


## ORIGINAL ARTICLE

# Evolution of bulbar function in spinal muscular atrophy type 1 treated with nusinersen

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## Funding information

National Institute for Health Research

**Aim:** To assess the evolution of bulbar function in nusinersen-treated spinal muscular atrophy type 1 (SMA1).

**Method:** This single-centre retrospective study identified 24 patients (14 females and 10 males) with SMA1, treated with nusinersen between 2017 and 2020. We adapted and validated the Paediatric Functional Oral Intake Scale (p-FOIS), which is an outcome measure to assess bulbar function. Analysis considered SMA1 subtype, nutritional support, and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and p-FOIS scores at initiation of nusinersen treatment (baseline) and at 6, 12, and 24 months after initiation.

**Results:** The median age at baseline was 11 months (range 1 month–7 years 6 months). Median age at initiation of tube feeding was 8 months (range 0–2 years 2 months). Fourteen patients were tube fed at baseline. The median p-FOIS score was 3 at baseline and 2 at 12 and 24 months. Four patients, all with type 1c SMA, remained orally fed at 24 months. Median CHOP INTEND scores increased from 32 at baseline to 42 at 12 and 24 months.

**Interpretation:** Impaired bulbar function persisted as a significant complication in most nusinersen-treated patients with SMA1, in contrast to the improvement in motor abilities demonstrated in the majority. p-FOIS allows for tracking of bulbar function progression and treatment response. Larger, prospective studies investigating the longer-term impacts of nusinersen on bulbar function are warranted.

**Abbreviations:** CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NIV, non-invasive ventilation; p-FOIS, Paediatric Functional Oral Intake Scale; SMA, spinal muscular atrophy; SMA1, Spinal muscular atrophy type 1; SMN, survival motor neuron.

Giovanni Baranello and Eleanor Conway are joint senior authors.

\*Members of the SMA p-FOIS Working Group are listed in the [Acknowledgements](#).

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Spinal muscular atrophy (SMA) is caused by degeneration of alpha motor neurons in the spinal cord and is characterized by hypotonia, weakness, and muscle wasting. SMA is an autosomal recessive disorder caused by deletion, or less frequently other mutations, of the *SMN1* gene, resulting in deficiency of the survival motor neuron (SMN) protein. Patients with SMA rely on the second form of the gene, *SMN2*, to produce sufficient SMN protein for survival. *SMN2* differs from *SMN1* by a single nucleotide, which results in the exclusion of exon 7 during transcription, producing approximately 10% of functional SMN protein.<sup>1-3</sup>

Paediatric-onset SMA is classically defined into three main subtypes, types 1 to 3, based on maximal achieved motor milestones and age at onset. SMA type 1 (SMA1), the most severe type, is defined as onset between birth and 6 months, and as patients who are never able to sit without support. SMA1 is further divided into subtypes 1a (neonatal presentation), 1b (symptom onset before 3 months), and 1c (onset between 3 months and 6 months of age).<sup>4</sup> However, recent therapeutic developments have resulted in significant improvement in outcomes, thereby altering these natural history phenotypes.

Nusinersen was the first approved disease-modifying treatment for SMA. It is an antisense oligonucleotide drug, which modifies pre-mRNA splicing to promote inclusion of *SMN2* exon 7, leading to increased production of full-length SMN protein.<sup>5</sup> In clinical trials, nusinersen was demonstrated to provide significant improvement in motor function and overall survival.<sup>6,7</sup>

Among the several comorbidities that can affect patients with SMA, feeding and swallowing difficulties play a significant role, and regular assessments of nutrition and swallow form part of the standards of care. In patients with SMA1 a proactive approach is recommended if there are growth difficulties or an abnormal swallow due to bulbar dysfunction, with placement of tube feeding to prevent aspiration, respiratory infections, and poor weight gain.<sup>8</sup> The natural history of nutritional support requirements for SMA1 have been well established.<sup>1,9,10</sup> However, since the evolution of SMA1 phenotypes with the development of treatments such as nusinersen, there is increasing need for better understanding of the bulbar function trajectories for these patients. Although swallowing and feeding difficulties have been demonstrated to persist in infants with SMA1 treated with nusinersen, despite the improvements seen in motor function and survival, studies on the progress of bulbar function in children with SMA1 treated with nusinersen are still limited.<sup>11-13</sup> This is due to both the lack of validated tools to assess swallow function in SMA1 and to the limited availability of longitudinal data.

