Cedar

Healthcare Technology Research Centre

Nusinersen Managed Access Agreement treatment eligibility criteria evidence review: 5q Spinal Muscular Atrophy type III non-ambulant cohort

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Contents

Abbreviations

Term	Definition
6MWT	Six Metre Walk Test
AE	Adverse Event
CASP	Clinical Appraisal Skills Programme
CMI	Clinically Meaningful Improvement
EAC	External Assessment Centre
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
HFMSE	Hammersmith Functional Motor Scale Expanded
MAA	Managed Access Agreement
NICE	National Institute for Health and Care Excellence
PCEF	Peak Cough Expiratory Flow
RULM	Revised Upper Limb Module
SAE	Serious Adverse Event
SMA	Spinal Muscular Atrophy
SMN	Survival of Motor Neuron
ULM	Upper Limb Module

Executive Summary

Spinal Muscular Atrophy (SMA) is a genetic condition that causes muscle weakness and problems with movement. There are several different sub-types with the most severe causing death within weeks of birth. It affects an estimated 6.2 people per 100,000 births in the UK and currently there is no cure. A recently developed treatment called Nusinersen is the first approved drug for the treatment of SMA.

Following a review of available evidence, the current NICE Managed Access Agreement recommends nusinersen for people with presymptomatic, types I and II and ambulant type III SMA (subject to the eligibility criteria within the MAA). The purpose of this review is to assess additional new evidence to evaluate whether eligibility for nusinersen should be extended to non-ambulant type III SMA patients.

A review of the new evidence submitted identified 4 journal articles and 1 abstract relevant to this review with a total of 157 participants, 60 of who were type III non-ambulant. European registry data from 168 type III non-ambulant SMA patients was also provided by Biogen.

Hammersmith Functional Motor Scale Expanded (HFMSE) results for type III non-ambulant patients showed equal numbers of patients improving as declining. Most remained stable throughout follow-up. (Revised) Upper Limb module score (RULM) results suggest that type III non-ambulant patients are already at ceiling or scoring very highly on this measure. Therefore there is little room for improvement and so patients tend to remain stable over time. The 6 metre walking test was performed in one study on the non-ambulant patients and showed that 2 out of 4 regained the ability to walk but it was not stated how far and whether this was clinically meaningful.

The registry data included motor function results split by paediatric and adult populations. Using statistical modelling, the data showed predicted increases in HFMSE and RULM scores for both populations (in Nusinersen treated patients) over 12 months. However, these predicted increases were not clinically meaningful. Respiratory function did not improve for participants. Mild adverse events (most frequently headaches) were common across all participants. Anecdotal evidence was submitted by Biogen. Patients and families of patients who have had nusinersen presented positive results from the treatment. However, as they are self-reported results it was not appropriate for the EAC to use it for the purpose of this review.

The quality of the evidence was assessed using the Critical Appraisals Skills Programme (CASP) cohort study checklist. The quality of the evidence was poor with the main issues being low number of studies and very small sample sizes. The results therefore must be interpreted with caution as there is not enough evidence to generalise to a real-world setting.

Due to the poor quality of evidence and low efficacy of Nusinersen in type III non-ambulant patients, the new evidence does not provide a comparable clinical benefit for non-ambulant type III patients. Therefore it is the recommendation of the EAC to not extend the current MAA eligibility criteria to include non-ambulant type III patients.

Background

Spinal muscular atrophy (SMA) is a genetic condition that causes muscle weakness and problems with movement. It has an estimated prevalence of 6.2 per 100,000 births in the UK and is caused by genetic mutations on the survival of motor neuron (SMN) 1 gene that codes for SMN, a protein needed for the survival of motor neurons. It is also referred to as 5q SMA.

Typical symptoms include floppy or weak arms, difficulty hitting movement milestones such as sitting up, crawling and walking, twitching or shaking muscles, bone and joint problems including scoliosis, swallowing problems and breathing problems. It is a progressive condition and based on the severity and type of diagnosis, the prognosis can vary greatly:

- Type 1 – develops before 6 months of age and is the most severe type. Children with this subtype rarely survive beyond the first few years of life.
- Type 2 – develops in children 7-18 months old and is less severe than Type 1. Children with this subtype usually live well in to adulthood.
- Type 3 – develops after 18 months and is the least severe type affecting children. Children with this subtype have a usual life expectancy.
- Type 4 – develops in adulthood. Adults with this subtype have a usual life expectancy.

