NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Onasemnogene abeparvovec for treating spinal muscular atrophy [ID1473]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating spinal muscular atrophy

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Novartis Gene Therapies	To enable the earliest possible access to onasemnogene abeparvovec single-dose gene therapy for the children who will benefit and their families, the company supports the recommendations detailed in the Evaluation Consultation Document (ECD), including the proposed Managed Access Agreement (MAA) to enable rapid treatment of pre-symptomatic babies with spinal muscular atrophy (SMA). The company acknowledges that the trials for onasemnogene abeparvovec in patients treated pre-symptomatically are still ongoing (i.e., the SPR1NT trial including 2- and 3-copy cohorts). The company undertakes to supply these completed trial data to inform the MAA as requested.	Thank you, no change required.
Novartis Gene Therapies	The company appreciates that the committee has consulted carefully throughout this appraisal with the SMA community, including patient groups and clinical experts. In line with NICE HST process and methods programme, we agree that the three-year review period seems appropriate.	Thank you, no change required.
Novartis Gene Therapies	The company welcomes this guidance, and the opportunity provided to agree the commercial access arrangements with National Health Service England (NHSE) in parallel (announced by NHSE on 8th March 2021). We look forward to rapid access for the children who will benefit and their families.	Thank you, no change required.
Muscular Dystrophy UK	We welcome the recommendations as a sound and suitable basis for the option of using onasemnogene abeparvovec for those who are eligible and we welcome the establishment of a managed access agreement for presymptomatic babies who meet the criteria which has been set.	Thank you, no change required.

Consultee	Comment	Response
Muscular Dystrophy UK	We are keen to ascertain how the criterion of babies having a '70% chance of being able to sit independently' is going to be measured/adopted, as referenced in Section 1.2. We feel that this should be defined as soon as possible so that families and clinicians have a clear understanding of the expectation for acceptance to receive the treatment.	NHSE are commissioning 4 organisations to provide the service. They will be provided with criteria for assessment and standard operating procedures. The national MDT (NMDT) is using this criterion as a guide to their discussions and will be considering a number of factors in their review of cases. These factors will include clinical and physiological parameters. It is planned that the NMDT will regularly audit cases and decision making to decide which parameters are relevant.
Muscular Dystrophy UK	We acknowledge the capacity increase for members of the national multi-disciplinary team, who will be reviewing cases to ascertain eligibility of infants for this treatment. We hope that adequate resources will be made available to ensure that the members are sufficiently supported to review cases so that treatment can be delivered as seamlessly as possible to those who are eligible.	NHSE are commissioning 4 organisations to provide the service. NHSE is moving at pace to get the service established. There is awareness of the prevalent pool of patients and proposals are being worked on to evaluate these cases as soon as possible.
Muscular Dystrophy UK	Every day counts for families waiting to receive this treatment and we therefore hope that there will be no delays in setting up the patient pathways at the designated treatment sites.	NHSE are commissioning 4 organisations to provide the service. We anticipate the service will be in place by early summer.
Muscular Dystrophy UK	We also support the points which SMA UK make in their submission.	Thank you, no change required.
The Royal College of Pathologists	In my opinion, I believe that this treatment could be of great benefit to patients and their families. However, I do have some points that would like clarification (see below).	Thank you, no change required.
The Royal College of Pathologists	It is stated that the following patients can be treated: "Bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1" I think that there needs to be clarification that patients who are a SMN1 deletion and point mutation are suitable.	The diagnosis for purposes of use of gene therapy requires both the mutation and a clinical diagnosis and so cannot be given in the pathology report. 90%+ of the mutations are deletions of exon 7 but there are a minority of cases with other mutations. At a practical level the pathologist should report what they have found, and the MDT can consider the specific mutation along with the clinical diagnosis.

