National Institute for Health and Care Excellence

Highly Specialised Technologies (HST)

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4015]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Novartis Gene Therapies (company)	Novartis Gene Therapies agrees in principle with the draft remit of the draft scope. The population being considered in this submission is described by NICE as: *'People with presymptomatic 5q spinal muscular atrophy and up to three copies of the SMN2 gene.'* Novartis Gene Therapies has conducted a UK advisory board in which clinical experts highlighted that it is theoretically possible for infants to have symptoms of SMA that are unobserved at the time of screening, meaning the term 'presymptomatic' does not fully capture and typify the patient population (1). Therefore, in the submission, Novartis Gene Therapies will refer to the patient population as the 'screened population', which aligns with advice from and the terminology used by UK clinical experts. Therefore, Novartis Gene Therapies suggests replacing the wording with:	Thank you for your comment. This evaluation is a partial review of HST15. It will evaluate onasemnogene aberparvovec in people with pre-symptomatic SMA with up to 3 copies of the SMN2 gene. This reflects section 1.3 of the HST15 recommendation. The company can outline their comments further

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		To appraise the clinical and cost effectiveness of onasemnogene abeparvovec within its marketing authorisation for treating patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene, in a patient population with SMA identified through screening. **For clarification, the population with up to three copies of *SMN2* described in the Summary of Product Characteristics (SPC) (3), includes infants with three copies of *SMN2*.**	within their submission. No action required.
	Spinal Muscular Atrophy UK	Yes [appropriate].	Thank you for your comment. No action required.
	Muscular Dystrophy UK	The wording is appropriate.	Thank you for your comment. No action required.
Timing Issues	Novartis Gene Therapies (company)	No treatments are currently routinely commissioned for the screened population in England. All untreated patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene will experience the irreversible loss of motor neurons associated with symptomatic SMA (4), substantially affecting their survival and impairing their quality of life, and the quality of life of their caregivers. It is therefore imperative to diagnose SMA and begin treatment as early as possible to halt this loss and disease progression (5, 6). Novartis Gene Therapies has evidence from the SPR1NT trial that patients in the screened population genetically diagnosed with SMA and two or three copies of SMN2 who received a single-dose IV infusion of onasemnogene	Thank you for your comment. This evaluation has been scheduled into the highly specialised technology programme. No action required.

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		abeparvovec achieved age-appropriate milestones that would never be achieved in untreated patients (7)	
	Spinal Muscular Atrophy UK	This is **very urgent** for families where there is a medical history of SMA. Early treatment is best, therefore pre-symptomatic treatment represents the very best option for babies with SMA. **Having this in place before the National Screening Committee reviews the case for Newborn Screening is essential for this to become a reality.**	Thank you for your comment. This evaluation has been scheduled into the highly specialised technology programme. No action required.
	Genetic Alliance UK	Treatment is most effective when administered early or pre-symptomatically therefore it is urgent to complete this technology appraisal as soon as possible so that it may benefit as many families as possible before they are no longer eligible. Additionally, in order for the newborn screening committee to even consider screening for SMA in newborns, there has to be a treatment available. Therefore it is imperative that this technology is appraised quickly as the sooner this condition is authorised for newborn screening the sooner babies can be treated.	Thank you for your comment. This evaluation has been scheduled into the highly specialised technology programme. No action required.
	Muscular Dystrophy UK	Access to this treatment for patients diagnosed through targeted screening (i.e. not diagnosed following the presentation od symptoms) is very urgent for families where there is a medical history of SMA. Clinical trials and real-world experience have consistently demonstrated early treatment is essential for the best possible outcomes and should be given pre-symptomatically. Newborn Population screening for SMA is equally urgent for those who do not know they are carriers of the SMN1 gene. The National Screening Committee is due to start its 3-year review this year. It is essential that this treatment has been assessed by NICE and recommended for routine NHS provision as it is	Thank you for your comment. This evaluation has been scheduled into the highly specialised technology programme. No action required.