There is no cure for SMA, and treatments are generally limited to physiotherapy, exercises to improve movement and breathing, and braces or surgery to treat problems with the spine and joints (NHS website). A recently developed treatment called nusinersen (SPINRAZA, Biogen) is the first approved drug for the treatment of SMA. Nusinersen is an antisense oligonucleotide that increases the production of the SMN protein, thereby helping to compensate for the defect in the SMN1 gene (NICE https://bnf.nice.org.uk/drug/nusinersen.html).

Current guidelines and objectives

Following a review of available evidence, nusinersen is recommended for people with presymptomatic SMA, types I and II SMA and ambulant type III SMA (NICE Guidance TA588) subject to the eligibility criteria within the Managed Access Agreement (MAA). The purpose of this report is to assess additional new evidence to evaluate whether newly available evidence for nusinersen provides information concerning non-ambulant type III SMA patients to address the following objectives:

1. Is the new evidence of sufficient quality for decision-making concerning the existing eligibility criteria with respect to non-ambulant type III SMA patients?
2. Does the new evidence demonstrate a comparable clinical benefit for non-ambulant type III patients, as with patients who were able to sit independently but never had the ability to walk independently, compared to best standard of care for all of the following outcomes collectively?
    - motor function (including, where applicable, age-appropriate motor milestones and evidence of retention of fine motor skills)
    - respiratory function

- complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures)
- need for non-invasive or invasive ventilation
- stamina and fatigue
- mortality
- adverse effects of treatment
- health-related quality of life (if available)

3. Does the available evidence demonstrate a comparable clinical benefit for non-ambulant type III adult patients, as with non-ambulant type III paediatric patients, in relation to the criterion which allows paediatric patients who have lost independent ambulation in the preceding 12 months to access treatment?
4. Does the new evidence provide sufficient new information and demonstrate a comparable clinical benefit for non-ambulant patients to support a recommendation to amend the MAA eligibility criteria to expand access to non-ambulant type III SMA patients?

Clinical evidence

Biogen submitted 78 references for assessment. Of these 66 were peer reviewed research articles or conference poster presentations (abstracts), and of these 4 articles and 1 abstract were deemed relevant to this report. The most common reasons for exclusion were they did not use nusinersen, the participants were not type III non-ambulant and/or the outcomes measured were not relevant to this review.

Clinical Evidence quality appraisal

The quality of the evidence was appraised using the CASP (Critical Appraisal Skills Programme) Cohort Study Checklist. The main issues with the evidence base as a whole were the lack of evidence itself as only 4 studies and 1 abstract were found to be relevant, and the very low numbers of participants in 4/5 of the included evidence. There are therefore issues with generalisability and validity of the results. As most of the studies were not prospective there is no way to assess selection criteria which introduces a risk of selection bias. There are also major gaps in the reported evidence for the type III non-ambulant sub-group, such as mean levels of improvements in outcome measures, when patients lost ambulation, which is a major point of consideration for the administration of nusinersen, and some type III results are pooled so that results for the non-ambulant sub-group cannot be extracted and compared.

However, the Maggi study did have a good sample size and in all of the full articles the outcomes were objectively measured by a third party, reducing the risk of bias in reporting of outcomes.

Clinical evidence results

When reviewing the evidence included in our review, we were aiming to identify new evidence reporting results from validated clinical measures. The included measures, what they measure and their level of clinically meaningful improvement are listed in Table 1. Table 2 contains a breakdown of the clinical results from journal articles and Table 3 contains the results from the included abstract.

