Managed Access Agreement

Onasemnogene abeparvovec for pre-symptomatic 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene [ID1473]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Data Collection Arrangement

Onasemnogene abeparvovec for treating spinal muscular atrophy [ID1473]

Company name: Novartis Gene therapies

Primary source of data collection: Ongoing SPR1NT trial [NCT03505099]

Secondary source of data collection: Routinely collected clinical data in England, including patient baseline characteristics.

NICE Agreement Manager	Brad Groves
NHS England and NHS Improvement Agreement Manager	Fiona Marley
Novartis Gene Therapies Agreement Manager	Samantha Martin

1 Purpose of data collection arrangement

1.1 The NICE Highly Specialised Technologies (HST) committee has made a recommendation for onasemnogene abeparvovec as an option for treating pre-symptomatic 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene within the context of a Managed Access Agreement (MAA) [ID1473] (to be updated with Highly Specialised Technologies (HST) number after final guidance has been published).

1.2 The purpose of this agreement is to describe the uncertainties identified by the NICE HST committee, patient eligibility criteria, and the arrangements and responsibilities for further data collection intended to capture the data that may address these uncertainties.

2 Commencement and period of agreement

2.1 This Data Collection Agreement (DCA) shall take effect at the point that the NHS England and NHS Improvement begin funding onasemnogene abeparvovec or on publication of the MAA, whichever is earlier. This Data Collection Agreement took effect on (to be updated with date after final guidance has been published).

2.2 Estimated dates for data collection, reporting and submission for NICE guidance review are:

End of data collection (SPR1NT Trial: primary source)	SPR1NT Cohort 1: [redacted] (anticipated study database lock) SPR1NT Cohort 2: [redacted] (anticipated study database lock)
Data available for development of company submission	[redacted]
Anticipated company submission to NICE for guidance review	July 2022

2.3 Novartis Gene Therapies anticipate the additional data collected during the DCA period will be incorporated into an evidence submission and the new economic model by July 2022.

2.4 Novartis Gene Therapies acknowledge their responsibility to adhere as closely as possible to the timelines presented in the document.

2.5 The scope of the NICE guidance review for this topic will cover the population recommended for managed access as part of the NICE guidance for onasemnogene abeparvovec, that is, people with pre-symptomatic 5q

spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

2.6 NICE will, as far as is practicable, develop the scope and schedule a review into the HST work programme to align with the estimated dates for the end of data collection. Other than the clauses specified within this document the review will use the NICE process and methods in place at the time of the invitation to participate. For further details of the expected timelines for the NICE guidance review see the technology appraisal process guide.

2.7 The company is responsible for paying all associated charges for a full guidance review. Further information is available on the NICE website.

2.8 The company must inform NICE and NHS England and NHS Improvement of any anticipated changes to the estimated dates for data collection at the earliest opportunity.

2.9 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHS England and NHS Improvement.

2.10 If data collection is anticipated to conclude earlier than the estimated dates for data collection, for example due to earlier than anticipated reporting of an ongoing clinical trial, the company should note:

- Where capacity allows, NICE will explore options to reschedule the guidance review date to align with the earlier reporting timelines.
- It may be necessary to amend the content of the final real-world data report (for example if planned outputs will no longer provide meaningful data).

2.11 If data collection from the primary data source is anticipated to conclude later than the estimated dates for data collection, the company should note:

- The company must submit a written request to NICE and NHS England and NHS Improvement, with details of the extension requested, including an explanation of the factors contributing to the request.
- It may be necessary for the company to mitigate the impact of any delay, and reduce any risks of further delays.

2.12 NICE and NHS England and NHS Improvement may consider the data collection agreement no longer valid, and withdraw the technology from the MAA for the following, non-exhaustive, grounds:

- The primary sources of data are delayed, without reasonable justification.
- The primary sources of data are unlikely to report outcome data that could resolve the uncertainties identified by the technology appraisal committee.
- Amendments are made to the marketing authorisation that affect the patient population covered by this MAA.

