TreatSMA
Treat Spinal Muscular Atrophy

To:

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[redacted], GOSH
[redacted], Newcastle
[redacted], Biogen Idec Ltd
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17 June 2019

Dear Sir or Madam,

Re. Draft Managed Access Agreement – nusinersen: subpopulation review

This is a brief review of the selected nusinersen access criteria proposed in the draft Managed Access Agreement. It is not an appeal. We are sharing it in a constructive spirit and with a sole intention to help the Parties to address the key problematic parts of the MAA.

The proposed MAA, as it stands now, intends to exclude various subpopulations of patients. In this review, we conclude that certain criteria are problematic and can be challenged by way of a formal appeal. We are mindful of the high urgency to implement the nusinersen programme, especially in the weakest patients, and so we would prefer to avoid any delay to the implementation of the Agreement. However, it is also clear that the proposed MAA has intentionally excluded the weakest categories of patients in each SMA type without a reasonable justification.

We trust that the proposed MAA can be amended by the Parties in line with the unanimous opinion of the UK patient community and the clinicians and thus avoid triggering an appeal.

Below, we analyse the most contentious parts of the proposed MAA.

1. Mechanical ventilation

> *No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/tracheostomy requirement at baseline;*

Summary: The criterion lacks sound clinical justification and may be challenged as unlawful discrimination.

Analysis: There is no doubt that full-time reliance on mechanical ventilation constitutes a disability under the meaning of the Equality Act 2010. At the same time, it is entirely arbitrary to posit that the nusinersen treatment *is not* effective or cost-effective in people who use a ventilator for 16+ hours a day but *is* effective and cost-effective in people who use respiratory support for 15 hours a day or less.

The threshold of 16 hours/day stems from the FDA guidance on clinical trial design, whereby the US agency considers any use of respiratory support exceeding 16 hours a day for more than 21 days as *active treatment*. Consequently, such extended respiratory support cannot be normally used in combination with another active treatment in FDA-approved clinical trials.

However, it is incorrect to construe the FDA guidance on clinical trial design as clinical guidelines on therapeutic use. There is evidence to support nusinersen efficacy with prolonged mechanical ventilation both at baseline and during treatment (ref. slide 1, Appendix).

As it an equality-related issue, it may also be noted here that Equality Impact Assessment has not been shared with the stakeholders or published on NICE website.

Impact: One patient identified by TreatSMA (fairly strong for her age and condition). Unlikely to exceed 3–5 patients nationwide.

Recommendation: This criterion should be removed from both MAA and the guidance. The Equality Impact Assessment for nusinersen MAA should be published.

2. History of independent ambulation

> *If gained independent ambulation prior to initiation of therapy must still be independently ambulant. Independent ambulation is defined as per the WHO definition: patient takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object;*

Summary: The criterion is unreasonable in the light of the evidence submitted to NICE.

Analysis: The evidence submitted to NICE and/or available throughout the process included results of CS2/CS12 clinical trial of nusinersen that demonstrated clinically significant improvement in both children and adults who had lost independent ambulation prior to the initiation of treatment. Additional evidence was submitted by the consultees, as a significant number (hundreds) of non-ambulant type 3 patients have documented their improvements on nusinersen treatment in countries including Belgium, France, Germany, Italy, the Nordics, Poland, Spain, Switzerland, Turkey, and USA. To-date, both patients and clinicians have documented significant, life-changing improvements in their motor function.

Reference is to the slides 2–3 in the Appendix.

Impact: This criterion affects estimated 150 cases (including approx. 60 paediatric cases).

Recommendation: The said population should be included in the MAA. Should the evidence for a subset of this population be considered insufficient, a **MAA review should be mandated within the next 6–12 months** to consider new data that is being generated.

3. Administration OR measurement feasibility

- *Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated;*
- *Must not have received spinal fusion surgery following a diagnosis of scoliosis which prohibits safe administration of nusinersen;*
- *Must not have severe contractures which in the opinion of the clinician prohibits measurement of motor milestones;*

Summary: These criteria raise the issue of equity in access to treatment.

Analysis: The criteria have been formulated as discretionary and, by necessity, as based on a subjective opinion of the treating clinician. The experience of nusinersen programmes in other countries has shown that the expertise in intrathecal drug administration will vary among clinicians as will the availability of equipment (CT scanner, etc.) and their understanding of contractures and functional abilities.

Furthermore, the primary role of nusinersen treatment is to stabilise the disease progression; any improvements may take considerable time. Therefore, patients should not be routinely barred from accessing the treatment only because the clinician fears that they will not be able to measure future milestone attainments.

Impact: A large proportion of the patient population (at least 50%).

Recommendation: A steering committee should be formed to review individual cases and endorse or refuse treatment. Such committees operate successfully in nusinersen programmes in a number of countries and frequently include neuromuscular experts, orthopaedic surgeons, radiologists, physiotherapists, and representatives of patient organisations.