We modified the Functional Oral Intake Scale (FOIS), which is a tool to assess change in functional eating abilities in adult patients with stroke, so that it could be used in children of all ages, and assessed the interrater reliability and consensual and face validity of the adapted tool, termed the Paediatric Functional Oral Intake Scale (p-FOIS).<sup>14</sup> In this

### What this paper adds

- Feeding/swallowing difficulties persist and tend to deteriorate in nusinersen-treated spinal muscular atrophy type 1 (SMA1).
- The need for tube feeding increased in our cohort despite treatment with nusinersen.
- SMA1 with the least severe phenotype, type 1c, is more likely to maintain bulbar function.

study we aimed primarily to investigate the evolution of bulbar function in SMA1 treated with nusinersen by using the p-FOIS, along with other aspects, including nutritional, motor, and respiratory outcomes.

## METHOD

This was a single-centre retrospective study of children with SMA1 treated with nusinersen between 2017 and 2020 at Great Ormond Street Hospital for Children, London, UK. Children received nusinersen as part of the Early Access Programme, and/or Managed Access Agreement, or compassionate use. The p-FOIS, adapted from the FOIS for use in the paediatric population, was applied to this population with SMA1. The methods and results of the adaptation and validation of the p-FOIS are reported in Appendix S1. Patients who had at least 24 months of nusinersen treatment were included. No presymptomatically treated children were included in this study.

### Outcome measures

Medical records of included patients were reviewed for the following characteristics: date of birth, age at symptom onset, SMA type 1 subtype, *SMN2* copy number and age at initiation of nusinersen treatment, non-invasive ventilation (NIV) requirement, including NIV hours of use (as needed, nocturnal [including for naps], or >16 hours/day), and type of feeding (oral/nasogastric tube/gastrostomy). p-FOIS (Table 1) was applied retrospectively to patients with SMA1 at baseline, and 6, 12, and 24 months after initiation of nusinersen treatment.

### CHOP INTEND scores

To measure functional motor outcomes, we used the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND).<sup>15</sup> CHOP INTEND scores were collected at baseline and at 6, 12, and 24 months after initiation of nusinersen treatment.

**TABLE 1** Paediatric Functional Oral Intake Scale (p-FOIS)

1. Nothing by mouth (non-nutritive sucking/dummy dippers/mouthcare only)
2. Tube dependent for all nutrition/hydration needs with minimal attempts at oral intake for experience and/or pleasure
3. Tube dependent with consistent intake of food and/or fluid that meets some of the nutrition/hydration needs
4. Total oral intake but special preparation required, e.g. thickened fluids, puréed diet (where not age-appropriate)
5. Total oral intake but requiring special conditions/modification, e.g. slow flow teat/side lying/pacing or specific food limitations (e.g. soft or fork-mashable diet)
6. Total, age-appropriate, oral intake with no restrictions

## Statistical analysis

Groupwise medians and ranges were calculated from the data. The individual trajectories for p-FOIS, motor function, and feeding characteristics were plotted.

## Ethics approval

This study was reviewed and registered by the Clinical Audit Department at Great Ormond Street Hospital for Children. It was assessed that the work was in line with the criteria outlined by the NHS Health Research Authority for determining whether work was audit, service evaluation, or research, and therefore did not require any approval from research for ethics. It was confirmed that the work was conducted with sound principles in line with our hospital clinical audit policy.

## RESULTS

### Characteristics

We identified 24 infants with SMA type 1 treated with nusinersen for at least 24 months at our centre: three with type 1a, nine with type 1b, and 12 with type 1c. Patients' characteristics are summarized in [Table 2](#). No deaths were reported in the cohort during the study period.

### Feeding characteristics

Fourteen patients, consisting of three out of three with type 1a, five out of nine with type 1b, and six out of 12 with type 1c, were tube fed at baseline. Twenty of the 24 patients were tube fed at 24 months after initiation: all patients with type 1a and 1b SMA and eight out of 12 patients with type 1c. Four patients, all with type 1c (two with two *SMN2* copies and two with three *SMN2* copies), remained orally fed at 24 months after initiation. [Table 2](#) shows the feeding route by SMA1 subtype at baseline, and at time points after initiation of nusinersen.

## Age at initiation of nusinersen treatment

Patients were grouped into the following age ranges when nusinersen treatment was initiated: younger than 6 months, 6–12 months, and older than 12 months.

Seven patients were started on nusinersen younger than 6 months of age: one with type 1a SMA and six with type 1b. Of these, four were orally fed at baseline and all were fed by gastrostomy at 24 months follow-up. Seven patients, two with type 1b and five with type 1c, started on nusinersen between the ages of 6 and 12 months; all were tube fed at 24 months follow-up. Ten patients were started on nusinersen older than 12 months of age: seven with type 1c, one with type 1b, and two with type 1a; all these patients were born more than 12 months before nusinersen approval in the UK. At 24-months follow-up, four of these patients remained fully orally fed, while four had gastrostomy and two had nasogastric tubes. [Figure 1](#) shows feeding routes by SMA1 subtype and by age at initiation of nusinersen treatment.

## Videofluoroscopy

Videofluoroscopy swallow study reports were available for eight patients: four with type 1b SMA and four with type 1c. For all patients these were performed after starting nusinersen and at variable, unspecified time points. All patients with type 1b and two with type 1c were reported as being at risk of aspiration on all consistencies. Another with type 1c was at risk of aspiration on residue but had strategies to adapt to their overall weakness. The remaining patient with type 1c had a weak swallow and reduced pharyngeal clearance; no aspiration was seen but there was extensive residue on thick puree consistencies, placing them at increased risk of aspiration on thick/sticky consistencies. No follow-up videofluoroscopy swallow assessments were available for any of the eight patients.

## p-FOIS longitudinal scores

The median p-FOIS declined from baseline (three at baseline, one at 6 months after initiation of nusinersen, two at 12 months, and two at 24 months). Median p-FOIS for type 1a remained at 1 from baseline and at all follow-up points. Median p-FOIS for type 1b declined from 3 at baseline to 1 at 6 months, and 2 at 12 and 24 months respectively. For patients with type 1c, median p-FOIS was 5 at baseline, 2 at 6 months after initiation of nusinersen, and 3 at 12 and 24 months. Six patients had a 1-point improvement in their p-FOIS score: five had an improvement of 1 to 2; one patient with type 1c had an improvement of 2 to 3. [Figure 2](#) shows p-FOIS scores for SMA1 subtypes at baseline and at time points after initiation of nusinersen.

**TABLE 2** Patients' characteristics

	All patients	SMA type 1a	SMA type 1b	SMA type 1c
Number of patients, <i>n</i>	24	3	9	12
Median age at initiation of nusinersen, year:month (range)	0:11 (0:1–7:6)	2:2 (0:1–4:3)	0:4 (0:2–1:4)	1:7 (0:8–7:6)
Median age at initiation of tube feeding, year:month ( <i>n</i> , range)	0:8 (20, 0–2:2)	0:7 (3, 0–0:9)	0:7 (9, 0:2–1:1)	0:11 (8, 0:5–2:2)
Median age at initiation of NIV, year:month ( <i>n</i> , range)	0:8 (21, 0:2–3:6)	0:11 (3, 0:8–1:0)	0:6 (8, 0:2–0:7)	1:6 (10, 0:6–3:6)
SMN2 copy, number, <i>n</i>	23	3	9	11
Two copies <sup>a</sup>	17 (74)	2 (67)	9 (100)	6 (55)
Three copies <sup>a</sup>	6 (26)	1 (33)	0 (0)	5 (45)
Baseline, <i>n</i>	24	3	9	12
Tube fed <sup>a</sup>	14 (58)	3 (100)	5 (56)	6 (50)
Nasogastric tube <sup>a</sup>	11 (46)	3 (100)	4 (44)	4 (33)
Gastrostomy <sup>a</sup>	3 (13)	0 (0)	1 (11)	2 (17)
12 months after initiation, <i>n</i>	24	3	9	12
Tube fed <sup>a</sup>	20 (83)	3 (100)	9 (100)	8 (67)
Nasogastric tube <sup>a</sup>	12 (50)	3 (100)	4 (44)	5 (42)
Gastrostomy <sup>a</sup>	8 (33)	0 (0)	5 (56)	3 (25)
24 months after initiation, <i>n</i>	24	3	9	12
Tube fed <sup>a</sup>	20 (83)	3 (100)	9 (100)	8 (67)
Nasogastric tube <sup>a</sup>	5 (21)	2 (67)	0 (0)	3 (25)
Gastrostomy <sup>a</sup>	15 (63)	1 (33)	9 (100)	5 (42)
Baseline, <i>n</i>	24	3	9	12
NIV use <sup>a</sup>	13 (54)	2 (67)	5 (56)	6 (50)
None <sup>a</sup>	11 (46)	1 (33)	4 (44)	6 (50)
As needed <sup>a</sup>	0 (0)	0 (0)	0 (0)	0 (0)
Nocturnal use <sup>a</sup>	7 (29)	0 (0)	3 (33)	4 (33)
>16 hours/day <sup>a</sup>	6 (25)	2 (67)	2 (22)	2 (17)
12 months after initiation, <i>n</i>	24	3	9	12
NIV use <sup>a</sup>	20 (83)	3 (100)	8 (89)	9 (75)
None <sup>a</sup>	4 (17)	0 (0)	1 (11)	3 (25)
As needed <sup>a</sup>	1 (4)	0 (0)	0 (0)	1 (8)
Nocturnal use <sup>a</sup>	13 (54)	1 (33)	6 (67)	6 (50)
>16 hours/day <sup>a</sup>	6 (25)	2 (67)	2 (22)	2 (17)
24 months after initiation, <i>n</i>	24	3	9	12
NIV use <sup>a</sup>	21 (88)	3 (100)	8 (89)	10 (83)
None <sup>a</sup>	3 (13)	0 (0)	1 (11)	2 (17)
As needed <sup>a</sup>	2 (8)	0 (0)	0 (0)	2 (17)
Nocturnal use <sup>a</sup>	14 (58)	1 (33)	7 (78)	6 (50)
>16 hours/day <sup>a</sup>	5 (21)	2 (67)	1 (11)	2 (17)

Note: Data are *n* (%) unless otherwise stated.

