

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Managed Access Agreement**

**Nusinersen (SPINRAZA®) for the treatment of 5q  
spinal muscular atrophy**

|   |                                 |
|---|---------------------------------|
| <b>Date of Agreement</b>  |                                 |
| <b>NHS England</b>  | .....<br>NHS England            |
| <b>Biogen</b>   | .....                           |
| <b>Clinical Lead</b><br><br>.....   | .....<br><br>.....              |
| <b>Patient Organisation(s)</b><br><br><b>SMAUK</b><br><br><b>TreatSMA</b><br><br><b>Muscular Dystrophy UK</b> | .....<br><br>.....<br><br>..... |
| <b>NICE</b>   | .....                           |

# 1 Purpose of Agreement

- 1.1 The objectives of the document are to set out the agreed terms and conditions according to which patients will be entitled to access the drug called nusinersen (Spinraza<sup>®</sup>▼) for treatment for 5q SMA NICE ID1069. It also describes a set of auditable measures that will be used as an evidence base in this disease and to assess the compliance with this Managed Access Agreement in England and to ensure that all relevant stakeholders have a common understanding that such measures have the commitment of all involved and will be applied. This common perspective is aimed to address uncertainties raised by the NICE Committee in their reappraisal of nusinersen for 5q SMA NICE ID1069.
- 1.2 This Managed Access Agreement (**MAA**) has been entered into by NHS England, Biogen (the “Market Authorisation Holder” or “MAH”), and National Institute for Health and Care Excellence (**NICE**), the Clinical Expert named on page 1 and the patient organisations.
- 1.3 For the avoidance of doubt, the parties intend this Managed Access Agreement to be legally enforceable between them.

# 2 Background

- 2.1 5q spinal muscular atrophy (SMA) is a rare, genetic, neuromuscular disease, characterised by spinal motor neuron loss, muscle atrophy and motor impairment. SMA is debilitating for all patients and fatal for the worst affected; patients and their families can experience extremely high levels of burden.
- 2.2 NICE appraisal has developed positive recommendations conditional on a Managed Access Agreement (MAA) being developed and agreed by key stakeholders in the use of nusinersen in the NHS in England.
- 2.3 This MAA includes the following:

- A statement that sets out the clinical criteria for starting and stopping treatment with nusinersen
- A data collection plan to evaluate the performance of nusinersen over the 5 years of the MAA

### **3 Commencement and period of agreement.**

- 3.1 This MAA shall take effect on day July 2019 it will remain in force until the earlier of: (i) publication of a NICE reappraisal of nusinersen; or (ii) the expiry or termination of the MAA. Data collection will be in place for a minimum of three (3) years. For the avoidance of doubt, this MAA shall expire automatically on the 5th anniversary of its term if it has not expired earlier as a result of the publication of the NICE reappraisal of nusinersen. NICE will reissue guidance to the NHS in England based on a review of the data by the end of the fifth year of this MAA. For the purposes of this clause, “**Guidance**” means the guidance expected to be published by the National Institute for Health and Care Excellence in 2019 in relation to the use of nusinersen ID1069.

### **4 Patient eligibility**

- 4.1 Nusinersen’s full marketing authorisation includes the treatment of all patients with 5q SMA. The submission and this draft MAA focuses on a subset of the authorised population, specifically patients with early onset (type I), later onset (types II and III) SMA and presymptomatic patients (patients genetically destined to develop SMA). The proposed population is narrower than the marketing authorisation, which includes all patients with 5q SMA, because the current nusinersen evidence base does not cover type 0 (severe infantile SMA) or type IV (symptom onset in adulthood) SMA patients.

- 4.2 The MAA Oversight Committee will consider any significant new evidence made available by Biogen in relation to the non-ambulant Type III SMA patients that may impact the eligibility criteria of the MAA. This does not commit any stakeholder to making an amendment to the MAA unless justified.
- 4.3 For the purpose of the MAA, type-specific criteria have been introduced for post symptomatic SMA patients - those exhibiting symptoms of SMA prior to nusinersen therapy. Type-specific criteria are based on the minimal motor milestone gained prior to the therapy (aligned with the WHO motor milestones definitions) and don't refer to the age of symptom onset unless they are defining adult onset ambulatory (Type IV):
- Adult onset ambulatory (Type IV). Symptom onset aged 19 or older. The patient takes at least five steps independently in the upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.
  - "Walking unaided" ("ambulant" i.e. type III SMA patient): Symptom onset aged 18 or younger. The patient takes at least five steps independently in the upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.
  - "Sitting without support" ("sitter" i.e. type II SMA): The patient sits up straight with the head erect for at least 10 seconds. The patient does not use arms or hands to balance body or support position.
  - "Not sitting without support" ("Non-Sitter" i.e. type I SMA): The patient cannot sit up straight with the head erect for at least 10 seconds. The patient may use arms or hands to balance body or support position.

4.4 Presymptomatic SMA patient individual is defined as having the homozygous gene deletion or homozygous mutation, or compound heterozygous mutation of the SMN1 gene (Chromosome 5) found via presymptomatic testing of the patient. These patients are genetically destined to develop 5q SMA. Presymptomatic patients would be identified by targeted testing of related individuals (e.g. asymptomatic siblings of diagnosed SMA patients) testing techniques to include identification of SMN2 copy number. In order to be considered eligible for treatment within this MAA, patients should fulfil all criteria of the marketing authorisation, that is homozygous gene deletion or homozygous mutation, or compound heterozygous mutation detected in 5q SMA (including consideration of special warnings) and have 2 SMN2 copies. Immediate access to treatment should be offered with 1 SMN2 copy where Type 0 SMA is not yet apparent. Patients with 2 SMN2 copies will be eligible for treatment. Patients with 3 copies of SMN2 and an older sibling who was diagnosed with type I or II SMA will be eligible for treatment. Patients with 3 copies of SMN2 and who do not have an older sibling who was diagnosed with type I or II SMA will be monitored closely for onset of symptoms. Patients with 4 copies of SMN2 will be monitored closely for onset of symptoms.