Consultee	Comment	Response
The Royal College of Pathologists	Early molecular diagnosis is key for treatment and the detection of the SMN1 deletion and SMN2 copy number can be readily performed by MLPA analysis but point mutation detection will take longer. Additionally, it must be noted that some patients will also have testing for additional disorders such as Parder-Willi syndrome. Will there be defined national guidelines for turn around times (TAT) for SMA molecular diagnostic testing in light of this new treatment?	Thank you for your comment - SMA molecular diagnostic testing is beyond the remit of this evaluation, but your comments have been passed to NHSE who can forward them to colleagues in the genetics service for their consideration.
The Royal College of Pathologists	As mentioned in 3, MLPA analysis is the most common used test in most laboratories. Will there be guidelines that this or other tests are suitable for the detection of the SMN1 deletion and SMN2 copy number?	Thank you for your comment – as above this has been passed to NHSE for their consideration.
The Royal College of Pathologists	In my experience with reporting whether a DMD patient is suitable for Ataluren treatment, having the appropriate information in the diagnostic report ensures that the referring clinician and patients' family are clearly informed that the patient is suitable for treatment. This should be discussed with ACGS and clinicians so reports becomes standardised for clarity. For example, the reports should state that: a) Patient is SMA type 1, 2 or 3 b) SMN1 and SMN2 copy number should be included in all their reports if a bi-allelic mutation is identified Based on the molecular diagnostic results that this patient is suitable or not suitable for treatment	Thank you for your comment – as above this has been passed to NHSE for their consideration.
SMA REACH UK	My concern is regarding SMA type 1 babies who have been born in 2021 and we have commenced nusinersen, but will still be potentially under 6 months, or 7-12 months and will they be considered for gene therapy, as we have been preserving muscle function etc with nusinersen as a 'holding bay' whilst waiting for gene therapy.	In the trials considered by the committee babies who had received prior nusinersen were not included, but the NHSE deal with the company does allow children who have previously been treated with nusinersen or risdiplam to be considered by the NMDT.
SMA REACH UK	If age is used as a cut off for treatment eligibility, the point at which that age is reached must be clearly defined – the point of diagnosis ? the point of referral to infusion centre ? the point at which the infusion centre is able to arrange infusion?	Thank you for your comment – yes, it is at diagnosis. The recommendation states '*a clinical diagnosis of type 1 SMA*'.

Consultee	Comment	Response
SMA REACH UK	I am concerned that the task allocated to the MDT to consider babies aged 7 to 12 months, i.e. to develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them at least a 70% chance of being able to sit independently, is neither realistic nor feasible based on current knowledge. A system based on “reimbursement by results” could both offload the task of the national MDT, but it is not only the amount of work, is the possibility to develop strict criteria that could be difficult to audit, and could be legally challenged	NHSE are commissioning 4 organisations to provide the service. They will be provided with criteria for assessment and standard operating procedures. The national MDT (NMDT) is using this criterion as a guide to their discussions and will be considering a number of factors in their review of cases. These factors will include clinical and physiological parameters. It is planned that the NMDT will regularly audit cases and decision making to decide which parameters are relevant.
SMA REACH UK	For the national MDT; the 4 sites that will make up the MDT will need clear clinical guidance on assessing the 7-12 month cohort referred into the MDT. Will there be any recommendations regarding this (such as ventilation, feeding etc) or will it be up to the clinical centres and SMA REACH sites to decide on these criteria. I think it will be particularly difficult to predict the 70% probability of sitting and will the MDT be held accountable if we do not achieve this.	NHSE are commissioning 4 organisations to provide the service. They will be provided with criteria for assessment and standard operating procedures. The national MDT (NMDT) is using this criterion as a guide to their discussions and will be considering a number of factors in their review of cases. These factors will include clinical and physiological parameters. It is planned that the NMDT will regularly audit cases and decision making to decide which parameters are relevant.
SMA REACH UK	What would be the implications if the national committee is unable to devise an auditable criteria, would a case by case consensus decision of the national committee and NHSE be acceptable to proceed with treatment? There would be feasibility and timing issues regarding this, and potential delays for initiation of (any) treatment with families and physicians having apparently multiple choices, however both the rationale and the implementation of the 7-12 months would be problematic in the real world. A clear cut age and function inclusion / exclusion criteria rationale will be less complex to implement in clinical practice	NHSE are commissioning 4 organisations to provide the service. They will be provided with criteria for assessment and standard operating procedures. The national MDT (NMDT) is using this criterion as a guide to their discussions and will be considering a number of factors in their review of cases. These factors will include clinical and physiological parameters. It is planned that the NMDT will regularly audit cases and decision making to decide which parameters are relevant.