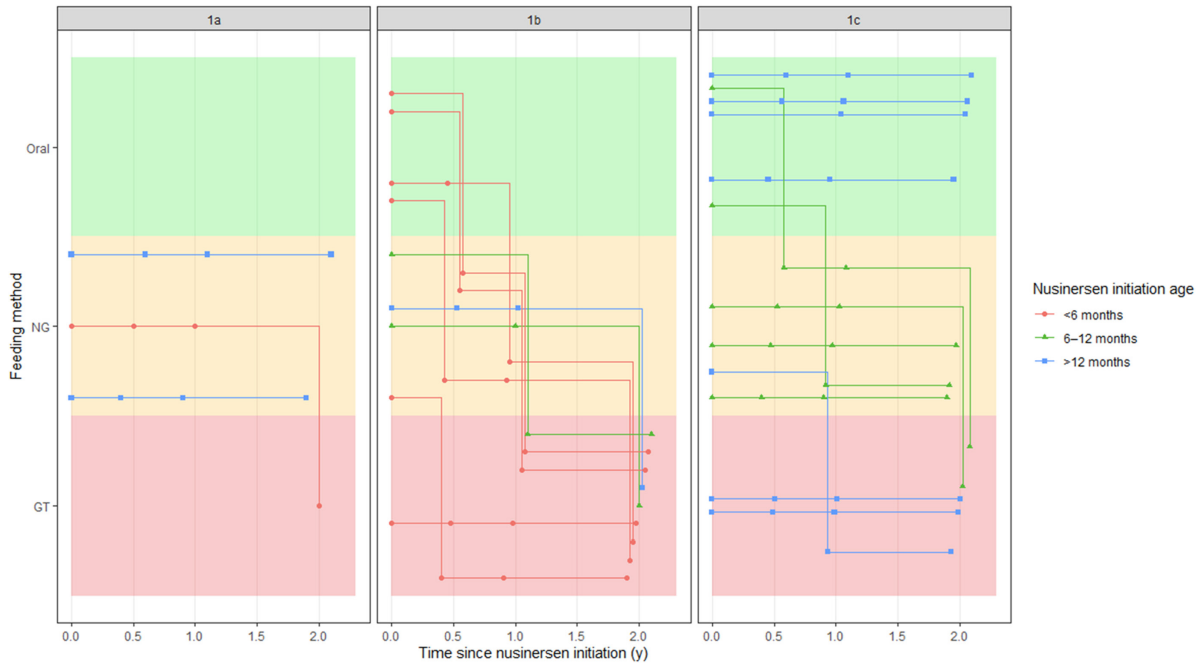
Abbreviation: NIV, non-invasive ventilation.

<sup>a</sup>Expressed as percentages of total number of available assessments at the specified time points.