4.5 Entry criteria:

All patients entering the MAA must fulfil the following entry criteria (this aligns to Type I, II, III, and presymptomatic):

- No permanent ventilation ( $\geq 16$  hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline;
- Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated;

- Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration of nusinersen;
- Must not have severe contractures which, in the opinion of the treating clinician, prohibit measurement of motor milestones;
- If gained independent ambulation prior to initiation of therapy must still be independently ambulant, with the exception paediatric patients who have lost independent ambulation in the previous 12 months. Independent ambulation is defined as per the WHO definition: patient takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object;
- Must not be type IV SMA patient i.e. must not have **symptom onset** at or after 19 years of age.
- Must not be type 0 SMA patient.

Providing a patient meets the entry criteria as specified above, due to equity considerations there is no upper limit of age on treatment initiation.

4.6 In order to be included as part of this MAA, patients must sign up to the patient agreement as specified in Appendix B. The treating clinician will be required to present the form to the patient and/or parent/guardians and submit this to NHS England.

4.7 Patients currently treated using nusinersen under other funding access mechanisms are eligible for treatment under the MAA providing they meet the stipulated entry criteria and may contribute to data collection efforts. However, they will be analysed separately as outlined in the section on data collection below (Section 5).

- 4.8 Patients currently funded through the EAP that meet the criteria (as outlined above) for the MAA should be transferred to MAA funding.
- 4.9 Patients from the EAP that are ineligible for treatment under the MAA will continue to be funded by Biogen as part of the current EAP mechanism, may contribute to data collection efforts, but will be analysed separately as outlined in the section on data collection below (Section 5).
- 4.10 Patients will become ineligible to participate in the MAA on treatment failure as outlined in the section on Table 2 Appendix D or where patients become non-compliant (failure to receive a maintenance dose without rescheduling).

Patients will not be eligible for nusinersen if any of the following apply:

- 4.10..1 the patient is diagnosed with an additional progressive life-limiting condition where treatment with nusinersen would not provide long- term benefit such as terminal cancer or catastrophic brain injury
- 4.10..2 the patient/family/carer is unwilling to comply with associated monitoring criteria as defined in Appendix D or refuses to sign consent
- 4.11 In all cases, patients will be treated/continue to be treated in line with the published standard of care (Mercuri et al, 2018 and Finkel et al, 2018). Patients/families will be expected to cooperate with treating centres so that the patient receives the standard of care in line with their disease status.

## **5 Data collection**

- 5.1 Data should be collected on all 5q SMA patients regardless of whether they meet the MAA criteria in order to provide comparative

data where possible, though if they fall outside the MAA criteria, their data collection will not be mandated.

5.2 Data collection process comprises of three parts to address uncertainties identified in the evidence base:

- Clinical data collection
- Patient Reported Outcome Measures (PROM) data collection
- Resource utilisation data collection

#### Clinical data collection

5.3 As a minimum of clinical data collection requirement, all fields linked to the NICE appraisal uncertainties and available in the SMA REACH database will be mandated. Please see the recommended data fields to be collected in Appendix E for more details.

5.4 Mandated clinical data should be entered into the SMA REACH Registry, to preserve data integrity, as per Appendix C by the clinical treatment team.

5.5 A minimum of two data entries per patient per year for each mandated field after the initial baseline assessment.

5.6 Any two entries need to be at least 4 months apart. Two data points a year will allow to counteract the outcome variability due to “off” days and acute, reversible illness. The time spacing is designed to coincide with either routine 6 monthly follow up clinic appointments or 4 monthly maintenance doses.

5.7 Though the SMA REACH forms contain a range of fields, only those related to the data uncertainties outlined above would be mandated for collection for pragmatic reasons.



- 5.8 Where possible, the newly diagnosed paediatric population should be prioritised due to inevitable and irreparable motor neuron loss that could be prevented with treatment unless the statistical analysis plan (SAP) states otherwise as per Appendix D.
- 5.9 Failure of the clinical treatment team to adhere to the data collection terms may result in reconsideration of the centre's treatment delivery status.
- 5.10 Adverse event (AE) data collection is not mandated as part of this MAA. Biogen are committed to post-marketing authorisation data collection/pharmacovigilance studies via various other mechanisms.
- 5.11 Clinical endpoints to be evaluated will be determined by patient motor milestones at initiation of therapy and patients age, but will conform to a standard set of top-line variables (more details can be found in Appendix D):
- Survival
  - Ventilation/respiratory events (e.g. infections)
  - Motor function
  - Scoliosis surgery

#### Patient Reported Outcome Measures (PROM) data collection

- 5.12 PROM data collection will focus on collecting data that describe patient's and caregivers' quality of life, physical functioning and other outcomes
- 5.13 Biogen has contracted an academic institution (University of Strathclyde) to define the relevant PROMs and any additional information that should be collected (including the frequency of data collection) for patients receiving nusinersen or their carers to inform commissioning decisions

5.14 As the additional time is required for research approval, identification and defining the appropriate, valid and reliable measures alongside relevant stakeholders (patient advisory groups and clinicians), a time lag of approximately 4 months is anticipated between clinical and PROM data collection