Consultee	Comment	Response
SMA REACH UK	Is there going to be ability for young babies to 'switch' between nusinersen and gene therapy, if these babies fulfil criteria otherwise. Would they stop nusinersen or continue?	In the trials considered by the committee babies who had received prior nusinersen were not included, but the NHSE deal with the company does allow children who have previously been treated with nusinersen or risdiplam to be considered by the NMDT.
SMA REACH UK	I am concerned that very young babies naturally sleep more than 16 hours per day and may therefore have ventilation for this period not because it is needed but because they are advised BIPAP for "night and naps". These babies would be excluded.	Babies requiring permanent ventilation for more than 16 hours a day are excluded from the recommendation.
SMA REACH UK	4.42 – The committee indicates that it has not made recommendations of patients who are currently on Nusinersen based on lack of trial data evidence but then the inclusion criteria is all SMA1 up to 1 year of age. Most of the SMA1 prevalent population in UK will be on Nusinersen and many are likely to fit the inclusion criteria for Zolgensma. How will the decision to offer Zolgensma be made? Will it be via the national committee even for those <6 months and fit all the other inclusion criteria. There needs to clarity for Nusinersen treated SMA1 patient group in this recommendation.	In the trials considered by the committee babies who had received prior nusinersen were not included, but the NHSE deal with the company does allow children who have previously been treated with nusinersen or risdiplam to be considered by the NMDT.
SMA REACH UK	The earlier we treat these babies ultimately gives better results, we will not see the benefits if we do not have new-born screening, as we still get late referrals unless we have a family history and pre-natal screening in mum. How can this be accelerated to therefore improve outcomes and cost effectiveness with this expensive drug?	Newborn screening programmes are the remit of the UK National Screening Committee. The Screening Committee is due to review the case for screening for SMA again this financial year and they aim to hold a stakeholder workshop to discuss the issues in July 2021.
SMA REACH UK	The gene therapy costing; does this cover costs of physiotherapy etc to improve outcomes and develop physical goals? Increase in OPD appointments to monitor outcomes?	In the health economic model babies who can sit are assumed to have the ongoing costs of those with type 2 SMA and those who can walk with type 3. Physiotherapy costs have been included in the modelling.

Consultee	Comment	Response
SMA REACH UK	Whilst there is currently no evidence for use in children with SMA type 2 even if less than 12 months old, and that it is rare to diagnose SMA type in infants now, we are concerned that with increased awareness of the condition and need for timely diagnosis that this may be a higher occurrence in the near future. Potentially there may be inequalities in care with some centres diagnosing SMA, including SMA type 2 earlier ie less than 18 months or even in infancy. We are concerned that this group of patients with SMA type 2 who may benefit from onasemnogene aberparvovec and otherwise fulfil the SmPC of the product apart from the age at diagnosis of SMA type 2 would not have access to the drug. I am concerned that without Newborn Screening there may be a disparity in age of diagnosis in different areas, dependent on local services, and some babies may not receive diagnosis within 6 month period. Whilst I acknowledge that these children could then be considered by the MDT committee this will result in delay in treatment.	Unfortunately, as you state, there is no evidence for the use of Onasemnogene in babies with type 2 SMA and as a result the committee was unable to make a recommendation for this group. Newborn screening programmes are the remit of the UK National Screening Committee. The Screening Committee is due to review the case for screening for SMA again this financial year and they aim to hold a stakeholder workshop to discuss the issues in July 2021.
SMA REACH UK	The report acknowledges the spectrum of SMA and the 'clinical continuum' – there is obviously a fine line between a weak SMA 2 who has achieved sitting for maybe a few seconds compared to a stable sitter with 'typical SMA 2', and who only have 2 or 3 copies of SMN2, is there discussion as to whether they could be eligible, if under 2 years and less than 13.5kg? The effect on these very weak type 2 babies would be immense and decrease care burden and ultimate clinical interventions. We have seen that left untreated these type 2 weak babies will ultimately have a worse outcome compared to a type 1 SMA baby who is treated either with nusinersen or gene therapy.	Unfortunately, there is no evidence for the use of Onasemnogene in babies with type 2 SMA and as a result the committee was unable to make a recommendation for this group. However, babies with type 2 SMA are eligible to receive Nusinersen.
SMA REACH UK	I am concerned that patients with an early diagnosis of Type 2 , early diagnosis suggesting that they have a more severe phenotype, cannot have access to this treatment, when clinically they may not achieve much more than a " good " type 1 functionally. This may result in a number of type 2 patients functioning at a lower level than treated Type 1 patients.	Unfortunately, there is no evidence for the use of Onasemnogene in babies with type 2 SMA and as a result the committee was unable to make a recommendation for this group. However, babies with type 2 SMA are eligible to receive Nusinersen.