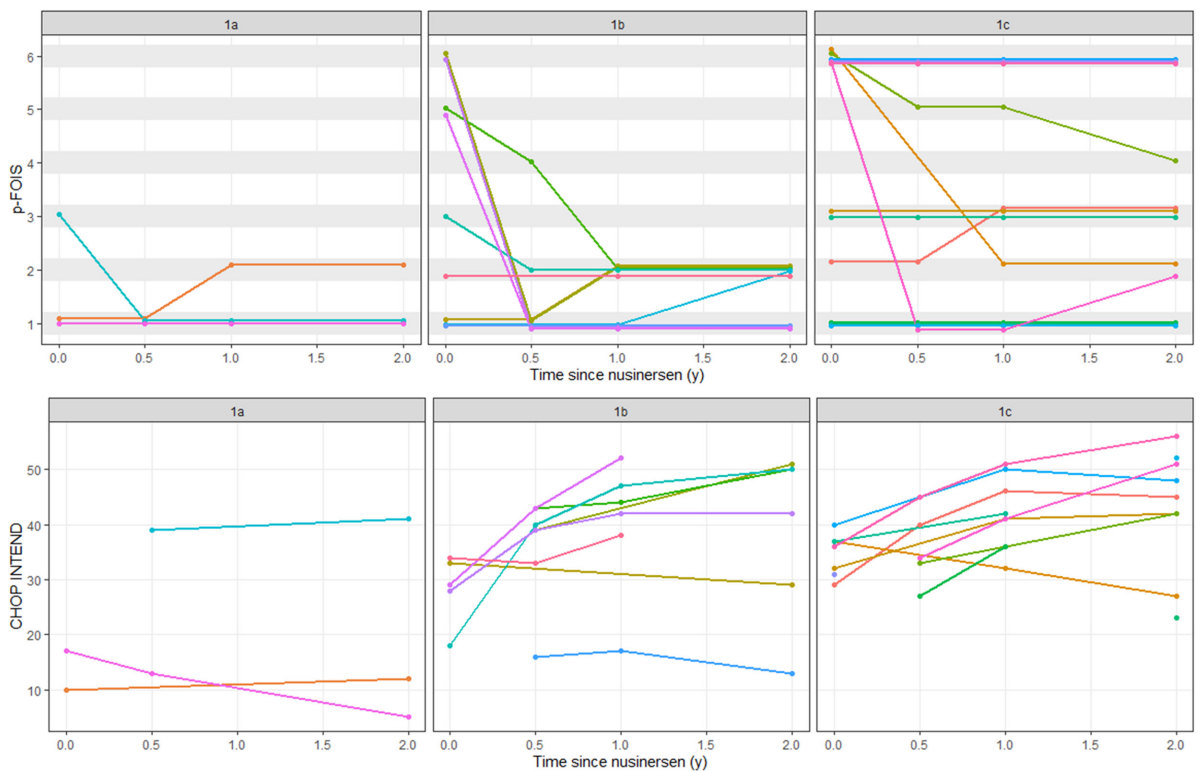
## NIV characteristics

Median age at the start of NIV was 11 months for those with type 1a SMA, 6 months for type 1b, and 1 year 6 months for type 1c. Thirteen patients required NIV

at baseline: seven required nocturnal use and six more than 16 hours per day. At 24 months after initiation of nusinersen 21 patients required NIV: 14 required nocturnal use, five required more than 16 hours per day, and two required 'as needed' use. Three patients, two with



**FIGURE 1** Progression of feeding characteristics by spinal muscular atrophy type 1 (SMA1) subtype and age at nusinersen initiation  
Abbreviations: GT, gastrostomy; NG, nasogastric tube.



**FIGURE 2** Paediatric Functional Oral Intake Scale (p-FOIS) and Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores over time for individual patients by spinal muscular atrophy type 1 subtype

type 1c and one with type 1b, remained without any NIV use at 24 months after initiation of nusinersen. Hours of use per subtype at specified time points are listed in Table 2.

**CHOP INTEND characteristics**

CHOP INTEND scores were available for 14, 14, 15, and 18 patients at baseline, 6, 12, and 24 months after initiation of

nusinersen respectively. Median CHOP INTEND scores across all available patients' observations increased from 32 at baseline, to 39, 42, and 42 at 6, 12, and 24 months after initiation of nusinersen respectively.

CHOP INTEND scores improved for two out of three patients with type 1a SMA. Six out of nine patients with type 1b had an improvement in their CHOP INTEND scores, and two showed minimal decline (16 at 6 months to 13 at 24 months for one patient; 33 at baseline to 29 at 24 months for the second patient). No CHOP INTEND data were available for one patient with type 1b SMA. Eight out of 12 patients with type 1c had an improvement in their CHOP INTEND scores. Three only had one CHOP INTEND score available so we were unable to assess change in score. One patient with type 1c had a decline in their CHOP INTEND score from 37 at baseline to 27 at 24 months after start of treatment.

## DISCUSSION

Our study shows that feeding and swallowing difficulties persist and worsen in the majority of symptomatic patients with SMA1 treated with nusinersen. We found that there was an increase in the need for tube feeding with only a very small proportion of patients ( $n = 4$ ), all having type 1c, remaining exclusively orally fed 24 months after treatment started. SMA standard of care recommends a proactive approach of tube feeding for those with growth failure or a failed swallow study. The fact that all patients were assessed and managed by the same speech and language therapy team, in line with the most updated standard of care, makes it more likely that the increased need for tube feeding demonstrated in our study reflects a real deterioration due to disease progression, rather than an effect of a more proactive management with time.<sup>8</sup> Although early treatment with nusinersen has been associated with reduced need for permanent assisted ventilation and improved motor function, there is limited evidence on the impact of early treatment on bulbar outcomes.<sup>6,16,17</sup> In this small cohort we did not find that younger age at initiation of nusinersen had an impact on maintaining bulbar function; however, of the seven patients who started treatment before 6 months of age, all were at the most severe end of the spectrum, type 1a and 1b, so it is difficult to draw clear conclusions. Our study did not include any presymptomatically treated children but preliminary evidence from the Nurture Study (NCT02386553) suggests that swallowing abilities are preserved among patients initiating nusinersen in the presymptomatic stage, with only a small proportion with two *SMN2* copies requiring tube feeding.<sup>18</sup> This further highlights the urgency to implement neonatal screening programmes to identify affected patients and start treatment presymptomatically.