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		one of the NSC's key criteria that must be met for SMA screening to be agreed.	
Additional comments on the draft remit	Novartis Gene Therapies (company)	Novartis Gene Therapies agrees that the HST appraisal route is appropriate given that the criteria for HST have been met, as outlined below. 1. The condition is very rare defined by 1:50,000 in England SMA is a very rare disease with an estimated prevalence of approximately 1–2 per 100,000 persons for all types of SMA (8). Due to the high mortality rate, estimates for the prevalence of SMA type 1 range from 0.04 to 0.28 per 100,000 population. The prevalence of later onset SMA (SMA type 2 and 3) has been estimated to be around 1.5 per 100,000 (8). All-type annual incidence of SMA is approximately 9.4:100,000 live births (9). These epidemiological data applied to the number of live births (585,195) reported in England in 2020 indicate that approximately 55 babies per year are born with an SMA genotype that, if untreated, will become symptomatic SMA (10). 2. Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications. As discussed above, SMA is a very rare disease. In addition, there is currently no national population-based newborn blood spot (NBS) screening programme for SMA in the UK. In routine clinical practice, infants are currently identified through genetic testing referrals due to a sibling history of SMA or a parent with confirmed carrier status (family screening). A UK population-based pilot study is also being conducted to evaluate the feasibility of conducting national population-based NBS screening for SMA. It is estimated by the NICE Resource Impact Assessment team that	Thank you for your comment. This evaluation has been scheduled into the highly specialised technologies programme. No action required.

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		approximately two pre-symptomatic infants may be identified each year as being eligible for treatment with onasemnogene abeparvovec through genetic testing referrals due to sibling history of SMA (11). Novartis Gene Therapies conducted a UK advisory board in Q1 2022, in which clinical experts agreed that one additional patient per year may be identified through the UK population-based NBS screening programme pilot study (population-based NBS screening of SMA to evaluate the uptake and feasibility in the UK context) (1, 2). All infants genetically diagnosed with SMA will go on to develop symptomatic SMA if they are not treated before symptoms arise. Infants identified through any national population-based NBS screening programme would be eligible for a genetic test to confirm SMA diagnosis. Screening programmes will not increase the total number of patients eligible for SMA treatment(s), but will allow for earlier identification of infants with SMA, allowing earlier treatment and improved prognosis. 3. The very rare condition significantly shortens life or severely impairs its quality SMA exists on a broad spectrum, and all types of SMA are devastating, significantly affecting survival and substantially impairing quality of life for patients and their caregivers. Without treatment, all patients who are identified with biallelic deletion of SMN1 will develop SMA. Motor development and subsequent survival of affected infants is partly determined by the number of copies of the SMN2 gene. Patients with two or three copies of SMN2 typically either never achieve a sitting position, or if they do achieve sitting, will either never walk unaided or eventually become wheelchair bound when managed with BSC only. Although in general, fewer copies of SMN2 may result in a more severe	

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		disease phenotype, some patients with three copies of SMN2 will develop a severe form of SMA (12). Quality of life (QoL) is impaired in SMA, mainly due to compromised physical health (13). Infants with SMA and their caregivers face a substantial humanistic burden as the disease progresses (14). The burden for patients and caregivers includes the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts. The emotional burden for caregivers of infants most severely impacted by SMA (Type 1) continues with bereavement as patients succumb to the disease (15). Families and caregivers of infants with SMA have lower QoL and higher levels of stress compared with families and caregivers of infants without SMA (16). 4. No satisfactory treatment options exist, or, if it does the technology is likely to be of significant additional benefit to those affected Without treatment, all patients with biallelic deletion of the SMN1 gene will develop SMA, including patients from the screened population in whom SMA symptoms have not yet been observed. Growing evidence suggests that early initiation of treatment for SMA, at a less advanced disease stage, is associated with better outcomes (17). There are currently no treatments routinely commissioned for the treatment of the screened population in England. However, expert recommendations and consensus statements recognise that the early initiation of treatment, ideally before symptoms become apparent, is associated with markedly better outcomes compared with later initiation of treatment and support immediate treatment following genetic diagnosis (6, 17-21). When SMA symptoms are observed, BSC has some impact on life expectancy, but it does not modify disease progression, improve motor function or the attainment of motor developmental milestones, and infants	

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		continue to have poor QoL (22). An unmet need remains for a routinely commissioned disease-modifying therapy that replaces the missing or non-functional SMN1 gene, which is the genetic root cause of SMA (23).	

Comment 2: the draft scope

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Background information	Novartis Gene Therapies (company)	1. Novartis Gene Therapies believes that the following sentence from the draft scope is misleading and should be replaced: *'The most severe types of SMA typically cause death before age 2 years, although people with later-onset types of SMA usually live into adolescence or adulthood'.* It is misleading to suggest that people with later-onset forms of SMA usually live into adolescence or adulthood. The life expectancy of people with later-onset SMA receiving BSC is not widely reported and, although patients can survive into adulthood, survival for patients with SMA type 2 is limited compared with the healthy population, ranging from 2.5–30 years (24). Novartis Gene Therapies suggests replacing the wording with: **The most severe types of SMA typically cause death before age 2 years, although people with later-onset forms of SMA can live into adolescence or adulthood.** 2. Novartis Gene Therapies believes that the following sentence from the draft scope is misleading and should be replaced: *'An individual with SMA who has more copies of the SMN2 gene will produce more functional SMN protein and may be better able to*	Thank you for your comments. 1. The draft scope has been updated to reflect this suggested change 2. No change required. The statement highlights that more SMN2 gene copy numbers potentially leads to less severe disease. Therefore the statement does

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		compensate for the loss of the SMN1 gene, potentially leading to less severe disease'. It is misleading to suggest that an individual with more copies of the *SMN2* gene will produce more functional SMN protein and may be better able to compensate for the loss of the *SMN1* gene, potentially leading to less severe disease, because it suggests that SMA may become less severe. Novartis Gene Therapies suggests replacing the wording with: **SMA exists on a broad spectrum, and although patients with different *SMN2* copy numbers are genetically distinct, there is overlap in clinical symptoms and disease severity. For example, although in general, fewer copies of *SMN2* may result in a more severe disease phenotype, some patients with three copies of *SMN2* will develop a severe form of SMA (12).** 3. Novartis Gene Therapies believes that the following paragraph from the draft scope, which discusses SMA types, is misleading and should be replaced: *'SMA is a heterogeneous condition, which is often grouped into 5 main types, based on the age of onset of symptoms and how much motor function the person has. The types of SMA decrease in severity from type 0, in which symptoms arise before birth and babies survive for only a few weeks, to type 4 (adult-onset) which is associated with mild motor impairment and a normal life span. Types 0 and 4 are rarely diagnosed. In SMA type 1, symptoms arise before age 6 months and babies are unable to sit independently; babies with SMA have low muscle tone (hypotonia) and severe muscle weakness which affects movement, swallowing and breathing. In type 2 SMA, the onset of symptoms is between age 7 and 18 months, and people with this*	not say that this is always the case. 3. No changes required. While the population under review are pre-symptomatic, without treatment this population would go on to develop a type of SMA, therefore the paragraph is relevant. 4. No changes required. Pre-symptomatic is the population wording in HST15 recommendations. The company can include discussion and