5.15 The tool will aim to capture outcomes important to SMA patients and caregivers that might not be captured with clinical data collection such as quality of life and physical functioning. Domains of a PROM tool could relate (but not limited to) the following fields

- Limitations with mobility / walking
- Inability to undertake daily activities
  - Feeding
  - Washing
  - Self-transfers etc
- Limb / joint weakness
- Pain
- Fatigue
- Bulbar function (breathing difficulties, choking or swallowing)
- Speech and other forms of communication
- Impaired sleep or daytime sleepiness
- Weight over/under gain
- Aspiration frequency
- Gut dysmotility and constipation
- Psychological impact
  - Impaired body image due to disease
  - Decrease performance/ satisfaction in social situations
  - Impact on siblings and family
- Out of pocket expenses

- Loss of earnings and productivity (employment)
- Ability to participate in society – continue education and employment
- Impact on family functioning

#### Resource utilisation data collection

5.16 Resource utilisation data will focus on the use of healthcare resources in terms of patient admissions, medical investigations and therapies, medical equipment and personnel associated with the management of the SMA patients.

5.17 For pragmatic reasons, it is envisaged that resource utilisation data will not be collected through SMA REACH. Instead, it is anticipated that the data will be collected by annual or biannual surveys that will be developed and deployed in collaboration with patient advisory groups and third-party agency.

If a patient meets a stopping rule as per the terms of the MAA, the decision to terminate or continue therapy should be made by the treating clinician. If treatment is terminated, Biogen and NHSE will not provide funding for further treatment or re-initiation of treatment on nusinersen for this patient. Data collection will continue for this patient but will be recorded as part of a separate group (see Appendix D) at the point of meeting the stopping criteria. The clinical treatment team will be responsible for completing an annual treatment continuation form on Blueteq.

NHS England will establish an expert Clinical Panel, whose role will be to provide advice to treating centres on interpretation of the MAA criteria, including: starting and stopping criteria, and diagnosis. The Panel will give advice to treatment centres on the feasibility of safe intrathecal administration of the drug, particularly in light of spinal surgery and taking into account spinal instrumentation. The Panel will also advise NHS England on any potential outliers identified via data collection, i.e. patients who appear to meet stopping criteria. The Panel will report to the MAA Oversight Committee.

**Table 1. Endpoints, assessments and stopping rules**

| ENDPOINT   | PROPOSED ASSESSMENT (more details in Appendix C)   | PROPOSED STOPPING RULE   |
|--|--|--|
| MOTOR FUNCTION   | <p>Current Gross WHO motor milestone, including the appropriate scale as indicated by patient motor ability:</p> <ul style="list-style-type: none"> <li>• HINE</li> <li>• Revised Hammersmith Scale (RHS);</li> <li>• CHOP INTEND;</li> <li>• RULM</li> </ul> <p>A scale will be chosen at initiation of therapy and at base line. Ideally the patient will remain on that scale for the length of the MAA. If this is unfeasible due to change in the patient's clinical status, then a final reading of one scale will be taken at the same time as a baseline for the next reading. The new scale will then be used for the patient's assessment.</p> | <p>Total worsening in scale score corroborated by two consecutive measurements*. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable**</p> <p>&gt;2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp</p> <p>&gt;4 points on the CHOP INTEND scale</p> <p>&gt;3 points on the RHS scale</p> <p>These scores are derived from the minimal clinical indicators of difference.</p> <p>* in order to allow for confirmation of worsening and not an 'off' assessment day</p> <p>**if contractures develop or fracture occurs, then the unmeasurable domain of the scale is removed, and the delta change of remaining domains are scaled up to ensure the total achievable score of the scale remains.</p> |
| VENTILATION REQUIREMENT  | <p>Patients, regardless of initially diagnosed motor milestone state, will be tracked for incidence, length and type of ventilation</p> <p>Rates of pneumonia</p>  | <p>Permanent ventilation (<math>\geq 16</math> hours/day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy.</p>  |
| AMBULATION (IN PAEDIATRIC PATIENTS WHO HAVE LOST AMBULATION IN THE PREVIOUS 12 MONTHS) | <p>Paediatric patients who have lost ambulation in the previous 12 months and who have been initiated on nusinersen, will be assessed for regaining of ambulation within the following 12 months</p>   | <p>Inability to regain ambulation within 12 months of nusinersen initiation</p>  |
| SCOLIOSIS  | <p>Patients, regardless of initially diagnosed motor milestone state, will be assessed for effects of scoliosis and spinal fusion surgery</p>  | <p>Inability to administer nusinersen by intrathecal administration because of spinal fusion surgery</p>   |

|          |   |                                    |
|----------|---|------------------------------------|
| SURVIVAL | Patients, regardless of initially diagnosed motor milestone state, will be assessed for mortality with any cause and for mortality linked to SMA by ICD-10 coding relating to SMA in either death certificate PART I (including a, b and c) (immediate cause of death) or PART II (significant conditions contributing to death) of death certificate | All patients stop due to mortality |
|----------|---|------------------------------------|

Abbreviations: CHOP INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; RHS, Revised Hammersmith Scale; HINE, Hammersmith Infant Neurological Exam; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; RULM, revised upper limb module; SMA spinal muscular atrophy; 6MWT, six minute walk test;

## 6 Ownership of the Data

- 6.1 Patients in England that agree to participate in the MAA will be required to consent to having their demographic and clinical data collected by their treating clinician, see Appendix B for more details.
- 6.2 The treating clinician will be required to enter patients into the SMA REACH registry within 1 month of treatment commencing. Further details on the registry can be found in Appendix B.
- 6.3 The clinical data will be owned by the SMA REACH, but shared by prior agreement with Biogen Idec Ltd., NHS England and NICE. The data use will be governed by data privacy laws. SMA REACH has governance structure to ensure correct use of the information. The data can also be repurposed for other research questions subject to appropriate ethical and legal checks provided these have been consented for by MAA participants.
- 6.4 The SMA REACH will be responsible for the collection and analysis of the data, as per the SAP in Appendix D and commit to providing NHS England and NICE with a yearly update, starting 1 year after the first patient is treated within the MAA, on the clinical effectiveness of nusinersen as based on the MAA data collected. Raw data will also be supplied to NHS England and NICE upon request.