Table 1. Included measures

Name	Measure	Clinically meaningful improvement
Hammersmith Functional Motor Scale Expanded (HFMSE)	40 item scale used to measure physical ability	Change of 3 or more points (Swoboda et al, 2010)
(Revised) Upper Limb module score ((R)ULM)	To assess motor performance in the upper limbs	Change of 2 or more points (Pera et al, 2019)
6 minute walk test (6MWT)	Measure distance covered in 6 minutes	More than 30 metres (Dunaway et al, 2016)
Forced vital capacity (FVC)	amount of air that can be forcibly exhaled from your lungs after taking the deepest breath possible	CMI levels for SMA not reported
Forced expiratory volume (FEV)	measures how much air a person can exhale during a forced breath	CMI levels for SMA not reported
Peak cough expiratory flow (PCEF)	the maximum flow obtained within the first 200 milliseconds of a forced expiratory manoeuvre after inhalation to total lung capacity	CMI levels for SMA not reported

Table 2. Clinical evidence

Study	Design	Results	Comments
Darras et al (2019)	Participants: • **Total n = 28** • Type II n = 11 (all non-ambulant) • Type III ambulant n = 13 • Type III non-ambulant n = 4 • All participants were able to sit independently	**Hammersmith Functional Motor Scale-Expanded (HFMSE):** • **Type II -** Scores improved by a mean of 10.8 points by day 1050. 9/11 demonstrated clinically meaningful improvements (CMI,) by day 253 and 7/9 patients who had follow up data recorded at day 1050 demonstrated CMI • **Type III ambulant** - Scores improved by a mean of 2.6 points from baseline by day	• Does not mention how long ago the non-ambulant patients lost ambulation • Some HFMSE results were not split by ambulation, therefore we cannot report type III non-

	• Participants were children aged between 2-15 years Analyses are from an extension to a Phase 1b/2a study with a 253-day, ascending dose (3, 6, 9, 12 mg) multiple dose, open label, multicentre study (CS2). This extension was a 715 day single dose level (12mg) study (CS12). No timeframe given for loss of ambulation	1150. CMI was seen in 2/12 children at day 253 (mean score not reported) and 4/9 who had follow-up to day 1050 • **Type III non-ambulant** - 1/4 (25%) demonstrated CMI by day 253. Mean scores not reported. **Upper limb module (ULM) score (only non-ambulant assessed):** • **Type II** - scores improved by a mean of 4.0 from baseline to day 1150. Five of 11 children demonstrated CMI by day 253 and 5/9 children demonstrated CMI by day 1050 • **Type III non-ambulant** - all patients assessed at day 350 had reached the maximum score of 18 points and maintained this through day 1150. Mean scores were not reported. **6 minute walk test (6MWT):** • **Type II –** 1/11 children gained the ability to walk by day 650 and showed continued improvements until day 1150 (25.5m-180m) • **Type III ambulant –** 6/12 children assessed at day 253 demonstrated CMI and 8/8 by day 1050 • **Type III non-ambulant** - 2/4 patients who were previously able to walk but had lost the ability before baseline assessment regained the ability to walk independently. However, it is not stated how far these patients walked, whether it was a CMI, whether this was a sustained effect or how long ago these children lost ambulation.	ambulant results specifically • Safety results were not split by ambulation, therefore we cannot report type III non-ambulant results specifically • Lots of missing data in relation to the type III non-ambulant sub-group
Barp et al (2020)	Prospective case study design	**HFMSE score:**	• Patients lost ambulation >

	Participants: • **Total n = 2** • Type III non-ambulant n = 2 Both adult patients who lost ambulation >12 months prior to treatment	• **Type III non-ambulant** – Patient 1's scores remained stable until 10 months (26) but decreased at 24 months to 21. Patient 2 remained stable at 10 months (38) and increased slightly at 24 months (39). **Revised Upper Limb Module (RULM) score:** • **Type III non-ambulant** – Patient 1 scores remained relatively stable at baseline, 10 and 24 months for right (37/37, 35/37 and 37/37) and left (35/37, 34/37 and 34/37). Patient 2 also remained stable at baseline, 10 and 24 months for right (37/37, 37/37 and 37/37) with slight improvements for the left (33/37, 36/37 and 37/37). **Forced Vital Capacity (FVC, %)** • **Type III non-ambulant –** Patient 1 started at 4.03 which decreased to 3.70 at 10 months and then increased slightly to 3.83 at 24 months. Patient 2 started at 3.83 which increased slightly to 3.90 at 10 months before decreasing to 3.21 at 24 months. **Forced Expiratory volume (FEV, %)** • **Type III non-ambulant –** Patient 1 started at 3.36, decreased to 3.04 at 10 months and then increased to 3.34 at 24 months. Patient 2 showed a steady decline from 3.34 to 3.24 to 2.96 over 24 months. **Peak Cough Expiratory Flow (PCEF, L/min)**	12 months prior to the study. We cannot therefore compare to paediatric population who lost ambulation within 12 months. • The focus of this paper was using MRI as a biomarker, not the effects of nusinersen. However, it is included as patients did receive nusinersen and the outcomes were relevant to this review.