We used the 6-point graded p-FOIS which had excellent interrater reliability and validity, similar to previous studies in adults and paediatric cohorts and enabling tracking of functional abilities using a single measure across all time

points.<sup>14,19,20</sup> Of note, we evaluated the p-FOIS in children aged 0 to 16 years in the validation process, reflecting the full age range of SMA assessed in most paediatric settings.

Although the importance of regular nutritional assessments for children with SMA is well acknowledged, there is currently a lack of systematically collected agreed outcome measures of swallow and bulbar function for the population with SMA, thereby making multi-centre collaborative studies more difficult.<sup>8</sup> An outcome tool, such as the p-FOIS, enables monitoring of disease progression and treatment response. Another tool has recently been developed to assess swallowing abilities in patients with SMA type 1 and has been applied retrospectively to historical untreated patients with SMA1. However, this study did not assess bulbar function progression in treated patients with SMA1 and requires further validation.<sup>21</sup>

We have shown that, overall, the p-FOIS declines or remains static in SMA1 treated with nusinersen, reflecting worsening or lack of improvement in bulbar function, despite the majority showing improved motor abilities. Only six children had improvements in their p-FOIS score of 1 point which does not reflect a substantial functional change in swallowing, as all remained tube fed. More importantly, we found that only a small proportion of patients with the least severe phenotype, 1c, were able to maintain a p-FOIS score of 6, which encompasses total, age-appropriate oral intake with no restrictions. An Australian study has demonstrated that all ( $n = 4$ ) newly diagnosed patients with two *SMN2* copy numbers (all type 1b) required gastrostomy after a median nusinersen treatment time of 30 months, while all newly diagnosed patients ( $n = 3$ ) with three *SMN2* copies (two type 1c, one type 1b) remained orally fed after a median treatment time of 28 months.<sup>11</sup> However, *SMN2* copy number does not always predict response to treatment, as in our study two out of four patients with type 1c who remained completely orally fed had only two copies of *SMN2*.<sup>2,12</sup>

Similar to previous studies, we observed that our population had an increase in the number of patients requiring nocturnal-only NIV after 12 months of treatment, but this was followed by a stability with no additional patients requiring more than 16 hours of ventilator support.<sup>22,23</sup>

Despite the observed effects on motor and respiratory function, nusinersen-treated patients with SMA1 remain vulnerable to the significant comorbidity of bulbar impairment. Our findings of persistent feeding difficulties in nusinersen-treated infants with SMA1 are consistent with other studies.<sup>11,13</sup> A comparison of natural history SMA1 controls to nusinersen-treated patients with SMA1 would allow more conclusive evidence of the effect of nusinersen on bulbar function. However, given the significantly shortened life expectancy of historical untreated patients with SMA1, it is difficult to gather sufficient retrospective data on bulbar function for this cohort; therefore this was not performed in this study. Recent findings suggest that motor function benefits can continue to be obtained after the first year of nusinersen treatment, and even up to 3 years of treatment.<sup>12,24</sup> Therefore, longer follow-up studies in larger SMA nusinersen-treated cohorts may capture additional

findings of nusinersen's impact on bulbar function to those demonstrated in this study.

Post-mortem studies have shown invariable and early brainstem motor nuclei abnormalities in SMA. Neuropathological studies have also documented that, similar to spinal cord motor neurons, high levels of SMN protein are developmentally expressed at early stages of fetal and postnatal development in brainstem nuclei, where they are required for their function and survival.<sup>25</sup> Additionally, magnetic resonance imaging abnormalities in bulbar muscles have been demonstrated.<sup>26,27</sup> Bulbar denervation alongside head posture due to weak neck muscles probably lead to the dysphagia and weak suck/swallow seen in SMA.<sup>27,28</sup> Interestingly, nusinersen concentrations have been reported as higher in the caudal than rostral regions in autopsy findings of infants with SMA1, which resulted in higher SMN protein levels in the lumbar motor neurons compared with the cervical and bulbar motor neurons. A combination of selectively high and early vulnerability of brainstem nuclei and a lower bioavailability of the medication at this level in treated patients may explain the limited effects seen on bulbar function compared with its benefits for limb motor function.<sup>29,30</sup> Of note, a recent study on two patients with SMA1 who passed away during a clinical trial with the intravenous administration of the AAV9-mediated gene therapy onasemnogene abeparvovec showed widespread biodistribution of vector genomes and transgenes throughout the central nervous system, including pons, medulla, and upper cervical spine.<sup>31</sup> This may suggest that systemic treatment could be more effective in preserving bulbar function; however, longitudinal real-world data will be needed to evaluate whether this corresponds to a clinical benefit for treated patients.

