

June 14th, 2019

TO: NICE

Dear Sir/ Madam

Regarding: NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE, Managed Access Agreement - DRAFT Nusinersen (SPINRAZA®) for the treatment of 5q spinal muscular atrophy

We are writing in response to the draft consultation document that NICE has published, in which the community was asked to provide feedback by the **17th of June 2019**.

We are aware of the further letter circulated by NICE on the 7th of June 2019, indicating that the criteria in the MAA have now been set and agreed. We appreciate that NICE is aware that there might be gaps in the eligible populations included in the criteria; and that this is due to a combination of uncertainties with the clinical evidence and the cost-effectiveness of Nusinersen in specific subpopulation of patients.

In this letter we summarise:

- the outcome of discussion held within the medical SMA community, including SMA REACH UK, and the PAGs regarding some of the MAA proposed eligibility population, *and also*
- quoted criteria that we feel are going to be problematic in the implementation at a national level and which, without adequate oversight, could lead to inequality of access to Nusinersen.

We write this letter with a spirit of constructive collaboration, as we are aware that a further delay in the implementation of the MAA will result in many patients who now would meet the set criteria to access this effective therapy having their treatment delayed. This would have negative consequences both on their health, and in the outcome of the therapy especially for those patients who have been recently diagnosed, in whom maximum benefit can be expected if treatment is initiated promptly.

1. Exclusion of paediatric patients with type III SMA who have lost the ability to walk independently.

Since the guidance was originally prepared, there is now clear peer reviewed evidence of the positive effect of Nusinersen in children with type III SMA who have lost the ability to walk or who are only able to walk with walking aids. In Darras et al (Neurology. 2019 May 21;92(21):e2492-e2506. PMID: 31019106), there is clear evidence of Nusinersen for children with SMA II and III:

- *one of the 11 children with SMA type II (age 2.1 years at first dose in CS2) gained the ability to walk independently during the course of the studies. The child first completed the 6MWT at the day 650 visit (total distance walked was 25.5 meters) and demonstrated continued improvements over time; by the day 1,150 visit, the child's 6MWT was 180 meters.*
- *Children with SMA type III demonstrated progressive improvements from baseline in the 6MWT over time, with mean (SE) distances improving by 92.0 (21.5) meters by day 1,150 (figure 3B).*
- *Two of the 4 children who were previously able to walk, but had lost that ability before the baseline assessment, regained the ability to walk independently during the course of the studies. In addition, 6 of the 12 (50%) children assessed at the day 253 visit demonstrated clinically meaningful improvements in the 6MWT (previously defined as ≥ 30 -meter increase from baseline) and 8 of 8 (100%) demonstrated clinically meaningful improvements by day 1,050.*

These are unprecedented improvements for SMA type III children who lost the ability to walk independently, and who retain partial independent mobility with the use of orthoses. As currently phrased, the MAA would allow clinicians to recruit a SMA type II child who is partially mobile, e.g. using walking

aids, into the Nusinersen program, but would not allow a SMA type 3 child of the same age, who with a similar level of partial mobility with the walking aids, to receive therapy.

Clinicians of SMA REACH UK conducted a national survey and are aware of 59 children with type III SMA who have lost the ability to walk. Of these, the majority are still partially mobile with orthoses. There is evidence from published literature (Darras et al, Neurology 2019) that these patients will show a substantial improvement following Nusinersen therapy, with a considerable probability of regaining ambulation or at least of remaining mobile with walking aids for a long time. In addition we wish to indicate that while a lot of emphasis is placed on ambulation for this group of patients, there is clear evidence from the RCT trials of improved upper limb motor function for patients with SMA II and III treated with Nusinersen (*Mercuri E, Darras BT, Chiriboga CA, et al; for the CHERISH Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018;375:625-635.*

Improving arm function is essential for this group of patients, as it improves participation and quality of life and is regarded as a crucial aspect of function by patients themselves, – as raised many times by the Patient Experts at NICE committee meetings and fully acknowledged in its final guidance and also summarised in the following published article: *Rouault F et al, Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. Neuromuscul Disord. 2017 May;27(5):428-438.*

We would also like to point out that the classification into SMA type II and III patients is artificial and was never intended to assign treatment or care options. Indeed SMA is a disease with a continuous spectrum of disease severity.

Request. As clinicians involved in the care of these patients we strongly feel that this modest number of paediatric cases with SMA III should receive Nusinersen and we would ask the committee to consider this request based on the already published evidence of the benefit of Nusinersen for this group of patients.

2. Exclusion of adult patients with type III SMA who have lost the ability to walk independently.

As for non-ambulant adult patients affected by SMA III. We are aware that many adults will be bitterly disappointed by their exclusion from the MAA and have already voiced their concerns to the advocacy groups. Nevertheless, we are also aware that it will take some time for the local services to be in a position to provide Nusinersen in a systematic way to this group of adults. In addition we are aware of ongoing studies, both in the US and in Europe, in which the efficacy of Nusinersen in this group of patients is being evaluated. We expect relevant peer reviewed publications regarding this group of patients to become available late in 2019 and early 2020.

Request. We ask NICE to consider an alternative option for the adult patients with type 3 SMA, i.e. to add a further clause to the MAA that the evidence for this group of patients is reviewed on a six monthly basis, and that if further clinical evidence is forthcoming, eligibility criteria will be swiftly reviewed and amended appropriately, so that also this group of patients could benefit from this therapy.

As a more general point, and considering that new evidence is likely to emerge from the real world evidence of the use of nusinersen in other group of patients currently excluded from the MAA, we request that the inclusion criteria for all patients with SMA is reviewed on a regular basis.

3. Exclusion of patients with severe contractures or with scoliosis that could make the Nusinersen administration difficult. Establishment of a National MDT Steering committee

We feel that these criteria as currently worded could lead to confusion in their implementation, hence creating disparity in the access to treatment to individual patients.

As in the past when the EAP for SMA I was implemented and we created an SMA REACH steering committee to prioritise patients and to discuss complex cases, we propose to create a national multidisciplinary steering committee that could provide further advice for complex cases in whom further discussion could be necessary. We propose that this national multidisciplinary committee is composed of clinical and academic colleagues from the UK SMA community including expert physiotherapists. We

would obviously be very happy for NICE designated physician(s) to join this committee for additional oversight. This initiative is strongly supported by the PAG, concerned as we are about the potential for inequality of access to Nusinersen.

In view of the high level of distress that the proposed limitations in the MAA has induced in a proportion of patients affected by SMA, it would be helpful to know when we will know NICE / NHSE's response to the letter, so that we can work with families and patients and manage their expectations

Signatories:

SMA REACH UK (<http://www.smareachuk.org/>)

Muscular Dystrophy UK

Spinal Muscular Atrophy UK

TreatSMA