Urgent Clinical Commissioning Policy Statement: Nusinersen for genetically confirmed Spinal Muscular Atrophy (SMA) type 1 for eligible patients under the Expanded Access Programme (EAP)

NHS England Reference: 170038P

A clinical commissioning policy statement is an interim commissioning position pending the formation of a Clinical Policy.

1 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of this policy statement, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

2 Background

Spinal Muscular Atrophy (SMA) is caused by mutations in the survival motor neuron 1 (SMN1) gene that results in the lack of functional SMN protein. This causes the loss of motor neurons in the spinal cord. The nerves affected in SMA are those that enable walking, crawling, arm and hand movement, head and neck movement. The muscles used for swallowing and breathing are also affected. SMA Type 1 is the most severe form of SMA and babies with this condition are too weak to be able to sit or control their own head position when supported sitting. SMA Type 1 is a life-limiting condition with life-span limited to below one year in the majority (unless treated with nusinersen), but with the current standard management, survival beyond one year has become more common.

3 Evidence Summary

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish the urgent clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This includes the most clinically impactful publication, identified using a literature search strategy defined by the clinical lead. This publication is summarised below.

Publication 1 (European Medicines Agency (2017) European Public Assessment Report Spinraza).

A double-blind, randomised, sham-procedure controlled study of nusinersen was conducted at 31 centres worldwide in patients with infantile onset SMA (study reference CS3B). Results are reported in the marketing authorisation summary of product characteristics of the European Medicines Agency (EMA).

The primary end points for CS3B were:

- the proportion of motor milestone responders, assessed by Section 2 of the Hammersmith Infant Neurological Examination (HINE);
- Time to death or permanent ventilation (≥16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event OR tracheostomy).

The main efficacy analysis presented to the EMA was the percentages of motor milestones responders. The analysis was based on non-missing values at the later of the Day 183, Day 302, and Day 394 assessments. Subjects who died or withdrew from the study were counted as non-responders.

A 'motor milestones responder' was defined as follows:

(i) The subject demonstrated at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND

(ii) Among the 7 motor milestone categories (with the exclusion of voluntary grasp), the subject demonstrated improvement in more categories than worsening.

Permanent ventilation was defined as tracheostomy or ≥16 hours of ventilatory support per day continuously for >21 days in the absence of an acute reversible event.

A total of 149 subjects were screened of whom 122 were randomised in a 2:1 ratio to receive nusinersen (81 subjects) or undergo a sham procedure (41 subjects in this control group). Apart from one subject randomised to receive nusinersen who was withdrawn from the study prior to receiving study treatment, all subjects received study treatment according to their randomization assignment.

Of the 121 subjects who received treatment, 89 (74%) completed the study (81% of subjects in the nusinersen group and 59% of subjects in the control group). All but two of the discontinuations were due to death of the subject.

Motor milestones were assessed using Section 2 of the HINE. Eight categories of motor milestones are evaluated, including voluntary grasp, head control, ability to kick, rolling, sitting, crawling, standing, and walking, with 2 to 4 milestones that can be achieved within each category.

For motor milestones, the final primary efficacy result was as follows:

51% of subjects in the nusinersen group achieved a response compared to 0% in the control group ($p<0.0001$).

The EMA assessment of the full results is as follows:

‘The data supports the position that nusinersen-treated subjects achieved progressive and sustained increases in total motor milestone over time compared to baseline whereas control group subjects showed slight improvement at the first assessment (Day 64) followed by a decrease over time. The loss of motor milestones gained prior to symptom onset, as seen in the control group, is consistent with the natural history of Type I SMA, while a gain in motor milestones after symptom onset, as seen in the nusinersen group, is highly inconsistent with Type I SMA natural history.’

For event free survival, the primary efficacy result was as follows:

Time to death or permanent ventilation was significantly prolonged in subjects treated with nusinersen. Overall, there was a 47% reduction in the risk of death or permanent ventilation compared to control. Nusinersen-treated subjects who were below the median for disease duration at baseline had a markedly decreased risk of death or permanent ventilation (76% reduction in risk) compared with control subjects who were below the median, suggesting that early treatment with nusinersen may confer a strong benefit for event-free survival.