		• **Type III non-ambulant -** Patient 1 increased from 660 to 704.4 over 10 months but then decreased to 527 by 24 months. Patient 2 showed a steady decline from 560 to 552 to 486 over 24 months.	
Maggi et al (2020)	Retrospective cohort study Participants: • **Total n= 116** • Type II n = 13 • Type III ambulant (walkers) n = 52 • Type III non-ambulant (sitters) n = 51 No timeframe given for loss of ambulation	**HFMSE score:** • **Type II** – No statistically significant changes at any time-point (mean range 0.15-1.2 increase) • **Type III ambulant –** statistically significant changes from baseline were observed at 6 months (mean 1.58 increase, p<0.0001), 10 months (mean 2.38 increase, p<0.0001) and 14 months (mean 2.37 increase, p=0.00016) • **Type III non-ambulant –** Statistically significant changes from baseline were observed at 6 months (mean 1.37 increase, p<0.0001), 10 months (mean 2.51 increase, p<0.0001) and 14 months (mean 3.53 increase, p=0.0014) **It should be noted that although significant, only one of these results (type III non-ambulant at 14 months follow-up) is classed as clinically meaningful (≥3 point increase).** **RULM score:** • **Type II –** No significant changes at any time point (mean range 0.8-1.67 increase, ns) • **Type III ambulant -** No significant changes at any time point (mean range 0-0.4) • **Type III non-ambulant –** There was no significant change from baseline to 6 months. There was a significant change from baseline to 10 months (mean 1	• Good sample sizes

		increase, p=0.021) and 14 months (mean 1.47 increase, p = 0.018) **It should be noted that although significant, none of these reported means reach CMI (i.e +/- 2 points or more).** **6MWT:** • **Type II –** No results reported • **Type III ambulant –** significant changes from baseline were observed at 6 months (mean 14.66m, p=0.0005), 10 months (26.45m, p = 0.00019) and 14 months (23.11m, p=0.00016 • **Type III non-ambulant –** No results reported **It should be noted that although significant, none of these results are clinically meaningful.** **Whilst the means reported are all positive for HFMSE and RULM, indicating improvement, the ranges reported for the groups as a whole do show some participants deteriorated across all measures.** **FVC (%):** • **Type II –** No significant changes at an time points (-0.25, 0.75 and NA) • **Type III ambulant –** No significant changed at 6 and 0 months follow-up (1.16 and 5.8). Significant change at 14 months compared to baseline (9, p = 0.031). However the number of included participants decreased from 52 at baseline to 7 at 14 months) • **Type III non-ambulant –** No significant changes at any time point (0, 3.3 and 4.25)	
Yeo et al (2020)	Prospective cohort design	**HFMSE score:** • **Type III ambulant** – 2/4 (50%) had CMI. Two participants	• Both non-ambulatory participants

	Participants: • **Total n = 6** • Type III ambulant n = 4 • Type III non-ambulant n = 2 15-21 month follow-up Both non-ambulant participants lost ambulation >12 months prior to treatment	remained stable over 14 months follow-up • **Type III non-ambulant –** 1/2 (50%) had CMI. One remained stable over 14-month follow-up. **RULM score:** • **Type III ambulant** - 1/4 was at ceiling and remained stable of 21 months follow-up. 2/4 improved by 2 points to ceiling by 6 months and remained stable. 1/4 was not at ceiling but remained stable over 14 months • **Type III non-ambulant** – all non-ambulatory participants had CMI over 15-18 months	lost ambulation more than 12 months prior to treatment