- 6.5 Biogen Idec. Ltd are responsible for ensuring all the MAA patient data in the SMA REACH database is complete and of high quality. Biogen will also provide as a minimum on an annual basis summary data on all patients on nusinersen to the MAA Oversight Committee. Biogen and SMA REACH are to ensure appropriate agreements and contracts are in place to facilitate this data transfer.
- 6.6 It is envisaged that PROM data collection will be matched with and fully accessible by the SMA REACH. The data will be shared by prior agreement with Biogen, NHS England and the NICE.
- 6.7 The resource utilisation data will be stored by the third-party agency that will assist in development and deployment of the survey. Further, the data will be fully accessible by SMA REACH and shared by prior agreement with Biogen, patient advisory groups, NHS England and NICE.
- 6.8 Patients will be matched between SMA REACH, University of Strathclyde and third-party agency via an appropriate pseudo-anonymised mechanism that will be defined. Biogen will be provided with a yearly update of the matched analysis to enable Biogen to compile reports that will be submitted to the NICE to address potential sources of uncertainty within the evidence package for nusinersen.

## **7 Funding**

- 7.1 Treatment for Type I SMA patients provided under this MAA will be funded by NHS England from the issue of the NICE Final Appraisal Document (FAD) to consultees and commentators for ID1069.
- 7.2 Treatment for Type II and Type III SMA patients under this MAA will be funded as soon as individual trusts are able to make services available within 90 days of publication of the NICE guidance ID1069.

7.3 For the avoidance of doubt “**Guidance**” means the guidance expected to be published by the National Institute for Health and Care Excellence in 2019 in relation to the use of nusinersen ID1069.

7.4 The MAH has registered a confidential patient access price with NHS England as detailed in Appendix F.

## **8 Exit strategy**

8.1 If at the termination or expiry of this MAA: (i) NICE does not recommend nusinersen for NHS funding for patients, NHS England funding for nusinersen will cease to be available and treatment will cease (in which case cessation shall be managed between the MAH and NHS England to ensure it is effected in a controlled manner, this will be agreed in collaboration with the MAA Oversight Committee which includes clinicians and patient groups); or (ii) NICE recommends nusinersen for NHS funding, funding from NHS England will not be automatic and will be conditional on the agreement of commercial terms in relation to such funding between NHS England and the MAH.

8.2 The cessation of funding and the conditionality of further funding as specified in clause 8.1 above apply notwithstanding any desire which patients and their NHS clinicians may have for continued treatment with nusinersen. NHS England and the MAH shall use their reasonable endeavours to ensure that any patient being treated with nusinersen which is funded by NHS England under the terms of this MAA is made aware of these funding limitations and accepts them when they sign the ‘Informed Assent Form’ (Appendix B).

## **9 Counterparts**

9.1 This MAA may be executed in any number of counterparts, each of which when executed and delivered shall constitute a duplicate

original, but all the counterparts together shall constitute one agreement.

- 9.2 Transmission of the executed signature page of a counterpart of this MAA by (a) fax or (b) email (in PDF, JPEG or other agreed format) shall take effect as delivery of an executed counterpart of this MAA. If either method of delivery is adopted, without prejudice to the validity of the MAA thus made, each party shall provide the others with the original of such counterpart as soon as reasonably possible thereafter.
- 9.3 No counterpart shall be effective until each party has executed and delivered at least one counterpart.



## Appendix A: List of abbreviations

| Abbreviation | Definition   |
|--------------|--|
| 6MWT         | Six minute walk test   |
| AE           | Adverse event  |
| CHOP-INTEND  | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders                     |
| EAP          | Expanded Access Programme  |
| EMA          | European Medicines Agency  |
| FAD          | Final appraisal document   |
| HINE         | Hammersmith Infant Neurological Exam   |
| ICD-10       | International Statistical Classification of Diseases and Related Health Problems 10th Revision |
| MAA          | Managed access agreement   |
| NICE         | National Institute for Health and Care Excellence  |
| NHS          | National Health Service  |
| RHS          | Revised Hammersmith Scale  |
| RULM         | Revised upper limb module  |
| SAP          | Statistical analysis plan  |
| SMA          | Spinal muscular atrophy  |
| SmPC         | Summary of Product Characteristics   |
| WHO          | World Health Organization  |

## Appendix B: Informed Assent Form

To be signed by patient and/or parent or guardian AND clinician

I understand the conditions of the Managed Access Agreement (including the conditions under which access to nusinersen will stop being provided as part of this agreement) and agree to give my treating clinician permission to enter collected data as specified in the Managed Access Agreement into the SMA Reach registry. I also agree to co-operate with my treating centre to ensure that I/my child receives the standard of care as indicated by the status of my/my child's condition. You may withdraw your consent for your participation, or the participation of your child in the Managed Access Agreement at any time without prejudice. Withdrawal of participation in the Managed Access Agreement will effectively stop access to Spinraza treatment. A patient may inform their physician of their decision to withdraw consent at any time.