In a separate open label study of 20 patients (study CS3A), fifteen (75%) were alive and continuing in the study at the time of the data cut-off. Of these 15 subjects, all were >24 months of age, 7 were >30 months of age, and 2 were >36 months of age.

Thirteen subjects (65%) were alive, free from permanent ventilation, and continuing in the study at the time of data cut-off. A median time to event-free survival could not be estimated due to an insufficient number of events.

Safety

In Study CS3B, adverse events (AEs) were reported in 96% of subjects who received nusinersen treatment and 98% of subjects who received sham (control) treatment. A lower percentage of subjects in the nusinersen group had a severe or moderate event (nusinersen vs. control: 88% vs. 95%), a severe event (56% vs. 80%), or a serious adverse event (SAE) (76% vs. 95%). No SAEs were considered by the Investigator to be related or possibly related to the study treatment. A lower percentage of nusinersen-treated subjects discontinued treatment due to an AE (16% vs. 39%). All discontinuations, in both groups, were due to fatal SAEs.

The most commonly reported AEs in 20% or more of subjects (nusinersen versus control) were respiratory and/or infectious in nature: upper respiratory tract infection (nusinersen vs. control: 30% vs. 22%), respiratory distress (26% vs. 29%), pneumonia (29% vs. 17%), respiratory failure (25% vs. 39%), atelectasis (23% vs. 29%), acute respiratory failure (14% vs. 24%), viral upper respiratory tract infection (10% vs. 17%), oxygen saturation decreased (13% vs. 24%) and cough (11% vs. 20%). Other commonly reported events include pyrexia (56% vs. 59%), constipation (35% vs. 22%), vomiting (18% vs. 20%),

gastroesophageal reflux disease (13% vs. 20%), and dysphagia (11% vs. 20%). The nature of these events in the nusinersen-treated arm was generally consistent with those reported in the sham-control arm, and in line with what is expected for subjects with infantile-onset SMA.

The EMA assessment concluded that:

'Review of the available data demonstrated no safety concerns due to nusinersen exposure. The majority of adverse events and severe adverse events reported in subjects exposed to nusinersen were consistent with the nature and frequency of events typically occurring in the context of SMA.'

4 Commissioning Position

Rationale for a clinical commissioning policy statement

Nusinersen to treat children with SMA which is genetically confirmed and clinically Type 1 is of such significant clinical importance that an immediate clinical commissioning policy statement has been adopted. The time taken to develop a full clinical commissioning policy proposition for relative prioritisation and implementation would not meet the immediate need for patients, clinicians and the NHS to have clarity about whether an intervention is or is not routinely commissioned.

Clinical commissioning position

Based on a limited scoping of the evidence, NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for SMA Type 1 as outlined in the starting criteria below.

Starting criteria

- Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
- Onset of clinical signs and symptoms consistent with SMA at ≤6 months (180 days) of age.
- Receiving adequate nutrition and hydration (with or without gastrostomy).
- Body weight ≥3rd percentile for age using appropriate country-specific guidelines.
- Medical care, such as routine immunisations (including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis (palivizumab) if available), meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA (Appendix D of the protocol).

Stopping criteria

- For patients on 24 hour non-invasive ventilation (NIV), if there is no

improvement in motor score, assessed by the Hammersmith Infant Neurological Examination (HINE), or NIV requirement improvement - then treatment should discontinue after the 5th dose of nusinersen treatment.

- For patients on less than 24 hour NIV, maintenance of respiratory function with NIV (i.e. need for the same number of hours NIV (for example a patient receiving 16 hours NIV per day continues to need 16 hours per day, or one on 22 hours per day continues to need 22 hours) may be viewed as stabilisation and an indication of benefit - so nusinersen treatment will continue.
- HINE score will also be calculated, and stability or improvement on the HINE score will be considered an indication to continue nusinersen administration.
- If in the parents view the quality of life is poor because of SMA1 disability progression, or adverse effects of nusinersen administration procedure or drug, side effects, then there is a need to discuss nusinersen discontinuation.
- If the view of the treating physician is that the handling and positioning required for lumbar puncture or a general anaesthetic required for this procedure, impose significant life-threatening risk in a fragile SMA1 infant, this would be considered as an indication to stop nusinersen EAP participation.
- There may be additional unforeseen circumstances / worsening of clinical status, which may necessitate a discussion with the parents to discontinue nusinersen treatment.