Table 3 Clinical evidence from abstracts

Study	Design	Results	Comments
Muntoni et al (no year given)	**Participants**: • **Total n = 5** • Type II n = 1 • Type III ambulant n = 3 • Type III non-ambulant n = 1 No timeframe given for loss of ambulation	**Difference in score from baseline to last visit (median 1952 days)** **HFMSE scores:** • **Type II** - improved by 5 points • **Type III ambulant –** improvement of 4 points for one participant, decrease of 3 points for another and no change was reported for the last participant • **Type III non-ambulant -** decreased by 2 points **ULM scores:** • **Type II –** no change • **Type III ambulant** – one participant reported no change. No results for reported for the other two participants • **Type III non-ambulant** – no change **6MWT**	• Limited results • Does not report when non-ambulant participant lost ambulation

		• **Type II –** no results reported • **Type III ambulant** – distance increased for all three participants (24, 69 and 81m) • **Type III non-ambulant** – no results reported	

Clinical Evidence description

N.B Type III ambulant results were included in the results table for reference. As they do not relate to the objectives of this report they will not be discussed here.

The evidence reported includes 157 participants, 60 type III non ambulant participants (51 of which were from a single study), from 5 studies. It is not clear whether nusinersen is clinically effective based on the quality evidence available. This is due to a number of factors such as small samples sizes, mixed populations (all types of SMN), results for type III not separated by ambulant/non-ambulant.

Maggi et al (2020) reported that mean HFMSE scores for type III non-ambulant participants were statistically significantly improved for each time point compared to baseline measurements. However, the mean was only considered a clinically meaningful improvement (CMI) for 14 months follow-up. In addition, for each time point the range of scores showed negative figures, indicating deterioration for some participants. The breakdown of figures is not reported but the fact some participants from all SMA types deteriorated should be considered. Darras et al (2019), Baro et al (2020) and Yeo et al (2020) showed 3/8 type III non-ambulant participants across all 3 studies had a CMI in scores, however, not all means were reported. Barp et al (2020) and Yeo et al (2020), showed 2/4 participants in total were stable across time. Barp et al (2020) and Muntoni et al reported 2/3 participants had a decline in scores of between 2 and 5 points across an undefined maximum follow-up period. When compared with type II participants, Darras et al (2019) and Muntoni showed CMI of up to a mean of 10.8 points. Darras also reported 9/11 participants achieved CMI over 1150 days. Maggi et al (2020) however, showed no significant change in HFMSE scores for type II participants over 14 months.

Several ULM /RULM results show that type III non-ambulant participants start at ceiling, or with very high scores, and then remain stable up to 14 months follow-up (Darras et al, 2019; Barp et al, 2020 and Muntoni et al). Yeo (2020) showed 2 participants achieved a CMI over 15-18 months whilst Maggi et al (2020) showed significant improvements at 6, 10 and 14 months but it should be noted the improvements at all time points did not meet the level of a CMI. Again, the range of scores showed negative figures, indicating deterioration for some participants. The number of patients who deteriorated is not reported but the fact some participants deteriorated while on treatment should be considered. Type II participants showed an increase of 4 points with 4/11 achieving CMI by day 253 and 5/9 by day 1050. Two further studies however showed either no change in score (Muntoni) or no significant change in scores over 14 months follow-up (Maggi et al, 2020).

The 6MWT was rarely assessed in the type III non-ambulant or type II participants however Darras et al. 2019 reported that 2 out of 4 type III non-ambulant and 1/11 type II participants regained the ability to walk. The type II participant increased from 25.5m to 180m (CMI) over 1150 days. The study did not detail how far the type III non-ambulant participants were able to walk or whether it could be classed as a CMI.

Respiratory measures were rarely measured however, Barp et al (2020) showed that 2 type II non-ambulant participants showed a steady overall decline in FVC, FEV and PCEF measures. Maggi et al (2020) showed no significant changes from baseline in FVC measures for both type II and type III non-ambulant participants. However the numbers of included participants dropped significantly from baseline to 14 months follow-up; 13-0 for type II and 52-7 for type III non-ambulant.