**Name of Patient:** \_\_\_\_\_

**Signature of Patient (if over 16):** \_\_\_\_\_

**Date:** \_\_\_\_\_

### **If patient is under 16 without informed assent**

I understand the conditions of the Managed Access Agreement including the conditions under which access to nusinersen will stop being provided as part of this agreement) and agree to give the treating clinician permission to enter collected data as specified in the Managed Access Agreement into the SMA Reach registry. I also agree to co-operate with my treating centre to ensure that I/my child receives the standard of care as indicated by the status of my/my child's condition. You may withdraw your consent for your participation, or the participation of your child in the Managed Access Agreement at any time without prejudice. Withdrawal of participation in the Managed Access Agreement will effectively stop access to Spinraza treatment. A patient may inform their physician of their decision to withdraw consent at any time.

**Name of Parent or Guardian (if patient under 16):** \_\_\_\_\_

**Signature of Parent or Guardian (if patient under 16):** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Name of treating clinician:** \_\_\_\_\_

**Signature of treating clinician:** \_\_\_\_\_

**Date:** \_\_\_\_\_

## Appendix C: Network for data collection

Data collected as per the MAA will be entered by clinicians into the SMA REACH registry hosted on the Certus platform. SMA REACH is a pre-existing disease specific database which collects data from all available SMA patients independent of their treatment regimen.

This registry allows collection of real-world data from routine clinical visits, within a network with transparent governance. It will employ technical solution to enable cross border scientific and epidemiological partnership.

The data is independently owned by the HCP community.

The registry is coordinated by UCL Institute for Child Health.

Current data fields captured cover the majority of fields in the this proposed MAA, except for Quality of life measures. Data fields currently already available include:

- Patient & assessment details
- Molecular genetic diagnosis
- Motor ability based on the WHO criteria and Vignos
- Mobility
- Nutrition
- Scoliosis
- Respiratory
- Musculoskeletal issues
- Following mobility tests (RHS, HFMSE, RULM, 6MWT, HINE, CHOP-INTEND, EK2)

## **Appendix D: Data Collection and Statistical Analysis Plan**

- The purpose of this Statistical Analysis Plan (SAP) is to outline a set of auditable measures that can be used to address potential sources of uncertainty within the evidence package for nusinersen as reviewed by the National Institute for Health and Care Excellence (NICE; ID1069).

### **Patient eligibility and screening**

- After informed consent/assent is obtained, patients will undergo a screening up to 21 days prior to first dose administration, during which their eligibility for the MAA will be determined.
- In order to be considered eligible for treatment within this MAA, patients should fulfil all criteria of the marketing authorisation (including consideration of special warnings); any patients who are currently enrolled as part of the Expanded Access Programme (EAP) are automatically eligible for data collection within the MAA regardless of whether they meet the criteria as outlined in section 4.4.
- For the purpose of the proposed analyses, all SMA patients for whom data has been collected under the MAA will be included either as part of the main analyses or subgroup analyses. Prioritisation should be given to newly diagnosed patients, in line with SMA disease pathophysiology and the progressive motor neuron degradation that may occur. Patients should fulfil all starting criteria. Data collection will only be mandated for collection for data fields that specifically address uncertainties in the NICE assessment of nusinersen and for patients who are receiving funding for access with the MAA.
- Subsets of authorised population for separate and/or additional analysis:
  - Patients who are currently enrolled as part of the EAP who meet MAA criteria
  - Patients who are currently enrolled as part of the EAP who do not meet reimbursement criteria

- Patients currently treated using nusinersen under other funding access mechanisms may not be eligible for treatment under the MAA but may contribute to data collection efforts as outlined in the section on data collection (Section 5). Patients who have been travelling abroad to receive individual treatments can join the MAA so long as they meet the MAA eligibility criteria. Where a patient/family has been residing abroad to receive treatment, they can join the MAA so long as they meet the MAA eligibility criteria and their treating centre confirms that they are eligible for NHS treatment. Patients who have been receiving treatment privately can join the MAA so long as they meet the MAA criteria and their NHS clinician is content that the proposed ongoing NHS treatment is clinically appropriate in light of the privately funded treatment that the patient has received. In all these cases, it is for the patient/family to ensure that there is an appropriate handover between the organisation currently treating the patient and the NHS treating centre in England. In light of the need to prioritise for treatment those patients in whom motor neuron loss can be minimised, it may be necessary for those patients receiving nusinersen under other funding mechanisms to continue to access treatment via these routes until other similar NHS patients are prioritised for treatment.
- Patients who become ineligible to participate in the MAA on discontinuation or where patients become non-compliant (failure to receive a maintenance dose without rescheduling)
- Best supportive care (BSC) patients who are not eligible for nusinersen stratified by the subgroups defined (non-sitters, sitters, ambulatory)

## **Description of objectives and endpoints**

The objectives of these MAA analyses are to evaluate survival, ventilation/respiratory events, motor function, resource utilisation, quality of life

of SMA patients and their caregivers to fill uncertainties in the current data and modelling for incident and prevalent 5q SMA patients after expiration of the MAA.

## Endpoints for assessment

- There are several key endpoints related to the 6 themes ranked as follows:
  - survival
  - ventilation/respiratory events
  - motor function
  - scoliosis
  - PROM/ quality of life (to be developed by the Strathclyde University)
  - resource utilisation (to be developed in collaboration with patient groups).

Full details of assessed endpoints are available below.