Exclusion criteria

- SMA1A (also called SMA0) is a special category by virtue of its extreme severity, and which requires discussion with the parents on the basis that SMA1A infants are very unlikely to respond to Nusinersen. Thus nusinersen EAP will not be an appropriate intervention for SMA 1A infants.
- Comorbidities that might preclude lumbar puncture.
- Hypoxaemia (O2 saturation awake <96% or O2 saturation asleep <96%, without ventilation support) during screening evaluation.
- Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy.
- History of brain or spinal cord disease that would interfere with the lumbar puncture procedures, cerebrospinal fluid (CSF) circulation, or safety assessments.
- Untreated bleeding disorders or any other existing condition which precludes lumbar punctures.
- Spinal fusion in most instances (needs further assessment with orthopaedic surgeons).

Contraindications

Nusinersen will not be offered to patients with other life limiting conditions or if it is contraindicated to treatment as set out in the Summary of Product

Characteristics.

Expanded access programme

Administration of nusinersen via an agreed Expanded Access Programme will be agreed with providers who can demonstrate all of the following:

- Paediatric Neurologist with experience in managing infants with Type 1 and 2 SMA; respiratory paediatrician; Physiotherapist; Care Coordinator.
- Suitably qualified and trained staff and the appropriate protocols to administer Intrathecal Injections to infants who may require sedation or anaesthesia.
- The health care professional who will be administering nusinersen is aware of the risks of intrathecal injection and anaesthesia sedation in infants and children with SMA, and will use internal protocols for sedation or anaesthesia as appropriate.
- Availability of the following methods to establish the diagnosis 'SMA': SMN 1 Deletion Test, SMN 1 Point Mutation Test.
- Adoption of the standard-of-care consensus guidelines for patients with SMA (JCN 2007 Consensus statement for standard of care in spinal muscular atrophy).
- The Provider is approved as an EAP site (in accordance with the criteria set out by Biogen).

Nusinersen is administered intrathecally via lumbar puncture, with 4 loading doses required in the first 2 months, then a dose every 4 months thereafter (i.e. 6 doses in year 1, and 3 doses in subsequent years).

Patient factors will determine whether a baby / infant or child will require general anaesthesia or sedation during administration and whether nusinersen will be administrated via a day case admission or as an inpatient admission with overnight observation.

Clinical commissioning policy development plan

It has been assessed that the development of a full clinical commissioning policy is not needed at this time. It is expected that nusinersen for SMA will be appraised or evaluated by the National Institute for Health and Care Excellence (NICE). This urgent clinical commissioning policy statement will be formally reviewed after the outcome of the NICE appraisal or termination of the EAP scheme.

Should the subsequent published clinical commissioning policy be revised to 'not routinely commissioned', patients started on treatment under this policy statement will continue to have access to it provided they and the clinician responsible for their care continue to believe that it is the right treatment for them and the pharmaceutical company agree to provide the drug according to the commercially confidential arrangements.

5 Mechanism for funding

NHS England will reimburse activity undertaken within the terms of this policy statement, as follows:

- NHS England will reimburse the administration costs for nusinersen.
- Under the Expanded Access Programme, nusinersen will be available to eligible children under commercially confidential arrangements.

6 Date of policy statement approval and review

The policy statement is effective from March 2018.

A clinical commissioning policy is not planned to be developed at this stage. If a clinician, supported by peers, seeks a reappraisal by the Clinical Panel then a new 'Preliminary Policy Proposition' should be submitted. For guidance email england.specialisedcommissioning@nhs.net.

This policy statement will be formally reviewed after the outcome of the NICE appraisal or termination of the EAP scheme.

7 References

European Medicines Agency (2017) European Public Assessment Report: Spinraza.