Awareness of persistent feeding difficulties in nusinersen-treated patients with SMA1 helps guide discussions with families, including prognosis and treatment, as well as informing healthcare resource allocation and standards of care. Despite treatment with nusinersen, the need for close attention to nutritional status of children with SMA1 remains as outlined in standards of care.<sup>8</sup>

Our study indicates that the p-FOIS can be adapted for children across a wide age range and with different feeding disorders, while maintaining the excellent interrater reliability that is seen in the adult version of the tool.<sup>14</sup> This suggests the p-FOIS is applicable for use in the paediatric population with SMA; however, larger studies investigating its use in this population will be needed to confirm its psychometric properties.

## CONCLUSION

To our knowledge, this is the first study of nusinersen-treated patients with SMA1 that has quantified bulbar dysfunction using a validated tool and compared between the SMA1 subtypes. The p-FOIS is a six-point, ordinal, clinician-rated outcome measurement scale for use with a paediatric feeding-disordered population. International collaboration to achieve consensus on a single adaptation of the tool is

required, as well as studies to further validate this tool in SMA. A validated outcome measure for children with SMA that demonstrates change over time in swallowing abilities will enable monitoring of individual progress and tailoring of treatment. This will help provide guidance and comparison with those patients treated with other systemically distributed novel treatments, such as the gene-replacement therapy onasemnogene abeparvovec and the oral *SMN2* splicing modifier risdiplam, recently approved by both the US Food and Drug Administration and the European Medicines Agency.

## ACKNOWLEDGEMENTS

Members of the SMA p-FOIS Working Group are as follows: Adnan Manzur, Pinki Munot, Marion Main, and Claudia Kate Au-Yeung.

GB, GS, and FM are supported by a grant from the Great Ormond Street Hospital Children's Charity and Muscular Dystrophy UK. All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. FM is partly supported by the National Institute for Health Research Centre at Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children. The authors also thank the SMA reach grant from Biogen for its support to the Great Ormond Street team involved in SMA research.

## CONFLICT OF INTEREST

GB has received speaker and consulting fees from Biogen, Novartis Gene Therapies (AveXis), and Roche, and has worked as principal investigator of SMA studies sponsored by Novartis Gene Therapies and Roche. FM has received speaker and consulting fees from Biogen, Novartis, and Roche, and has worked as principal investigator of SMA clinical trials sponsored by Biogen, Novartis, and Roche. He is also the principal investigator of an investigator-initiated registry study funded by Biogen (SMA REACH UK). HW has worked as the sub-investigator of SMA clinical trials sponsored by Biogen, Novartis, and Roche. MS has received speaker and consulting honoraria from Biogen, Novartis gene therapy (AveXis), and Roche, and has worked as principal investigator and sub-investigator for SMA studies sponsored by Biogen and Novartis gene therapy. EJ has acted as a paid consultant for Roche and has collected data for SMA studies sponsored by Novartis gene therapy.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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## SUPPORTING INFORMATION

The following additional material may be found online:

**Appendix S1:** Adaptation and validation of p-FOIS.

**How to cite this article:** Weststrate H, Stimpson G, Thomas L, Scoto M, Johnson E, Stewart A, et al. Evolution of bulbar function in spinal muscular atrophy type 1 treated with nusinersen. *Dev Med Child Neurol*. 2022;64:907–914. <https://doi.org/10.1111/dmcn.15171>