Safety

Adverse events were reported in 3 studies. Only Maggi et al (2020) split the results by SMA type. However, it was still not split by ambulant/non-ambulatory type III. See Table 4 for adverse events.

Table 4. Adverse events

Study	Adverse events (AEs)
Darras et al (2019)	All 28 participants experienced ≥1 AE. The most common AEs (occurring in ≥20% of children) were post-lumbar puncture (LP) syndrome (n = 16), headache (n = 13), nasopharyngitis (n = 12), upper respiratory tract infection (n = 12), puncture site pain (n = 11), back pain (n = 9), scoliosis (n = 8), pyrexia (n = 7), joint contracture (n = 6), rhinorrhea (n = 6), and vomiting (n = 6). Most AEs were mild or moderate in severity and were considered by investigators as unrelated to the study drug. Serious AEs (SAEs) were reported by 5 (18%) children and included post-LP syndrome (n = 2); lower respiratory tract infection, respiratory distress, and viral pneumonia (n = 1); acute respiratory failure and respiratory syncytial viral pneumonia (n = 1); and vesicoureteral reflux and pyelonephritis (n = 1). No SAEs were considered related to study drug, and no children discontinued treatment due to AEs.
Barp et al (2020)	None reported

Maggi et al (2020)	Two (1.7%) patients with type III stopped nusinersen treatment after 6 months, due to lack of subjective benefit and poor tolerability of repeated lumbar puncture. AEs were reported in 48 (41.4%) patients (6 type II (46%) and 42 type III (41%)). Post procedure headaches, occured at least once in 43/116 (37.1%) patients. Headache resolved in a few days, except for five patients (4 type III and 1 type II) who required hospitalisation. Lumbar pain was reported in 10/116 (8.6%) patients. Two patients with type III reported transient (1–2 months) worsening of existing hand tremor, one after baseline and one after 14 months. One renal colic requiring hospitalisation occurred in a patient with type II at 10 months follow-up. Except for those requiring hospitalisation, AEs were judged not related to Nusinersen itself, but rather to the administration procedure.
Yeo et al (2020)	All (n=6) participants had one or more adverse events. Two serious AEs resulted in hospitalisation: a fall with comminuted sacral compression fractures requiring extended hospitalisation for pain control and rehab, and leg cellulitis requiring IV antibiotics. Four of 6 participants reported post LP headaches on one or more occasions although none required a blood patch. Two participants reported vertigo post dosing, one acutely, resulting in an afterhours emergency room visit, and another whose vertigo persisted for a week after dosing in association with postural headache. All post LP adverse events occurred during the loading phase.
Muntoni	None reported

Three out of the six studies reported adverse event data. Of those only Maggi et al split the results by SMA type. However, this was not split further into ambulatory or non-ambulatory type III. In two studies (Yeo et al, 2020; Darras et al, 2019) all participants reported at least 1 adverse event with the

most common being headaches and LP puncture syndrome. Maggi et al (2020) reported similar levels of AEs for both type II and type III patients, however, there were many more type III patients in this study. Again the most common AE was post-procedure headaches. Serious AEs requiring hospitalisation were reported in a few cases in all studies. Maggi et al reported more type III serious AEs requiring hospitalisation than type II. None of the studies deemed the AEs to be related to Nusinersen, but more the administration procedure itself.

Registry data

Registry data was provided by Biogen containing data on 168 European type III non-ambulant patients, 159 of whom had received nusinersen treatment. Nine were therefore classed as untreated. Comparisons were made between 'Treated' and 'Untreated' groups and also between 'Paediatric' and 'Adult' groups. Table 5 is a reminder of what is defined as a clinically meaningful improvement for the included measures and Tables 6-9 present the data.

