CONTRACT VARIATION AGREEMENT No.2

Contract/Variation Reference: NHS England, Biogen, Spinal Muscular Atrophy UK, TreatSMA, Muscular Dystrophy UK, SMA REACH UK and NICE entered into a managed access agreement dated 3 July 2019, and varied on 18 May 2021, relating to the agreed terms and conditions according to which patients will be entitled to access the drug called nusinersen (Spinraza®) for treatment for 5q Spinal Muscular Atrophy (SMA) NICE TA588 (the "**MAA**").

Contract documentation and documents relied upon	
MAA	Signed: 3 July 2019
MAA Contract Variation Agreement No.1	Dated: 18 May 2021
Relevant guidance ("Guidance")	
Nusinersen for treating spinal muscular atrophy Technology appraisal guidance (TA588)	24 July 2019

Date of this Variation Agreement: 16 January 2022

This variation agreement relates to the variation of the MAA as set out below (the "Variation Agreement No.2").

Capitalised words and phrases in this Variation Agreement No.2 have the meanings given to them in the MAA.

1. In consideration of their respective obligations under the MAA (as varied by this Variation Agreement No.2) the Parties have agreed to the following variation to the MAA:

    1.1. The following paragraph shall be deleted in its entirety from clause 4.4:

        4.4 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.

    1.2. The following wording in bold will be amended in clause 4.4:

        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 1-4 SMN2 copies.**

1.3. Clause 4.5 shall be deleted in its entirety and replaced with:

Entry criteria

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

- Patient has a confirmed genetic diagnosis of 5q autosomal recessive SMA and meets one of the following criteria:
    - Has SMA type 1, 2, or 3.
    - Pre-symptomatic of SMA and has one to four SMN2 copies.
- Nusinersen is used as a monotherapy.
- Must not have had successful treatment with onasemnogene abeparvovec. Non-successful treatment is defined in appendix F.
- No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline. Patients who do not meet this criterion but otherwise meet the eligibility criteria should be discussed with the NHS England Clinical Panel.
- 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.

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

1.4. Table 1. Endpoints, assessments and stopping rules on page 12 will be deleted in its entirety and replaced with:

MAA Table 1. Endpoints, assessments and stopping rules

ENDPOINT	PROPOSED ASSESSMENT (more details in Appendix C)	STOPPING CRITERIA
MOTOR FUNCTION	Current Gross WHO motor milestone, including the appropriate scale as indicated by patient motor ability • HINE • RHS; • CHOP INTEND; • RULM Scale(s) will be chosen at baseline (prior to the initiation of therapy) based on the patient's motor function ability. Ideally the patient will remain on 1 scale for the length of the MAA however it is recognised that in some cases it is appropriate to capture a range of assessments and functional abilities (e.g. in type III ambulant patients). In the case of a 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 assessments.	**Where 1 scale has been measured from baseline**: 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** >2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp >4 points on the CHOP INTEND scale >3 points on the RHS scale These scores are derived from the minimal clinical indicators of difference. **Where 2 (or more) scales have been measured from baseline:** total worsening in scale score(s) in the absence of any stability or improvement in other scales corroborated by two consecutive measurements*. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable** . For example, if a patient deteriorates on one scale (e.g. loses >3 points on the RHS scale) but maintains stability or demonstrates

		improvement on another scale that has been measured since baseline (e.g. RULM), **AND** in the opinion of the treating clinician the patient continues to receive clinical benefit from treatment then continuation of treatment may be considered. **These cases should be discussed with the NHS England Clinical Panel.** * in order to allow for confirmation of worsening and not an 'off' assessment day **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.
VENTILATION REQUIREMENT	Patients, regardless of initially diagnosed motor milestone state, will be tracked for incidence, length and type of ventilation Rates of pneumonia	Permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy. **Patients who meet this criterion should be discussed with the NHS England Clinical Panel.**
SCOLIOSIS	Patients, regardless of initially diagnosed motor milestone state, will be assessed for effects of scoliosis and spinal fusion surgery	Inability to administer nusinersen by intrathecal administration because of spinal fusion surgery
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;

2. All other definitions terms and conditions contained in the MAA shall continue to apply in full force and effect.

3. The variations set out in this Variation Agreement No.2 take effect on 16 January 2022.

IN WITNESS OF WHICH the Parties have signed this Variation Agreement No.2 on the date(s) shown below

NHS England John Stewart	…….. Signature …… Title …… Date
Biogen Jonathan Randell	…….. Signature …… Title …… Date
Clinical Lead **(SMA REACH UK)** Francesco Muntoni	…….. Signature …… Title …… Date
Patient Organisation(s)	

Spinal Muscular Atrophy UK Liz Ryburn **TreatSMA** Dr Gennadiy Ilyashenko **Muscular Dystrophy UK** Kate Adcock	…….. Signature …… Title …… Date …….. …….. Signature …… Title …… Date …….. Signature …… Title …… Date
NICE Brad Groves	…….. Signature …… Title …… Date

APPENDIX F
USING OTHER DISEASE-MODIFYING MEDICINES FOR SPINAL MUSCULAR ATROPHY (SMA) AFTER ONASEMNOGENE ABEPARVOVEC TREATMENT

Group 1: children who have had onasemnogene abeparvovec only and have not previously been treated with other disease-modifying medicines for SMA

Group 2: children who have had onasemnogene abeparvovec and who have had previous treatment with other disease-modifying medicines for SMA

Children in these two groups can only access other medicines for SMA within the NHS if treatment with onasemnogene abeparvovec is not successful, as defined below AND following advice from the NHS England Clinical Panel.

The role of the NHS England Clinical Panel is to provide expert advice to treatment centres about individual patients in respect of the Starting and Stopping Criteria. It is for individual treatment centres to take decisions about individual patients.

The eligibility criteria of nusinersen and risdiplam will include, or be amended to, the following:
Starting criteria:

- Must not have had successful treatment with onasemnogene abeparvovec.

Stopping criteria:

- Has successful treatment with onasemnogene abeparvovec.

All other eligibility criteria for the corresponding treatment will apply.

Non-successful treatment with onasemnogene abeparvovec is defined as per the criteria below.

Definition of non-success of onasemnogene abeparvovec

(a) **A reduction in motor ability**, defined as:

Total worsening in scale score corroborated by two consecutive measurements from any two of the following three scales:

- >2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp
- >4 points on the CHOP INTEND scale
- >3 points on the RHS scale

A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable. These scores are derived from the minimal clinical indicators of difference. For example, if a patient deteriorates on one scale (e.g. loses >3 points on the RHS scale) but maintains stability or demonstrates improvement on another scale that has been measured since baseline (e.g. RULM), the patient's treatment with onasemnogene abeparvovec would be considered to be successful. A treating clinician must refer any case to the NHS England Clinical Panel for advice on non-success in respect of deterioration in scale scores.

AND/OR

(b) **A deterioration in respiratory function**, defined as an increasing requirement for respiratory support overnight and/or, for that patient, an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease.