted] | [redacted] |
| **6 months** | [redacted] | [redacted] | [redacted] |
| **1 year** | [redacted] | [redacted] | [redacted] |
| **18 months** | [redacted] | [redacted] | [redacted] |

### 5.7 Time to event analysis (SAP 2.11.1.3)

#### 5.7.1 Mortality

**(There have been no additional deaths since original report in December 2023)**

There are not enough events to run a formal analysis.

[redacted]

[redacted]

[redacted]

#### 5.7.2 Patients meeting stopping criteria / switched treatment

**(There have been no additional patients stopping treatment since original report in December 2023)**

[redacted]SMA type II/III sitter-walker patient stopped Risdiplam, due to side effects. In December 2023 report we indicated there was [redacted]who stopped Risdiplam and switched to Zolgensma, however have received updated information that [redacted]started treatment abroad, hence was not in the final analysis cohort for this report. There are insufficient numbers to run an analysis.

#### 5.7.3 Permanent ventilation

**(There have been no changes to permanent ventilation status for patients since original report in December 2023)**

No patient has been recorded as being on permanent ventilation, either at baseline or at the most recent visit.

(For us: At baseline 56/164 have no information recorded and at last visit 75/164 have no information recorded)

**Appendix 8**

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

**SMA Type I**

| | Follow-up visits | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | 6 months | 12 months | 18 months | 2 years | 30 months | 3 years |
| **Number of Patients** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **WHO Motor Achievement** | | | | | | | |
| **Non-sitters** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Sitting Without Support** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Crawling** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Standing with Assistance** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Walking with Assistance** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Standing Alone** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Walking Alone** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Missing** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**SMA Type II/III Non-Sitters**

| | Follow-up visits | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | 6 months | 12 months | 18 months | 2 years | 30 months | 3 years |
| **Number of Patients** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **WHO Motor Achievement** | | | | | | | |
| **Non-sitters** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Sitting Without Support** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Crawling** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Standing with Assistance** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Walking with Assistance** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Standing Alone** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Walking Alone** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Missing** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**SMA Type II/III Sitters/Walkers**

| | Follow-up visits | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | 6 months | 12 months | 18 months | 2 years | 30 months | 3 years |
| **Number of Patients** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **WHO Motor Achievement** | | | | | | | |
| **Non-sitters** | | | | | | | |
| | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Sitting Without Support** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Crawling** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Standing with Assistance** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Walking with Assistance** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Standing Alone** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Walking Alone** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Missing** | | | | | | | |
| **N (%)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Appendix 15**: **Additional items requested by NICE / EAG: 26/02/2025**

Proportion of patients who achieve an increase of 1 point in their HINE-2 score from baseline to last follow-up (Based on Section 5.8 of the nusinersen for SMA report).

Note that this scale is not suitable for children > 2 years of age

**Table 15: Proportion of patients achieving a 1-point increase in HINE-2**

**At Last Visit**

| | Type I | Type II/III- Non-Sitters | Type II/III-Sitters/Walkers | Total |
|---|---|---|---|---|
| **Number of patients** | [redacted] | [redacted] | [redacted] | [redacted] |
| **No improvement** | [redacted] | [redacted] | [redacted] | [redacted] |
| **1 point increase** | [redacted] | [redacted] | [redacted] | [redacted] |
| **More than 1 point increase** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Missing** | [redacted] | [redacted] | [redacted] | [redacted] |

**At Latest Visit with available HINE score**

| | Type I | Type II/III- Non-Sitters | Type II/III-Sitters/Walkers | Total |
|---|---|---|---|---|
| **Number of patients** | [redacted] | [redacted] | [redacted] | [redacted] |
| **No improvement** | [redacted] | [redacted] | [redacted] | [redacted] |
| **1 point increase** | [redacted] | [redacted] | [redacted] | [redacted] |
| **More than 1 point increase** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Missing** | [redacted] | [redacted] | [redacted] | [redacted] |

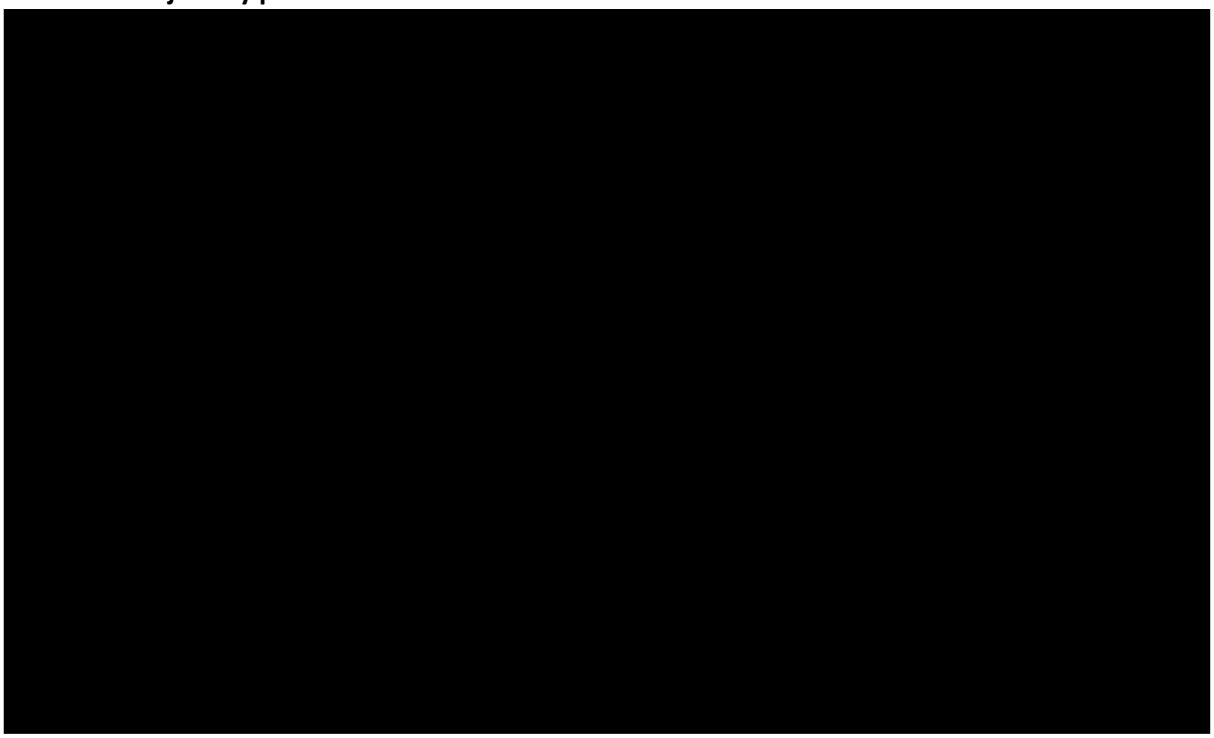
It is noticeable with longer follow-up that maintenance, and in some cases improvement, are documented, confirming long lasting treatment effect, even with expected disease progression (i.e. increased contractures/scoliosis).

The natural history of SMA has been well described and is characterised by progressive deterioration in motor function, as well as respiratory and bulbar. 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 heterogeneous cohort of real-world data, where patients started treatment when heavily symptomatic and chronically affected by the disease, there is a clear treatment effect resulting in stabilisation.

**Appendix 16**: **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.

**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 patients decline; i.e. their score increases over time.

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