3 Patient eligibility

3.1 Key patient eligibility criteria for the use of onasemnogene abeparvovec for pre-symptomatic SMA during the period covered by the MAA include:

- patient has a confirmed genetic diagnosis of 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and up to 3 (three) copies of the SMN2 gene,
- patient does not display any clinical manifestations that are strongly suggestive of SMA,
- patient has not received any prior treatment with nusinersen or risdiplam,

- patient has confirmed anti-adeno-associated virus 9 (anti-AAV9) antibody titres below 1:50,
- onasemnogene abeparvovec will be otherwise used as set out in its Summary of Product Characteristics (SmPC).

3.2 The estimated patient numbers per year in England for this technology within the MAA period are:

As estimated by the company	• Current practice: Approximately 2 per year (sibling identified) • Up to 4 per year (should a newborn screening pilot be implemented) • Up to approximately 48 per year if a national newborn screening programme is introduced
As estimated by NICE Resource Impact Assessment team	• Current practice: Approximately 2 per year (sibling identified) • Up to approximately 50 per year if a national newborn screening programme is introduced

4 Area(s) of clinical uncertainty

4.1 The NICE HST committee concluded the key uncertainty relates to the robustness of the economic modelling for pre-symptomatic SMA with up to 3 copies of SMN2. The current company model assumes that everyone with pre-symptomatic SMA and up to 3 copies of the SMN 2 gene would develop type 1 SMA, whereas a substantial proportion of this population would be expected to develop other types of SMA. It considered a different model

structure would be needed to demonstrate cost-effectiveness in all relevant SMA types that can arise from infants with a genotype of up to three copies of the SMN2 gene (i.e. SMA type 1, SMA type 2 and SMA type 3).

4.2 The committee were aware that there are likely to be uncertainties that are not expected to be addressed by using data from the SPR1NT trial, such as generalisability of trial evidence to NHS clinical practice. However, the committee considered that it is currently unlikely that data that would address these uncertainties could be collected within a reasonable timeframe and any additional data collection would be burdensome for patients and clinicians.

4.3 The committee considered that evidence of people's experience having used onasemnogene abeparvovec will be very important at the point of guidance review. The committee did not consider it was necessary to mandate that this data be collected as part of the managed access, as they were mindful of the burden this could place on all stakeholders and were aware that Patient and Clinical experts will have the opportunity to submit these qualitative data during a guidance review.

4.4 The committee concluded that further data collection within a MAA could sufficiently resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Evaluation Document.

5 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	o Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 ("the SPR1NT Trial") [NCT03505099]

Secondary sources	o Routinely collected clinical data in England, including patient baseline characteristics.

Description of sources

5.1 Sources of data that could resolve the key uncertainties identified by the evaluation committee include:

- SPR1NT trial [NCT03505099]: SPR1NT is an ongoing Phase III, open-label, single-arm, single-dose, global, multicentre study of onasemnogene abeparvovec in pre-symptomatic infants with genetically diagnosed SMA with two or three copies of the SMN2 gene. After the study follow-up period (18 or 24 months of age), eligible patients have the option to enter the long-term follow-up study (LT-002). Enrollment is completed and there are two patient cohorts:
  - Cohort 1: infants with two copies of SMN2 (n=14), followed up to 18 months of age
  - Cohort 2: infants with three copies of SMN2 (n=15), followed up to 24 months of age

5.2 Data will be collected routinely from all patients who receive treatment with onasemnogene abeparvovec during the term of this MAA through the Blueteq system.

5.3 NHS England and NHS Improvement's Blueteq system is used to approve applications for high cost drugs in England. NHS England and NHS Improvement will be able to share Blueteq data for the purposes of a NICE guidance review, subject to data sharing agreements between NHS England and NHS Improvement and parties to this agreement.