Table 5. Included measures and CMI definition

Name	**Clinically meaningful improvement**
Hammersmith Functional Motor Scale Expanded (HFMSE)	Change of 3 or more points
(Revised) Upper Limb module score ((R)ULM)	Change of 2 or more points

Table 6 Comparisons between type II non-ambulant patients treated with nusinersen and those untreated for HFMSE scores

Treated (n=159) vs Untreated (n=9)		
Result	**Statistically significant**	**Clinically meaningful improvement**
Treated patients showed an estimated **increase of 0.80** points in 12 months.	Yes (p=0.0131)	No
Untreated patients showed an estimated **decrease of -5.67** points over 12 months	Yes (p=<0.0001)	n/a
Difference between groups of 6.47 points over 12 months	Yes (0<0.0001)	n/a

Table 7 Comparisons between type III non-ambulant patients treated with nusinersen and those untreated for RULM scores

Treated (n=159) vs Untreated (n=9)		
Result	**Statistically significant**	**Clinically meaningful improvement**
Treated patients showed an estimated **increase of 0.92** points in 12 months.	Yes (p=0.0007)	No
Untreated patients showed an estimated **decrease of -0.47** points over 12 months	No	n/a
Difference between groups of 1.39 points over 12 months	No	n/a

Table 8 Comparisons between treated paediatric and adult patients for HFMSE scores (95% CI)

	Paediatric	**Clinically meaningful improvement**	**Adult**	**Clinically Meaningful improvement**
Treated Paediatric (n=[redacted]) Adult (n=[redacted])	Estimated change in score of **0.676 (-0.78-2.132)** over 12 months	No	Estimated change in score of **0.78 (0.156-1.456)** over 12 months	No
Untreated Paediatric (n = [redacted]) Adult (n=[redacted])	Estimated change in score of **-5.668 (-8.112- -3.172)** over 12 months	n/a	Estimated change in score of **-0.624 (-2.652-3.89)** over 12 months	n/a

Table 9 Comparisons between treated paediatric and adult patients for RULM score (95% CI)

	Paediatric	**Clinically meaningful improvement**	**Adult**	**Clinically meaningful improvement**
Treated Paediatric (n=[redacted]) Adult (n=[redacted])	Estimated change in score of **1.196 (0.312-2.08)** over 12 months	No	Estimated change in score of **0.728 (0.052-1.404)** over 12 months	No
Untreated				

Paediatric (n = [redacted]) Adult (n=[redacted])	Estimated change in score of **-0.468 (-1.924-0.988)** over 12 months	n/a	Estimated change in score of **-0.676 (-4.004-2.6)** over 12 months	n/a

The registry data results are from standard linear mixed models and are not results from analysis of real data. Scores from a follow-up date (unreported) are used to model future scores. Therefore they are estimated results from the models produced. They were performed by Biogen and we have not been given access to the raw data itself. Tables 6 and 7 show that both HFMSE and RULM scores in nusinersen treated patients are estimated to increase by a statistically significant amount over 12 months; 0.8 and 0.92 respectively. However neither of these increases are classed as clinically meaningful using the definition described in Tables 1 and 5. The untreated patients showed decreases in both RULM (-0.47) and HFMSE (-5.67), the latter of which was statistically significant and clinically meaningful. The difference between treated and untreated patients was statistically significant for the HFMSE measures but not RULM. It should be noted that the untreated group consisted of only 9 participants and that any analysis using this group should be interpreted with caution.

The results in Tables 8 and 9 show that both paediatric and adult groups had an estimated increase in HFMSE scores (0.676 and 0.78 respectively) and RULM scores (1.196 and 0.728 respectively) over 12 months. The positive estimated increase indicates disease stabilisation. However, statistical analysis was not reported on these figures and they were not classed as clinically meaningful. One result to highlight is that the decrease in HFMSE scores for untreated paediatric patients was much larger than that of the adult patients over 12 months (-5.668 vs -0.624). Again, however, the numbers of untreated patients are very low and so any analysis using these groups should be interpreted with caution.

Anecdotal evidence

Anecdotal evidence from people with SMA and parents of children with SMA was provided by Biogen for the purpose of this report. There were relevant reports from 53 people who were type III non-ambulant. Forty-one reports were not relevant as were either type II, ambulant or not treated with nusinersen.