### Survival endpoints

- The primary endpoint is time to death or permanent ventilation (tracheostomy or  $\geq 16$  hours ventilation/day continuously for  $>21$  days in the absence of an acute reversible event).
- Secondary survival endpoints include:
  - Survival rate
  - Proportion of patients with cause of death linked to SMA by ICD-10 coding relating to SMA in either death certificate PART I (including a, b and c) (immediate cause of death) or PART II (significant conditions contributing to death) of death certificate and with any other cause not related to SMA as defined above
- All patients stop assessments if death occurs.

### Ventilation or respiratory events

- The primary ventilation endpoint is the proportion of subjects not requiring permanent ventilation. Secondary endpoints include:
  - The number of hours of ventilatory support
  - Type of ventilation

- If old enough and clinically indicated: Forced Vital Capacity sitting or lying and percentage of predicted for patients height / age
- If old enough and clinically indicated: Peak Cough Velocity and % of predicted
- Estimation of hours of ventilation
- The number of respiratory events

#### Motor milestones

- For patients initially diagnosed as non-sitters, the primary endpoint is the achievement of motor milestones. Motor milestones should be assessed for all patients using the World Health Organization (WHO) Motor Milestones criteria at screening and on each subsequent visit for a maintenance dose of nusinersen (i.e. once every 4 months).
- For SMA patients initially diagnosed as non-sitters secondary endpoints will be assessed as follows:
- For patients <2 years of age who have not yet achieved independent walking, motor milestones will also be assessed using Section 2 of the Hammersmith Infant Neurological Examination (HINE) and CHOP INTEND.
  - Proportion of patients who achieved standing alone
  - Proportion of patients who achieved walking with assistance
  - Change from baseline for the following:
    - HINE in infants;
    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND);
- For SMA patients initially diagnosed as sitters or ambulatory, the change in motor milestones is the primary endpoint. Motor milestones should be assessed for all patients using the World Health Organization (WHO) Motor Milestones criteria at screening and on each subsequent visit for a maintenance dose of nusinersen (i.e. once every 4 months).



- For SMA patients initially diagnosed as sitters or ambulatory, secondary endpoints should include change from baseline for the following:
  - RHS (which includes the timed 10-meter walk test which could be used as proxy for more standard 6 minute walk test);
    - Additionally, proportion of subjects who achieve a 3-point increase from baseline RHS score.
  - Revised upper limb module RULM.
- Definition of baseline will be the last non-missing assessment prior to the first dose of nusinersen treatment within the MAA.

### Scoliosis

- Patients, regardless of initially diagnosed motor milestone state, will be assessed for effects of therapy on scoliosis progression and need for spinal fusion surgery.

Table 2 presents additional information about the clinical endpoints.

**Table 2. Clinical endpoints, assessments and stopping rules**

| Endpoint                                  |   | Proposed stopping rule   |
|---|---|--|
| <b>Ventilation or respiratory events</b>  |   |  |
| Ventilator use incidence, length and type | Ventilator use incidence, length and type should be recorded. | Permanent ventilation ( $\geq 16$ hours/day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy. |
| <b>Motor milestones</b>                   |   |  |

|  |   |  |
|--|---|--|
| <p>Proportion of motor milestone responders HINE</p> | <p>For patients &lt;2 years of age who have not yet achieved independent walking, motor milestones will also be assessed using Section 2 of the Hammersmith Infant Neurological Examination (HINE) and the CHOP INTEND. The proportion of motor milestone responders, assessed by Section 2 of the HINE.</p> <p>A 'motor milestones responder' is 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.</p> <p>HINE is composed of 8 motor milestone categories as follows: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each motor milestone category, there are 3-5 levels that can be achieved. All 8 motor milestones will be tested during each assessment. A patient whose results after testing all appear in the first column (no grasp, no kicking, unable to maintain head upright, and so on) has not achieved any motor milestone. Motor milestone achievement is depicted by movement from the left side to the right side of Table 3 as denoted by the Milestone Level Progression arrow in the table (3).</p> | <p>Total worsening in scale score corroborated by two consecutive measurements*. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable**</p> <p>&gt;2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp</p> <p>* in order to allow for confirmation of worsening and not an 'off' assessment day</p> <p>**if contractures develop or fracture occurs, then the unmeasurable domain of the scale is removed, and the delta change of remaining domains are scaled up to ensure the total achievable score of the scale remains.</p> |
| <p>CHOP INTEND</p>                                   | <p>For patients &lt;2 years of age who have not yet achieved independent walking, motor milestones will also be assessed using Section 2 of the Hammersmith Infant Neurological Examination (HINE) and the CHOP INTEND. Patients who are ≥2 years of age but have not yet achieved the maximum score of 64 with CHOP INTEND will be assessed with both until a CHOP INTEND maximum score of 64 is achieved. The RHS should be performed after the CHOP INTEND with an approximately 15-minute rest period in between to allow the patient to be fully engaged with both assessments. The CHOP INTEND is an infant motor function comprised of 16 test items, nine of which are scored 0, 1, 2, 3, or 4 with greater scores indicating greater muscle strength, five are scored as 0, 2, or 4, one is scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4.</p>   | <p>Total worsening in scale score corroborated by two consecutive measurements*. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable**</p> <p>&gt;4 points on the CHOP INTEND scale</p> <p>* in order to allow for confirmation of worsening and not an 'off' assessment day</p>   |