6 Outcome data

Clinical trial

6.1 The outcome data that will be collected as part of the SPR1NT trial include:

Cohort 1: Infants with two copies of the SMN2 gene

Primary efficacy:

- Proportion of patients achieving the ability of functional independent sitting for at least 30 seconds up to 18 months of age

Secondary efficacy:

- Proportion of patients that have survived and have not required permanent ventilation in the absence of acute illness and perioperatively, assessed at 14 months of age. Permanent ventilation is defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation

- Proportion of patients that have achieved the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age

Cohort 2: Infants with three copies of the SMN2 gene

Primary efficacy:

- Proportion of patients achieving the ability to stand without support for at least 3 seconds up to 24 months of age

Secondary efficacy:

- Proportion of patients demonstrating the ability to walk alone defined as the ability to take at least five steps independently displaying coordination and balance at any visit up to 24 months of age

A number of exploratory efficacy endpoints will be collected across both cohorts including: Achievement of motor milestones as assessed by WHO Multicentre Growth Reference Study criteria at any visit up to 18 months of age (Cohort 1) and up to 24 months of age (Cohort 2), time to respiratory intervention, requirement for respiratory intervention at 18 months of age (Cohort 1) and at 24 months of age (Cohort 2), achievement of a CHOP-INTEND motor function scale score of ≥40, >50 and ≥58 at any visit up to 18 months of age (Cohort 1) and the proportion of patients achieving an improvement over baseline of ≥15 points on the Bayley Gross and Fine Motor Subsets (raw score) at any visit up to 18 months of age (Cohort 1) and up to 24 months of age (Cohort 2). This list of exploratory efficacy endpoints is non-exhaustive. In addition, across both cohorts safety data including of adverse events (AEs) and/or serious AEs and change from baseline in clinical laboratory parameters will be collected.

The completed SPR1NT trial will provide clinical effectiveness data for several patient-relevant outcomes, including the attainment of motor milestones and event [permanent-assisted ventilation]-free survival, for up to 18 months and 24 months of age for infants with SMA treated pre-symptomatically with two (Cohort 1) or three copies (Cohort 2) of the SMN2 gene, respectively. Such data are critical for informing an economic model for assessing the cost-effectiveness of onasemnogene abeparvovec versus best supportive care for infants with SMA treated pre-symptomatically and up to three copies of the SMN2 gene. Furthermore, it should be noted after the SPR1NT study follow-up period (18 or 24

months of age), eligible patients may enter the long-term extension trial (LT-002), which will monitor patients for up to 15 years.

Data collection in clinical practice

6.2 NHS England and NHS Improvement's Blueteq system will collect the following anonymised outcomes for the population covered by the MAA

- Number of applications to start treatment,
- Baseline patient characteristics, including gender, age, date of diagnosis, and SMN2 copy number.

7 Data analysis plan

Clinical trials

7.1 The final analyses will follow the analysis plan outlined in the trial protocol, with further details provided in the supporting statistical analysis plan. The primary efficacy analysis for each SMN2 copy number cohort will be completed separately at such time that enrollment in the respective cohort is complete and the last patient has completed the end of study (EOS) visit at the respective age: Cohort 1 (two copies of SMN2*)* EOS = 18 months of age and Cohort 2 (three copies of SMN2*)* EOS = 24 months of age. Statistical Analysis populations include: Intent-to-Treat Population (ITT), Efficacy Completers Population, All Enrolled Population and Safety Population. Patients with SMN1 point mutations or the SMN2 gene modifier mutation (c.859G>C) will be evaluated separately as part of additional subgroup analyses. The primary efficacy endpoint analysis for each cohort is as follows:

Cohort 1: Infants with two copies of the SMN2 gene

The proportion of patients who exhibit the motor milestone achievement of sitting without support for at least 30 seconds up to 18 months of age will be

summarised for the ITT population (bi-allelic SMN1 deletion, SMN2 copy number of two without the SMN2 gene modifier mutation [c.859G>C]). A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025.