4. Review interval

NICE will reissue guidance to the NHS in England based on a review of the data by the end of the fifth year of this MAA.

Summary: The proposal is unreasonable in the light of the evidence presented to NICE; in particular, the chronology of the available evidence.

Analysis: In the course of nusinersen appraisal proceedings, NICE has received an ever-growing body of evidence which went beyond the trial data from the initial submission. As marketing authorisation was granted to nusinersen barely 24 months ago, some clinical trials are still ongoing, and new academic research papers on the drug's effects are published regularly. Therefore, it is unreasonable to set a 5-year period before the NICE guidance on nusinersen is reviewed.

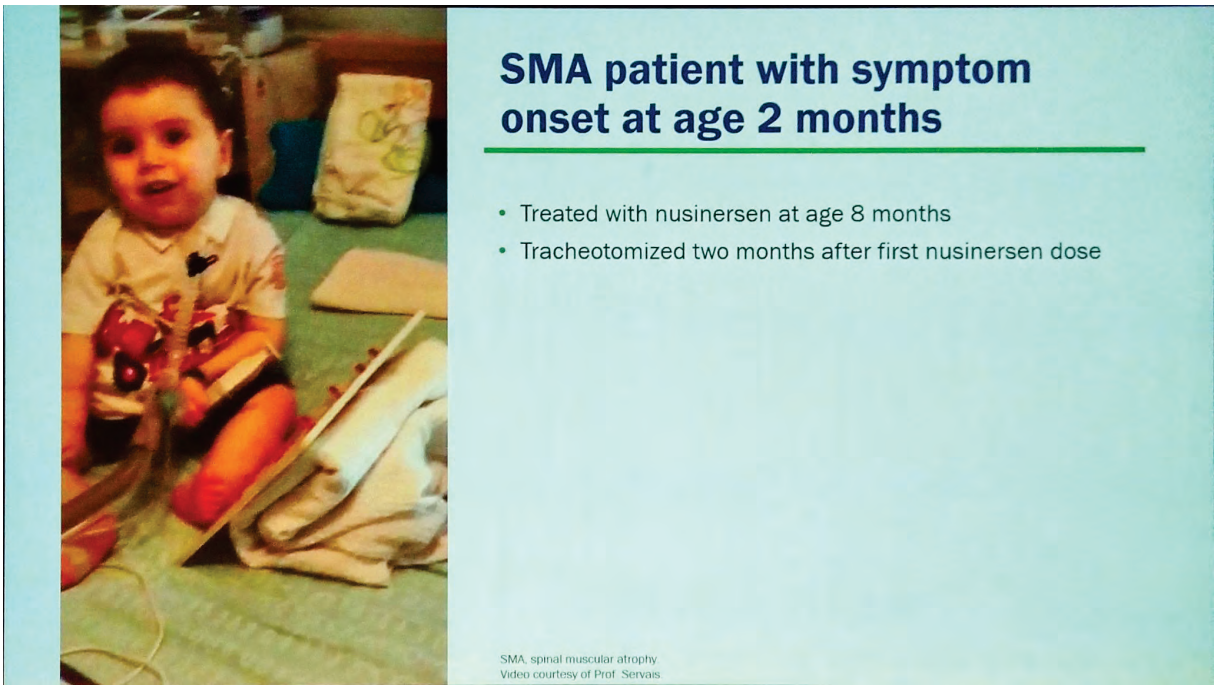
MAAs are a new formula; there have only been a handful of them to-date, and none for an orphan drug approved via the single technology appraisal process (i.e., in a relatively wide population). Given the unavoidable gaps in evidence early after marketing authorisation, as it frequently happens with drugs that carry the Orphan Drug designation, it sounds unreasonable not to mandate frequent reviews.

Impact: The entire population excluded from treatment under the proposed nusinersen MAA (approx. 15–20% of the total SMA patient population).

