The Dubowitz Neuromuscular Centre
UCL Great Ormond Street Institute of Child Health
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Nusinersen/ Spinaraza Extended Access Programme in England: Position statement from the North Star/ SMA-REACH UK clinicians

Seventy clinicians, physiotherapists; study coordinators; industry and advocacy groups representatives met today at the UCL Great Ormond Street Institute of Child Health for the annual consortium meeting. A programme of the meeting is attached at the end of this letter.
One of the topics under discussion related to the Extended Access Programme initiated by Biogen following the successful completion of the Endear phase III clinical trial in infants with type I (infantile) spinal muscular atrophy (SMA).

1. Current status of nusinersen treatment in the UK

Currently only 2 centres in England have been activated after months of internal negotiations (London and Newcastle, the 2 centres originally involved in the phase III clinical trial), while additional Centres activated are Belfast in Northern Ireland; Dundee in Scotland and Dublin in Ireland. Cumulatively these centres have so far treated 9 infants with SMA I. This contrasts with the recruitment in other EU countries such as Italy for example where more than 130 infants is now close to 150.
Now that an effective drug is available, for the first time, for this severe and extremely rapidly progressive disease, there is an increasing level of frustration from families, but also clinicians and members of the advocacy groups because of the delay in the rapid initiation of the EAP in England. A number of families are now regularly travelling to France, Germany and Austria to obtain this treatment. This is extremely unsatisfactory and poses a significant risk to these fragile infants.

2. Current availability and issues with nusinersen treatment in the UK

A number of clinicians involved in the UK paediatric neuromuscular networks North Star and SMA REACH have over the last few months been engaged with their individual trusts; the CRGS; NICE, Biogen and the patient advocacy groups to find ways to expedite the EAP and the opening of new sites. The group has produced treatment guidelines for inclusion criteria and discontinuation criteria based on the evidence derived from the data analysis of the concluded phase III trial in infantile SMA, to provide a rational guide to clinicians on a fair and equitable access to Nusinersen across the country. These criteria were also discussed in light of those used in other countries in which there is experience with Nusinersen EAP (US; Italy; Germany; Spain); and they were also discussed with representatives of ethics committees both in the UK and oversea.

3. **Obstacles for rapid EAP implementation in the UK**

The clinicians of the UK Neuromuscular North Star and SMA REACH networks have found significant obstacles in activating the EAP at their centres.

a. **CRG's commissioning process and resource allocation to centres involved in delivery of the therapy**
One of these factors relates to the fact that as the drug is still under EMA appraisal (following the FDA approval in December 2016) and has not been formally reviewed by NHS England and NICE, there is no clear mechanism to allow the CRGs to consider rapid commissioning of the resources necessary for the process of administering this drug (which requires intrathecal administration). Only after NICE has reviewed the evidence for a drug, will the CRGs consider them for commissioning. However the

timeline for this process can take years and thus this process is totally inappropriate for these children who are likely to die within months of diagnosis.

in view of the unequivocal and highly significant clinical response of treated infants, and positive effects on milestone acquisition and improved survival, and considering that Biogen has agreed to make the Nusinersen drug globally available free of charge until the drug will be adopted by local Health systems, we are not in an equipoise position anymore and face the ethical dilemma of not being able to initiate a drug which is effective, which is approved in the US, which most likely will be approved also in UK, and therefore see our SMA patient population having to go to other EU countries if they wish to access the drug promptly, or otherwise face progressive weakness which inevitably leads to early death.

So far each of the sites that has been able to initiate treatment for a few children under the EAP, had to identify internal resources to start the process. Due to the challenging financial situation of most of the NHS trusts, activation of the two centres in England has been extremely slow. In addition, the lack of a clear mechanism of resource allocation for the programme also means that only SMA children under the care of a hospital which has succeeded in the task of activating the EAP have started to receive treatment, as there is prioritisation of children already registered and followed in that hospital. However this contrasts with our desire to provide an equitable and fair access to this effective drug to all children in the UK, following the agreed clinical prioritisation criteria.

b. **HST assessment criteria by NICE**
Another factor that is slowing down the EAP initiation relates to the fact that a drug approved following HST assessment (a path that this group of clinicians considers appropriate) can usually be administered only in a small number of centres and this seems to be a limiting factor to the number of centres being approved under the EAP pending assessment through the HST pathway. A specific number is not determined although this number is typically small, usually not more than a handful. Considering the number of infants with SMA expected to be able to benefit from this drug at the moment (we anticipate at least 100 infants) and the burden (both in terms of capacity but also financial resource allocation) on the local hospitals it would be highly desirable that all the centres involved in the care of children with SMA, and who have worked with charity funding as part of a network for more than a decade, were in a position to be activated for the EAP, and able to administer the drug to their patients. A similar and successful model has already been implemented for children with Duchenne muscular dystrophy receiving Ataluren, where each of the sites involved in the North Star clinical network are in a position to prescribe Ataluren and follow up patients following a clear evaluation protocol.