Cohort 2: Infants with three copies of the SMN2 gene

The proportion of patients who achieve the ability to stand without support for at least three seconds up to 24 months of age for the ITT population (bi-allelic SMN1 deletion, SMN2 copy number of three without the SMN2 gene modifier mutation [c.859G>C]) will be compared with the natural history data of the matching cohort (Pediatric Neuromuscular Clinical Research Network [PNCR]), using a two sample 2-sided superiority Fisher exact test with a significance level of 0.05.

7.2 No formal interim analyses from SPR1NT will become available during the data collection period.

7.3 The anticipated dates for the database locks will occur in [redacted] for Cohort 1 and in [redacted] for Cohort 2. The different dates are due to the different follow-up periods of each cohort: 18 months of age (Cohort 1) and 24 months of age (Cohort 2). Data will be available to the company in [redacted]. The time period between the database lock and data availability is to accommodate standard quality control processes, data analysis and clinical study report writing.

Data collected in clinical practice

7.4 At the end of the data collection period NICE and NHS England and NHS Improvement will provide a final report based on the routinely collected population-wide data collected via the Blueteq system. The report will present anonymized summary data and the necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be

shared with Novartis Gene Therapies in advance of the planned review of guidance.

8 Data protection and ownership

8.1 Patient data collected as part of this interim access agreement will be in accordance with all applicable data protection legislation, including but not limited to the Data Protection Act 2018 and the UK General Data Protection Regulation.

8.2 Blueteq's system data is owned by NHS England and NHS Improvement. NHS England and NHS Improvement is responsible for implementing Blueteq data collection and use of these data. NHS England and NHS Improvement will be able to share Blueteq data for the purposes of a NICE guidance review, subject to data sharing agreements between NHS England and NHS Improvement and parties to this agreement.

8.3 This data shall be stored for no more than 5 years following the completion of the MAA guidance review by NICE. In the event that the guidance review does not take place, data will be stored for no more than ten years from the MAA start date.

9 Monitoring arrangements

9.1 NICE will convene a Managed Access Oversight Committee with representation from NHS England and Improvement, NICE and Novartis Gene Therapies.

9.2 The Managed Access Oversight Committee exists to oversee the operation of all aspects of the MAA and to address issues that may arise throughout the MAA term. The Managed Access Oversight Committee are responsible for monitoring the implementation of the MAA and recommending actions to support its operation. A detailed description of the Managed Access

Oversight Committee function will be available in a Terms of Reference document produced by NICE.

9.3 The Managed Access Oversight Committee will meet at 6 monthly intervals throughout the MAA period.

10 Publication

10.1 The final data report as described in section 9.4 will form part of NHS England and NHS Improvement's submission for the purposes of guidance review by NICE, and will therefore be publicly available at the conclusion of such guidance review.

10.2 Publications using data collected in clinical practice arising from the use of onasemnogene abeparvovec within the context of this MAA is not permitted until after the date of publication of the NICE committee papers (on the NICE website) following the first NICE guidance review committee meeting.

10.3 Authors must notify the Managed Access Oversight Committee when any requests to use the data collected in clinical practice arise, before any work on the publication starts.

10.4 Publications regarding the implementation or managed access process will be permitted prior to the publication of the NICE committee papers as long as no managed access data collected in clinical practice is included (e.g. patient leaflets, NICE presentations about operational aspects of MAAs). These publications are subject to compliance with 11.5 of this agreement.

10.5 The contribution of the following groups must be acknowledged in any publications using data collected in clinical practice arising from the use of onasemnogene abeparvovec within the context of this MAA, including a list of individual group members: NICE; NHS England and NHS Improvement and Members of the Managed Access Oversight Committee.

10.6 Authors will need to contact the NICE Managed Access Team for a full list of group members.

11 Equality considerations

11.1 Do you think there are any equality issues raised in data collection?

☐ Yes ☒ No

Commercial Access Agreement

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The contents of this document have been redacted as they are confidential