|      |  |   |
|------|--|---|
|      | <p>CHOP INTEND should be assessed in patients with early-onset SMA until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND should no longer be assessed. The CHOP INTEND test was specifically designed to evaluate the motor skills of infants with significant motor weakness, including infants with SMA.(2) The CHOP INTEND test captures neck, trunk, and proximal and distal limb strength in 14 elicited and 2 observational items. The CHOP INTEND has been established as a safe and reliable infant motor measure in early-onset SMA and has been validated.(3)</p>   | <p>**if contractures develop or fracture occurs, then the unmeasurable domain of the scale is removed, and the delta change of remaining domains are scaled up to ensure the total achievable score of the scale remains.</p>   |
| RHS  | <p>All patients <math>\geq 2</math> years of age will be evaluated using the RHS for the duration of the MAA. Patients who are <math>\geq 2</math> years of age but have not yet achieved the maximum score of 64 with CHOP INTEND will be assessed with both until a CHOP INTEND maximum score of 64 is achieved. The RHS should be performed after the CHOP INTEND with an approximately 15-minute rest period in between to allow the patient to be fully engaged with both assessments. The Revised Hammersmith Scale (RHS) for SMA,(4) consists of 36 items and two timed tests, was piloted in 138 patients with type 2 and 3 SMA in an observational cross-sectional multi-centre study across the three national networks. Rasch analysis demonstrated very good fit of all 36 items to the construct of motor performance, good reliability with a high Person Separation Index PSI 0.98, logical and hierarchical scoring in 27/36 items and excellent targeting with minimal ceiling. The RHS differentiated between clinically different groups: SMA type, World Health Organisation (WHO) categories, ambulatory status, and SMA type combined with ambulatory status (all <math>p &lt; 0.001</math>). Construct and concurrent validity was also confirmed with a strong significant positive correlation with the WHO motor milestones <math>r_s = 0.860</math>, <math>p &lt; 0.001</math>.</p> | <p>Total worsening in scale score corroborated by two consecutive measurements*. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable**</p> <p><math>&gt;3</math> points on the RHS scale</p> <p>These scores are derived from the minimal clinical indicators of difference.</p> <p>* in order to allow for confirmation of worsening and not an 'off' assessment day</p> <p>**if contractures develop or fracture occurs, then the unmeasurable domain of the scale is removed, and the delta change of remaining domains are scaled up to ensure the total achievable score of the scale remains.</p> |
| RULM | <p>All non-ambulatory patients <math>\geq 30</math> months of age will be evaluated using the RULM.(5) The RULM will continue to be performed should patients subsequently become ambulatory. The RULM is an outcome measure developed to assess upper limb functional abilities in patients with SMA,</p>   | <p>None</p>   |

|  |  |  |
|--|--|--|
|  | <p>including young children, and patients with severe contractures in the lower limbs in whom the possibility to detect functional changes, such as rolling or long sitting, is limited. This test consists of upper limb performance items that are reflective of activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container). The RULM is quickly administered and has been evaluated in patients with SMA 2-52 years of age.(5) The purpose of an upper limb scale for use in SMA is to assess change that occurs in motor performance of the upper limb over time. Motor performance in SMA is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be impacted by muscle strength, contractures, and maturational development (puberty), and the RULM aims to incorporate performance of the shoulder, elbow, wrist, and hand.</p> |  |
|--|--|--|

Abbreviations: CHOP INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Exam; MAA, managed access agreement; RHS, Revised Hammersmith Scale; RULM, revised upper limb module; SMA spinal muscular atrophy

## Statistical analysis

This section contains the proposed statistical analysis based on the collected data.

### Demographic and baseline data

- Demographic and baseline characteristics (demography, medical history, SMA history, and baseline disease characteristics) will be summarised using descriptive statistics. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables and counts and percentages for categorical variables will be used to summarise the data. All patients enrolled will be included in a summary of patient disposition.
- Demographic and baseline disease characteristics will be presented for the subset populations (as defined before) as appropriate.

### Analyses of endpoints

- These outcomes are being calculated to provide a description of the real-world picture, and to evaluate the relationship between ventilation, respiratory function and motor milestones using regression analyses.
- The median time and associated 95% confidence limits to death or permanent ventilation, survival rates over time, and the percentage of patients requiring permanent ventilation will be estimated using the Kaplan-Meier method.
- Proportions of motor milestones responders will be compared. The definition of a motor milestones responder is based on the motor milestones categories in Section 2 of the HINE with the exclusion of voluntary grasp using assessment as described in Table 3.

- Analysis of additional subgroups (EAP patients, patients treated under other function mechanisms and patients who become ineligible to participate) will be analysed separately using the same appropriate endpoints as the main population included for resubmission. BSC patients who are not eligible for nusinersen will form a comparative cohort for the main cohort of nusinersen patients but will need to be risk adjusted to allow for a comparison (if possible).

**Table 3. Hammersmith Infant Neurological Examination Section 2 - Motor Milestones**

| Motor Milestone Category    | Milestone Level Progression<br>(Age Expected in Healthy Infants) <sup>a</sup> |                                     |                                      |                                     |                                |
|-----------------------------|---|-------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|
|                             | —————→  |                                     |                                      |                                     |                                |
| Voluntary grasp             | No grasp  | Uses whole hand                     | Finger and thumb; immature grasp     | Pincer grasp                        |                                |
| Ability to kick (in supine) | No kicking  | Kicks horizontal; legs do not lift  | Upward (vertically) [3 months]       | Touches leg (4 to 5 months)         | Touches toes (5 to 6 months)   |
| Head control                | Unable to maintain upright (<3 months)  | Wobbles (4 months)                  | All the time upright (5 months)      |                                     |                                |
| Rolling                     | No rolling  | Rolling to side (4 months)          | Prone to supine (6 months)           | Supine to prone (7 months)          |                                |
| Sitting                     | Cannot sit  | Sit with support at hips (4 months) | Props (6 months)                     | Stable sit (7 months)               | Pivots (rotates) [10 months]   |
| Crawling                    | Does not lift head  | On elbow (3 months)                 | On outstretched hand (4 to 5 months) | Crawling flat on abdomen (8 months) | On hands and knees (10 months) |
| Standing                    | Does not support weight   | Supports weight (4 to 5 months)     | Stands with support (8 months)       | Stands unaided (12 months)          |                                |
| Walking                     | No walking  | Bouncing (6 months)                 | Cruising (holding on) [11 months]    | Walking independently (15 months)   |                                |