This is the preferred solution of the clinicians in the networks and the advocacy groups who met today in London at a network meeting, as it would allow the implementation throughout the entire NHS territory of equitable prioritisation criteria, and would also allow the largest number of children to receive treatment in the shortest period of time. As SMA I is an extremely rapidly progressive condition, the difference in recruiting children into the programme of only a few weeks or months can play a very significant role on outcome, as suggested by the analysis of the data from the concluded phase III trial.

4. Seeking a way forward

The clinicians in the 2 UK Neuromuscular networks and the advocacy groups who met today, strongly favour the option of opening all those sites involved in the clinical SMA-REACH UK clinical network that request EAP initiation, and that this should not be in conflict with HST designation, as there are clear precedents that we have dealt with effectively as a neuromuscular network before.
The opening of multiple sites will facilitate the setting up of a national priority list, which would ensure fair and equitable access to the drug. We have the support of the advocacy groups which are also prepared to facilitate

the national registry of patients interested in the programme. A clear indication from the CRGs on the pathway for commissioning and resource allocation to allow centres to be opened swiftly, without months of internal negotiations at the Trust level for internal resource identification, will also provide a powerful tool for opening multiple sites without delay. Once the CRGs commissioning has been finalised, the number of treatment centres could be potentially reviewed, or the way the networks function could be revised following feedback from the CRGs, to allow a rational approach to the continuing provision of nusinersen.
We realise that to achieve what is suggested above could take several months. We feel very uncomfortable not to pursue, for each of the centres, the best possible local strategy to allow EAP initiation, as this currently represents the only path to allow our patients to access this drug. We acknowledge that this "local path" cannot fully address the principle of global fair access to this drug, but we also consider that to deprive patients who can benefit from this drug only because a national solution is complex and is likely to continue to require lengthy negotiations, is not in the best interest of our patients.

5. **Request to NICE/ CRGs**:
   We are writing to ask:
   a. To expedite the NICE/ CRG assessment of the EAP and the allocation of resources to facilitate the opening of treatment sites.
   b. That in the short term centres that form part of our clinical network, and have expertise in dealing with children with SMA I, will be allowed to initiate the EAP, and that at this point in time there is not a cap that could affect later HST assessment of this drug, on the number of treatment centres.
   c. In the longer term, this network could work with the CRGs and the advocacy groups to identify the most rationale process (i.e. number of centres and best local networks) to allow access to this drug for children with type I SMA.

We would be most grateful if you could respond to this letter within the next 2 weeks to assure us that this work is being progressed.

Yours sincerely

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http://www.ucl.ac.uk/ich/research-ich/dubowitz
http://www.cnmd.ac.uk/

On behalf of the attendees of the meeting held at the UCL Great Ormond Street Institute of Child Health on the 24th of March 2017 (list attached).

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Muscular Dystrophy Campaign

NorthStar Clinical Network

First Name	Surname	Job title	Centre
Gautam	Ambegaonkar	Consultant Paediatric Neurologist	Nuffield Health Cambridge Hospital
Ian	Bamsey	Managing Director	Certus Technology Associates
Peter	Baxter	Consultant Paediatric Neurologist	Sheffield Children's Foundation NHS Trust
Sarah	Brown	Specialist Neuromuscular Physiotherapist	Queen Elisabeth University Hospital NHS Greater Glasgow and Clyde
Lauren	Buckley	Neuromuscular Physiotherapist	
Nic	Bungay	Director of Campaigns, Care and Information at the	Muscular Dystrophy Campaign
Julie	Burslem	Regional Paediatric Neuromuscular Physiotherapist and Care Advisor for the North of Scotland.	Raigmore Hospital Inverness
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Anne Marie	Childs	Consultant Paediatric Neurologist	The General Infirmary at Leeds
Emily	Crossley	Co-founder and director	Duchenne UK
Becky	Davis	Clinical Research Project Lead	International Centre for Life Newcastle Upon Tyne
Christian	De Goede	Consultant Paediatric Neurologist	Lancashire Teaching Hospitals
Marina	Di Marco	Principal Neuromuscular Physiotherapist	Queen Elisabeth University Hospital Glasgow
Isobel	Douglas	Neuromuscular Nurse Specialist	Royal Belfast Hospital for Sick Children
Jennifer	Dunne	Neuromuscular Clinical Nurse Specialist	Greater Glasgow and Clyde NHS Trust
Clare	Eadie	Paediatric Neuromuscular Specialist Physiotherapist	Royal Hospital for Sick Children Edinburgh

Nicholas	Emery	Neuromuscular Clinical Specialist Physiotherapist	RJAH Orthopaedic Hospital Oswentry
Michelle	Geary	Lead and Specialist Therapist in Neurology and Neuro-muscular	Southampton Children's Hospital
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Louise	Hartley		
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Sarah	Maxwell	Medical Science Liaison	Biogen
Anna	Mayhew	Consultant Research Physiotherapist	International Centre for Life Newcastle Upon Tyne
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