Consultee	Comment	Response
SMA REACH UK	I am concerned that pre-symptomatic babies under six months of age with 4 copies of SMN2 gene and a family history of SMA2 are a group that will benefit from treatment saving long term costs. Some of those babies, in particular in light of the family history, will be as affected as children with 3 copies of SMN2.	Thank you for your comment. NICE are only able to make recommendations within the marketing authorisation. Onasemnogene is indicated for the treatment of people: • with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or • 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene Babies with 4 copies of the SMN2 gene are outside of the marketing authorisation.
Spinal Muscular Atrophy UK	We thank NICE for the time and careful consideration that has clearly gone into decision making about this important new treatment that offers such potential for the future.	Thank you, no change required.
Spinal Muscular Atrophy UK	We welcome the recommendations as ones that follow NICE's processes and consider clinical trial evidence submitted by the Company. We note that this is currently limited to infants with a clinical diagnosis of SMA Type 1 who were six months and under, and to a study of pre-symptomatic infants that is still at an early stage. We also note the Company's economic modelling focuses on these same groups.	Thank you, no change required.
Spinal Muscular Atrophy UK	Given this evidence, we consider the recommendations outlined in 1.1 to be a sound and suitable basis for the option of using onasemnogene abeparvovec for those who are clinically diagnosed with SMA Type 1 and described as eligible.	Thank you, no change required.
Spinal Muscular Atrophy UK	We welcome the committee's recognition of the clinical skills and experience of our clinicians who, it is recommended in 1.2, will form a national multidisciplinary team (MDT) to develop auditable criteria for babies age 7 – 12 months.	Thank you, no change required.

Consultee	Comment	Response
Spinal Muscular Atrophy UK	We note that it was acknowledged in 4.14 that diagnosis may be delayed in some disadvantaged groups, and that this was one of the factors that led the committee to recommend treatment for infants who have SMA Type 1 and are between 7 and 12 months of age. The ongoing work to raise awareness of the symptoms of SMA and the possibility of treatment, will hopefully result in earlier diagnosis. Along with this, patient groups, clinicians and pharmaceutical companies are focusing on the need to ensure the earliest possible introduction of newborn screening for SMA. We are therefore comfortable that the upper age limit of 12 months will ensure the possibility of treatment for the current and future incident SMA Type 1 population. Given that NHS England's parallel agreement will enable some young children with SMA Type 1 who are older than 12 months to also be considered for treatment via the MDT, we are comfortable that the best safe treatment options for children in the prevalent Type 1 population will be considered individually with their families	Thank you, no change required.
Spinal Muscular Atrophy UK	We acknowledge the additional work and responsibility that will fall on members of the MDT and hope that they will be well supported and resourced. We are keen, in view of the earliest possible treatment being so vital, to see clinical criteria and processes developed that will, as far as possible, enable quick decisions that are sensitively and transparently relayed to individual families.	NHSE are commissioning 4 organisations to provide the service. They will be provided with criteria for assessment and standard operating procedures. The national MDT (NMDT) is using this criterion as a guide to their discussions and will be considering a number of factors in their review of cases. These factors will include clinical and physiological parameters. It is planned that the NMDT will regularly audit cases and decision making to decide which parameters are relevant.
Spinal Muscular Atrophy UK	We also welcome the recommendation in 1.3 of a managed access agreement for presymptomatic babies who meet the criteria which have been set. We are pleased that the further results due from the Company's clinical trial will be a key source of clinical effectiveness evidence.	Thank you, no change required.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
	None received.	

Comments received from commentators

Commentator	Comment	Response
	None received.	

Comments received from members of the public

Role*	Section	Comment	Response
		None received.	

Summary of comments received from members of the public

Theme	Response
None received.	

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.