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Specialised commissioning team
NHS England

23rd August 2017

Dear Edmond

Regarding: NHSE criteria for Expanded Access Program for Nusinersen.

We write with respect to the interim NHS commissioning policy for Nusinersen treatment for infants / children with spinal muscular atrophy type 1 under the expanded access programme.

We are grateful to the clinical panel for reviewing the evidence to support this treatment and for providing an interim commissioning policy pending the outcome of formal NICE evaluation.

We wish nevertheless to raise our concerns about, and request a review of, the inclusion criteria stipulated within the interim policy, specifically with respect to commissioning treatment only for those infants aged 7 months or under at entry, and only for those with 2 copies of the *SMN2* gene.

The reasons for bringing this to you and requesting a review are several fold:

SMN2 copy number.

Whilst the *SMN2* copy number is a factor that has been related to severity of the condition it is not the only factor – other genetic and environmental factors play a role. Indeed, a proportion of patients with typical type 1 SMA (approximately 10%) carry 3 *SMN2* copy number and approximately 1% 4 copy numbers. At the other end of the clinical spectrum, 15% of patients with 2 *SMN2* copy number have type 2 SMA; and 3% even milder forms (SMA 3). Figure 1.

SMN gene copy number and outcome

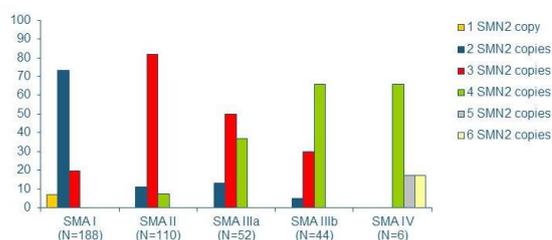
	SMA I	SMA II	SMA III
1 <i>SMN2</i> copy number	97%	3%	0%
2 <i>SMN2</i> copy number	82%	15%	3%
3 <i>SMN2</i> copy number	8%	62%	30%
4 <i>SMN2</i> copy number	<1%	18%	81%
5 <i>SMN2</i> copy number	0%	0.4%	90%
6 or more <i>SMN2</i> copy number	0%	0%	80% (or asymptomatic)

1. Wirth et al., *Hum Genet.* 2006;119(4):422-8;2. Feldkötter et al., *Am J Hum Genet.* 2002;70(2):358-68

While only children with 2 *SMN2* copy number were selected for the Ender phase III clinical trial, this was done for stratification purposes and to select a population of infants as homogenous as possible (figure 2).

Predictive value of *SMN2* copies?

Strong predictive value, but the correlation is not absolute
Important for stratification and recruitment in therapeutic trials



N=400

1. Wirth et al., *Hum Genet*, 2006;119(4):422-8; 2. Feldkötter et al., *Am J Hum Genet*, 2002;70(2):358-68

We are concerned that the exclusion of patients with type 1 SMA based on *SMN2* copy numbers from the EAP will be difficult to implement in clinical practice, and would exclude patients in need, such as for example those with 3 *SMN2* copy numbers, in whom a good response to treatment is expected.

We note that there is ample evidence that Nusinersen, a drug that increases the production of SMN in patients with SMA irrespective of the *SMN2* copy number, has been studied not only in patients with type 1 SMA and 2 *SMN2* copy numbers, but also in children with SMA type 2 (and 3 or 4 *SMN2* copy numbers); and also in children with type I SMA in the pre-symptomatic Nurture study (and 2 or 3 *SMN2* copy numbers). We understand that the data of Nurture has been made available from Biogen not only to FDA and EMA but also to NHSE. These data not only show that children with both 2 and 3 copies of *SMN2* responded to Nusinersen administration, but that in actual fact children with 3 *SMN2* copy numbers were even better responders.

We also note that the exclusion of children with type 1 SMA who do not have 2 *SMN2* copy numbers is uniquely being suggested by NHSE and that no other country in the world which has embraced the EAP has imposed this limitation.

Age of patients.

We believe that clinical severity is a more logical inclusion criterion than age or otherwise. A clinically based approach to reasonable start and stop points for treatment have already been agreed by the UK Neuromuscular experts dealing with these children in the clinical settings.

Our concern is that the consequence of applying these inclusion criteria is at the least to generate difficulties in provision of care locally because there will need to be 2 pathways of care for the same treatment, for patients affected by the same disease – those whose treatment is funded and those whose treatment is not. Of greater concern is that this is not consistent with the NHSE equality statement. The diagnosis of the sub-type of spinal muscular atrophy is a clinical diagnosis, there is no laboratory test which can determine the sub-type. There is therefore a real risk of discriminating against a subgroup of children with the same clinical and genetic condition. This results in inequity of provision within this country which compounds the already existing discrepancy between care provided in England compared with other European countries. Therefore whilst we understand that this is an interim policy we urge a re-consideration of the restrictive inclusion criteria.

We therefore urgently request that NHSE reconsiders the inclusion/ exclusion criteria for type 1 SMA children so that the worldwide used clinical criteria are applied and no discrimination of patients with the same clinical condition is imposed.

Yours sincerely

Signed by:

The paediatricians and paediatric neurologists of the UK NORTH STAR and SMA-REACH clinical networks (<http://www.northstardmd.com/about.html> and <http://www.smareachuk.com/>)

and

The patients advocacy groups SMA Support UK, Muscular Dystrophy UK, TreatSMA and SMA Trust (<http://www.masupportuk.org.uk/>; <http://www.musculardystrophyuk.org/>; <https://www.treatsma.uk/>; <https://www.smatrust.org/>)