Of the relevant sources, one was purely in relation to the impact of having been deemed ineligible to access treatment following the MAA decision. Another reported the importance of specific outcomes to patients. Three sources related to the impact of having the treatment in both children and adults. The vast majority of this was positive and suggested it improved patient's physical abilities. One of these sources did suggest that after the improvement following the first dose of nusinersen then the patient stabilised.

The vast majority of information provided was in favour of nusinersen in the type III non-ambulant population, however as it was provided by the patients themselves or parents of children with SMA, it is not appropriate for us to use this information in our decision making process. The data included

has not been objectively gathered or peer reviewed and so cannot be considered as evidence for the purpose of this review.

Key questions

1. **Is the new evidence of sufficient quality for decision making concerning the existing eligibility criteria with respect to non-ambulant type III SMA patients?**

The evidence included has several limitations. Firstly the sample sizes are extremely small in all but 1 of the studies, which is to be expected given the low prevalence of the disease, but this low volume of evidence means conclusions drawn from the results are not generalisable to a real world setting. In several studies it is not stated when patients lost ambulation which is a major point of consideration for the administration of nusinersen, and some results are pooled into a general type III group which means results for the non-ambulant participants cannot be extracted and compared.

2. **Does the new evidence demonstrate a comparable clinical benefit for non-ambulant type III patients, as with patients who were able to sit independently but never had the ability to walk independently, compared to best standard of care for all of the following outcomes collectively?**
    - **motor function (including, where applicable, age-appropriate motor milestones and evidence of retention of fine motor skills)**
    - **respiratory function**
    - **complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures)**
    - **need for non-invasive or invasive ventilation**
    - **stamina and fatigue**
    - **mortality**
    - **adverse effects of treatment**
    - **health-related quality of life (if available)**

None of the included clinical evidence compares with best standard of care. The registry data did compare with untreated patients; however, this was only [redacted] patients and they did not compare with type II patients. The only comparison that can be made from the evidence is whether the results for the outcomes above are deemed better or comparable for type III non-ambulant patients compared to type II patients (were able to sit independently but never had the ability to walk).

Motor function measures suggest that type III non-ambulant patients are already at ceiling or scoring very highly on these measures. Therefore there is little scope for CMI. This is compared to type II patients who can show marked CMI of 5 points or higher for the HFMSE and 4 points for the ULM. However, these are based on very small numbers. One study and registry data showed statistically significant improvements in motor function measures for non-ambulant patients but none of the means reported reached a level of CMI and ranges reported showed negative scores i.e. deterioration for some patients. The 6MWT was performed in one study on the non-ambulant patients and showed that 2 out of 4 regained the ability to walk but it was not stated how far and

whether this was a CMI. One of 11 type II patients in this study also regained the ability to walk with CMI.

The registry data included motor function results split by paediatric and adult populations. They showed predicted increases in HFMSE and RULM scores for both populations (in nusinersen treated patients) over 12 months. However, these increases were not clinically meaningful and analysis was not conducted to compare the increase between groups.

Respiratory measures did not show any clear benefit for both type II and type III non-ambulant participants.

Adverse events were common across all participants and from the one study who reported each group separately, AEs appeared to occur evenly between type II and type III participants, except those requiring hospitalisation which appeared to be more prevalent in type III non-ambulant participants.

3. **Does the available evidence demonstrate a comparable clinical benefit for non-ambulant type III adult patients, as with non-ambulant type III paediatric patients, in relation to the criterion which allows paediatric patients who have lost independent ambulation in the preceding 12 months to access treatment?**

As the evidence either does not state when patients lost ambulation or includes patients who lost ambulation >12 months ago, it is not possible to answer this question based on the current available evidence.

4. **Does the new evidence provide sufficient new information and demonstrate a comparable clinical benefit for non-ambulant patients to support a recommendation to amend the MAA eligibility criteria to expand access to non-ambulant type III SMA patients?**

No, as the quality of evidence is too poor and the results too inconclusive.

Recommendation

It is the recommendation of the EAC that due to the small amount of evidence, the low quality of the evidence and apparent low efficacy of nusinersen in non-ambulant type III SMA patients, the current Managed Access Agreement is not extended to include the administration of nusinersen to non-ambulant type-III SMA patients.

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