CONTRACT VARIATION AGREEMENT No.1

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 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
Relevant guidance ("Guidance")	
Nusinersen for treating spinal muscular atrophy Technology appraisal guidance (TA588)	24 July 2019

Date of this Variation Agreement: 18 May 2021

This variation agreement relates to the variation of the MAA as set out below (the "Variation Agreement No.1").

Capitalised words and phrases in this Variation Agreement No.1 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.1) the Parties have agreed to the following variation to the MAA:

   1.1. The following clause will be deleted in its entirety:

   > 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.

   1.2. The following clause will be deleted in its entirety:

   > 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.

1.3. The following bullet point shall be deleted in its entirety from clause 4.5:

- 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;

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 RULE
MOTOR FUNCTION	Current Gross WHO motor milestone, including the appropriate scale as indicated by patient motor ability • HINE	**Where 1 scale has been measured from baseline**: total worsening in scale score corroborated by two consecutive measurements*. A scaled equivalent of these losses

	• Revised Hammersmith Scale (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.	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 with nusinersen 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	Permanent ventilation (≥16 hours/day for 21 consecutive days in

	state, will be tracked for incidence, length and type of ventilation Rates of pneumonia	the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy.
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.1 take effect on 18 May 2021

IN WITNESS OF WHICH the Parties have signed this Variation Agreement No.1 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	…….. Signature …… Title

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