Dr E G Jessop TD DM FFPH
Specialised commissioning team
NHS England

25th October 2017

Dear Edmund

Regarding: NHSE criteria for Expanded Access Program for Nusinersen and the letter from Mr Palmer of September 2017.

Many thanks to you and Mr Palmer for the letter in response to our correspondence in relation to the criteria chosen for NHSE for the interim NHS commissioning policy for Nusinersen treatment for infants / children with spinal muscular atrophy type 1 under the expanded access programme.

We fully agree with you that high quality data are necessary when interpreting outcomes of clinical trials. Regulatory and health authorities also consider the totality of the data produced, and this is particularly relevant in the field of rare diseases, especially those characterised by a severe and early fatal clinical course. Severe type 1 SMA, with a mean age at death (or requirement for > 16 hours ventilation) of 9 months, clearly is a prototype for such disease. Nusinersen has demonstrated to improve significantly survival including ventilatory free survival of all infants affected by SMA1. Biogen is providing Nusinersen free of charge to all SMA1 patients across the globe in view of the unmet need in this population and the clear benefit provided by Nusinersen to these babies.

In this context we bring to your attention the data published in Neurology 2016 by Chiriboga et al [1] and in the Lancet by Finkel et al [1] in which data with typical SMA1 children and 3 SMN2 copy number are presented. We have copied below the relevant data from one of these 2 manuscripts in which there is clear evidence of a clinical response in SMA1 children, irrespective of the copy number.

Figure 1. From Finkel et al [1]

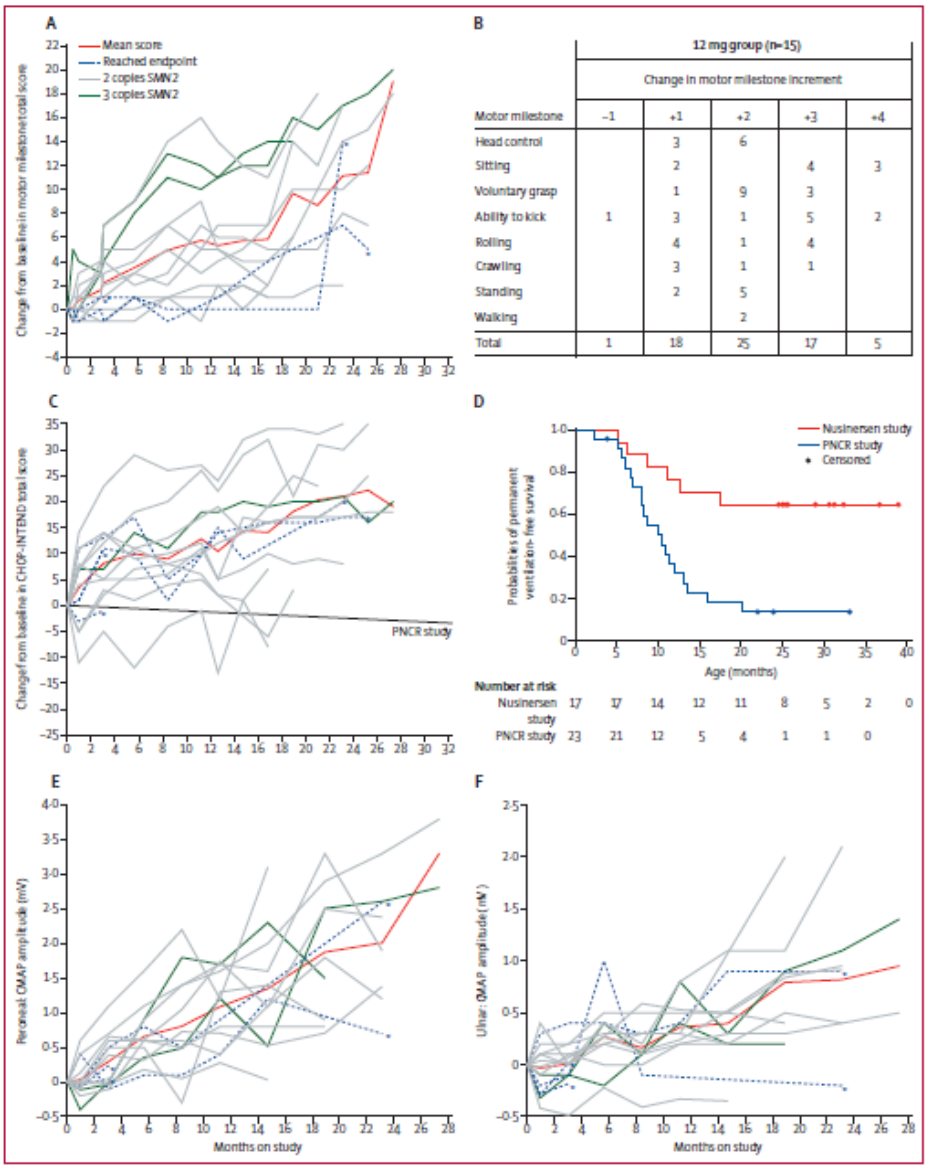

Figure 1: Clinical effects in infants with spinal muscular atrophy

(A) Change from baseline in the motor milestones as assessed by the Hammersmith Infant Neurological Exam–Part 2 (HINE-2) for participants in the 12 mg dose group. Red line=mean score. Dashed blue line=participants who reached the endpoint of death or permanent ventilation. Green line=participants with three copies of the SMN2 gene. (B) Changes in individual milestone categories as assessed by the HINE-2 for the 12 mg dose group. (C) Changes in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) infant motor function test for individual participants in the 12 mg dose group. Solid black line=Pediatric Neuromuscular Clinical Research (PNCR) natural history comparison for infantile spinal muscular atrophy.[5] Red line=mean score. Dashed blue lines=participants that reached endpoint of death or permanent ventilation. Green line=participants with three copies of *SMN2*. (D) Kaplan-Meier curves for participants with infantile-onset spinal muscular atrophy and two *SMN2* gene copies: nusinersen-treated versus untreated infants with spinal muscular atrophy from the PNCR natural history study (log-rank test, p=0·0014). (E and F) Change from baseline in peroneal (E) and ulnar (F) nerve compound muscle action potential (CMAP) negative peak amplitude for individual participants in the 12 mg dose group. Red line=mean score. Dashed blue lines=participants that reached endpoint of death or permanent ventilation. Green line=participants with three copies of *SMN2*.

This, and the data available to NHSE, FDA and EMA regarding the Nurture study, unequivocally indicate that SMA1 children with 3 SMN2 copy numbers respond to Nusinersen as well – in actual fact on average better- than the children with 2 SMN2 copy number.

As the interim NHSE policy for the access to SMA1 children to nusinersen via the Biogen sponsored EAP excludes children with SMA type 1 who have1 or 3 copy number of SMN2, this raises both practical and significant ethical issues that us, clinicians on the ground, have to face when delivering the optimal care for children affected by this condition.

Recent manuscripts have addressed the ethical issues related to the prioritization of access to this drug in the SMA population [3] and, as practiced by the EAP programmes in other countries, recommend access to the drug to all children with SMA1. We had independently, and in consultation with ethicists, arrived at the same conclusions and circulated a prioritization based on age of onset and clinical severity, so that all children affected by SMA1 can access the drug via the EAP.

We recognize that NHSE does not appear to have a structured pathway to deal in a timely way to emerging therapies for rare and extremely severe conditions; and that, compared with most of the other countries, this led to a delay of more than 10 months before the EAP was allowed to start in England. The Interim policy is helpful but we remain concerned that the interim policy exclusion from the EAP of children with SMA1 with 1 or 3 copy number of SMN2, contradicts the primary mission of NHSE of addressing health inequalities.

We would certainly be happy to work with NHSE to formulate a Preliminary Policy Proposition in which we can summarise the published evidence also indicated in this letter.

As a community of clinicians and advocacies groups involved in the delivery of the care and managing and supporting these families in this country, we certainly wish to ensure that there are no more obstacles for all SMA1 children to access this effective drug.

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.smasupportuk.org.uk/; http://www.musculardystrophyuk.org/; https://www.treatsma.uk/; https://www.smatrust.org/)

1. Chiriboga CA, Swoboda KJ, Darras BT et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. Neurology. 2016 Mar 8;86(10):890-7.

2. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet. 2016 Dec 17;388(10063):3017-3026. doi: 10.1016/S0140-6736(16)31408-8.

2. Jecker NS, Is There a 'Right to Try' Experimental Therapies? Ethical Criteria for Selecting Patients With Spinal Muscular Atrophy to Receive Nusinersen in an Expanded Access Program, The American Journal of Bioethics Oct;17(10):70-71