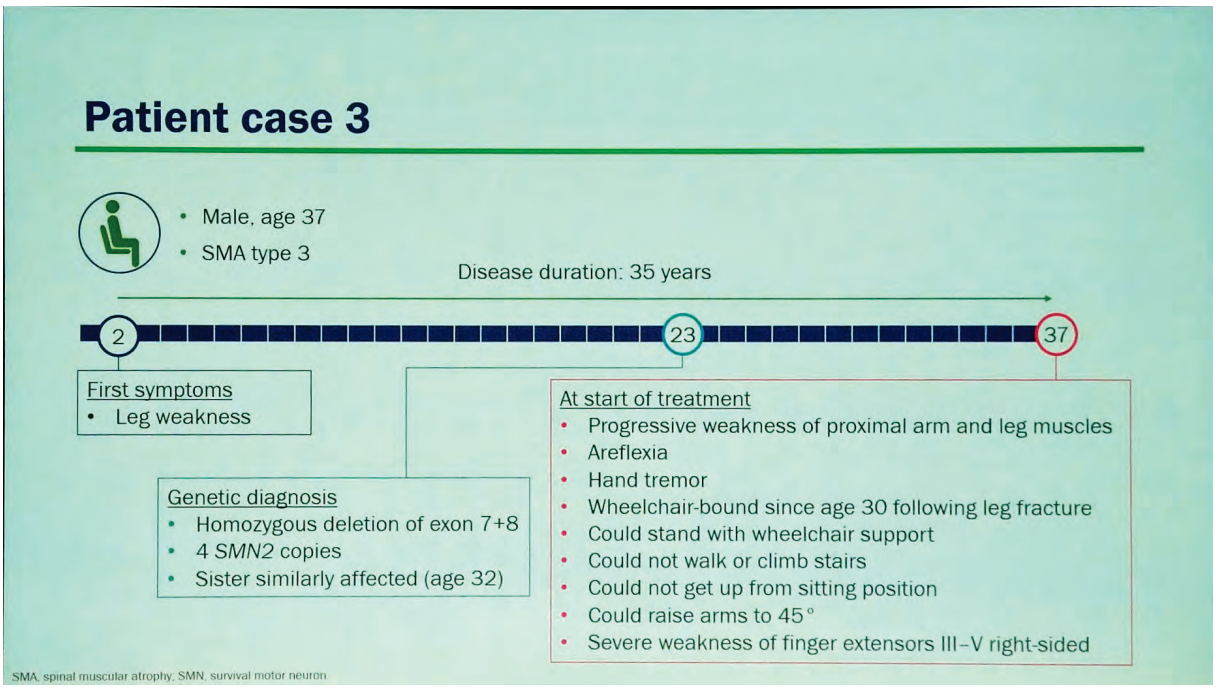
Recommendation: All new NICE guidance on SMA therapeutics should undergo mandatory reviews at 6–12-monthly intervals. This will allow NICE and the medical community to improve the guidance using new, emerging evidence.

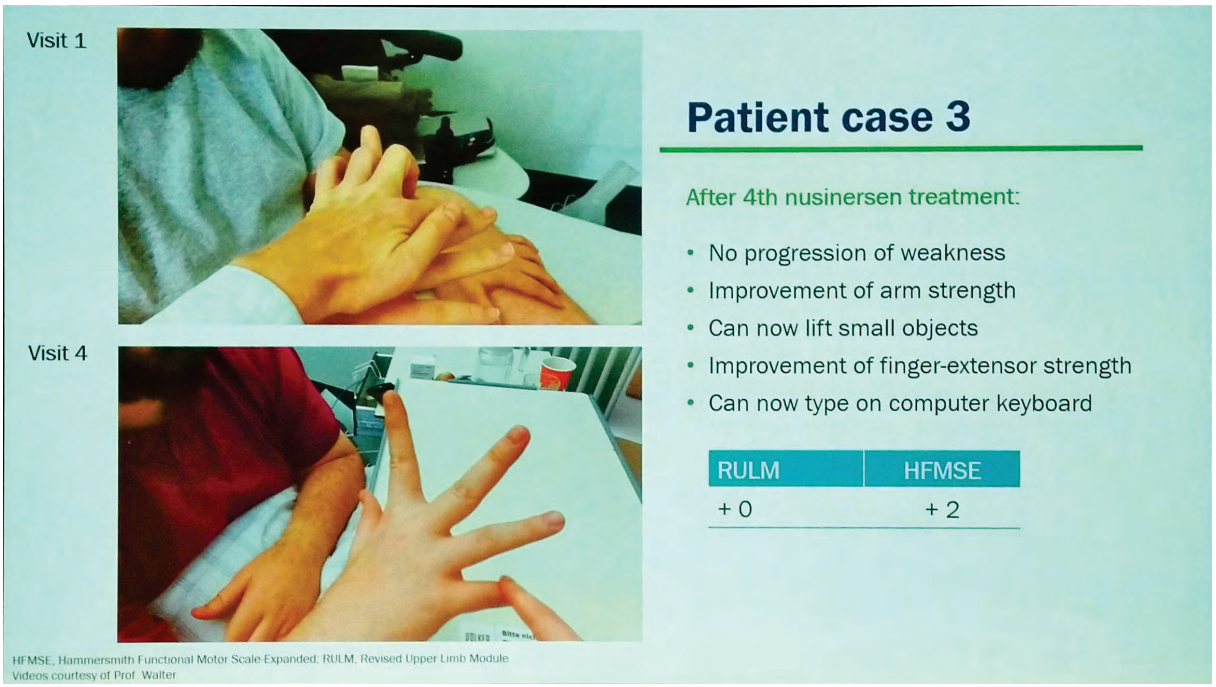
Appendix: conference slides

Source: presentation by Prof. Laurent Servais at Myology Conference, Bordeaux, March 2019.



Slide 1. Child with severe SMA type 1 achieves motor milestones on nusinersen treatment despite tracheotomy.





Slides 2-3. Improvements in a non-ambulant patient after barely 4 doses of nusinersen (CS2/CS12 trial).