Source: Haataja 1999(10)

- To illustrate the responder definition, some examples are considered. In all the examples below, it is assumed that there are no changes in other motor milestones categories.
  - A subject with a 2-point increase of ability to kick, a 1-point increase in rolling, and a 1 point decrease in head control is a responder.
  - A subject with a 1-point increase of ability to kick from “touches legs” to “touches toes” is a responder.
  - A subject with a 1-point increase of rolling and a 1-point decrease of ability to kick from “kicks horizontal, legs do not lift” to “no kicking” is a non-responder.
  - A subject with a 2-point increase of voluntary grasp is a non-responder.
- The remaining endpoints will be summarised using descriptive statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables and counts and percentages for categorical variables.

#### Distributional issues

- Diagnostic plots will be used to assess the severity of deviations from normality. Where necessary, log-transformations will be used. Results will be assessed as estimates with 95% confidence intervals, using bootstrapping with bias correction and acceleration where non-parametric methods are needed.

#### Procedure for minimising missing data

- Prior to analysis data will be checked for outliers and missing data. These will be dealt with either by deletion or correction as deemed appropriate. Extreme, but plausible values will be kept; but impossible values will be deleted. For the purpose of the main analysis we will make the assumption that missing data is missing at random; these assumptions will then be tested using appropriate sensitivity analyses on observed data using complete cases analysis.

## Software for analysis

- The software to conduct the analyses as described will be Microsoft Excel or other software if appropriate. Analyses will be carried out within 3 months of receiving the data from the registry. For instance, if data is submitted to Biogen on the 5th of January, then analyses will be concluded by the 5th of April, 3 months thereafter and shared with NHS England.

## General considerations

- The sample size is solely based on the number of patients enrolling in nusinersen treatment under the MAA as per the criteria outlined earlier.
- The analyses consist of all patients enrolled as part of the MAA.

## Additional analyses using other subset of patients

- The same analyses will be undertaken for subsets of patients, this data could also be used for re-appraisal.
  - Patients who are currently enrolled as part of the EAP
  - Patients currently treated using nusinersen under other funding access mechanisms who are not eligible for treatment under the MAA may contribute to data collection efforts.
  - Patients who become ineligible to participate in the MAA on discontinuation or where patients become non-compliant (failure to receive a maintenance dose without rescheduling) or have unforeseen worsening of disease not captured in the criteria laid out. These patients will be included in the resubmission until they fail under the conditions laid out above, at which point they will be analysed as a separate group.
  - BSC patients who are not eligible for nusinersen
- Interim analyses may be performed to provide content for reimbursement submissions, to support Biogen activities or when requested by NHS England or NICE.



- Patients who die or withdraw from the MAA will be counted as non-responders and will be included in the denominator for the calculation of the proportion for all endpoints. As a result, mortality will be accounted for in the analyses.

## Appendix E: Recommend fields to be mandated in the SMA REACH Case Report Form.

**Table 4. Mapping outcomes to the SMA REACH forms**

| Outcome  | Mapping to SMA reach forms  |
|--|---|
| survival from MF                                   | <ul style="list-style-type: none"> <li>• mortality</li> <li>• cause of death</li> </ul>   |
| ventilation / respiratory events (e.g. infections) | <ul style="list-style-type: none"> <li>• if compliant and clinically indicated: forced vital capacity sitting or lying and percentage of predicted for patients height / age (FSW AND FUM)</li> <li>• if compliant and clinically indicated: peak cough velocity and % of predicted (FSW AND FUM)</li> <li>• type of ventilation used (IE NIV, tracheostomy) (FUM)</li> <li>• estimation of hours of ventilation (FUM)</li> <li>• number of chest infections per annum (FUM)</li> </ul> |
| motor function: From FSW                           | <ul style="list-style-type: none"> <li>• RHS</li> <li>• WHO MOTOR SCALE</li> <li>• RULM</li> <li>• HINE</li> <li>• CHOP-INTEND</li> <li>• summary of contractures</li> </ul>  |
| scoliosis  | <ul style="list-style-type: none"> <li>• presence of scoliosis, Cobb angle in and out of TLSO, date of spinal surgery, spinal surgery with growing rods (PLUS AGE), spinal fusion (PLUS AGE) and use of TLSO. (FUM)</li> </ul>  |
| fractures  | <ul style="list-style-type: none"> <li>• yes/no (FUM)</li> </ul>  |
| nusinersen   | <ul style="list-style-type: none"> <li>• use, first dose, parental perceived benefit, dose given under, combination therapy, with which other therapy (FUM)</li> </ul>  |
| resource use                                       | <ul style="list-style-type: none"> <li>• nasogastric tube use (FUM)</li> <li>• gastrostomy placement (FUM)</li> </ul>   |

KEY: FUM follow up medical Case report form, FSW functional scale worksheet. MF manual follow up; TLSO, Thoracicolumbar sacral orthosis