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		condition are often severely disabled and unable to walk unaided. Type 3 SMA is a heterogeneous condition, with a varying degree of muscle weakness appearing between age 18 months and 18 years; most people with type 3 SMA can walk or sit unaided at some point, but many lose mobility over time. The number of SMN2 gene copies can differ by SMA type.' In the context of the screened population with SMA and two or three copies of the *SMN2* gene, it is misleading to discuss SMA types, as the severity of SMA is unclear prior to observation of symptoms. SMA exists on a broad spectrum, and although patients with different *SMN2* copy numbers are genetically distinct, there is overlap in the clinical symptoms and severity of disease (12). Therefore, Novartis Gene Therapies suggests replacing the paragraph with the following wording (split into several paragraphs for clarity) with: **SMA is a heterogeneous condition, and, while disease severity and clinical course of the disease are associated with the number of copies of *SMN2* (12, 25, 26), there is overlap in the clinical symptoms and disease severity of patients with different *SMN2* copy numbers.** **Almost all infants with two copies (79%) of *SMN2*, and 15% of those with three copies, will be non-sitters (12), with symptom onset before 6 months of age and failure to ever achieve a sitting position when managed with BSC only.** **Infants with two or three copies of *SMN2* who do achieve unsupported sitting will either never walk unaided or become wheelchair bound (12, 23, 24, 27).**	further comments on this point in its submission. 5. The draft scope has been updated to reflect that the statement refers to an untreated population. 6. The estimate of the number of babies born with SMA per year is based on the source used in the HST15 final scope. The company can provide further evidence in its submission on this estimate. No changes required. 7. No changes required. The

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		For sitters, symptom onset is typically at 6–12 months of age, and, on average, sitting unsupported is achieved at 1 year of age (27). **Patients achieving walking as their highest milestone may walk independently by approximately 7 years of age (27, 28), but milestones can be lost over the longer-term, and most will lose the ability to walk (24, 29, 30).** 4. Novartis Gene Therapies believes that the following sentence from the draft scope does not accurately describe current practice and should be replaced: *'Currently in England, only a small number of children are diagnosed with SMA before symptoms appear (known as pre-symptomatic SMA) if a sibling has been diagnosed with SMA'.* Novartis Gene Therapies has conducted a UK advisory board in which clinical experts highlighted that it is theoretically possible for infants to have symptoms of SMA that are unobserved at the time of screening, meaning the term 'presymptomatic' does not fully capture and typify the patient population (1). Novartis Gene Therapies suggests replacing this wording with: **Currently in England, only a small number of infants are diagnosed with SMA before symptoms appear (previously known as presymptomatic SMA). These infants are identified through screening.** 5. Novartis Gene Therapies believes that the following sentence from the draft scope is misleading and should be replaced: '*Pre-symptomatic SMA later develops into other SMA types 0 to 4, depending on when symptoms occur*'.	text refers to SMA type 1, which is associated with non-sitting status. The company can outline its comments further within its submission. 8. No changes required. This evaluation is a review of the recommendation (section 1.3) in HST15 which covered the pre-symptomatic population. The company can outline its comments further within its submission.

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		It is not possible to know which disease phenotype these patients would have gone on to develop without treatment, and therefore presymptomatic patients should not be discussed in terms of SMA 'type'. All infants genetically diagnosed with SMA will go on to develop symptomatic SMA if they are not treated before symptoms arise. However, if the screened population is treated, SMA patients may be expected to go on to achieve and maintain age-appropriate motor milestones within normal World Health Organization (WHO) developmental windows (7). Novartis Gene Therapies suggests replacing this wording with: **Without treatment, patients with a genetic diagnosis of SMA would later develop symptoms of SMA. SMA exists on a broad spectrum, and although patients with different *SMN2* copy numbers are genetically distinct, there is overlap in clinical symptoms and disease severity.** 6. Novartis Gene Therapies believes that the following sentences is incorrect and should be replaced: *'It is estimated that approximately 1 in 10,000 people are born with SMA, suggesting that about 65 people are born with SMA per year in England'.* The number of people born with SMA per year in England has been overestimated. Novartis Gene Therapies suggests replacing this wording with: The annual incidence of all SMA types is **approximately 9.4:100,000 live births (9). These epidemiological data applied to the ONS statistics for number of live births (585,195) reported in England in 2020 (31) indicate that approximately 55 babies per year are**	

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		born with an SMA genotype and will go on to develop symptomatic SMA. 7. Novartis Gene Therapies believes that the reference to SMA type 1 in the following sentence is misleading and should be replaced: *'Approximately 60% of all new diagnoses of SMA are SMA type 1'*. As patients in the screened population are genetically diagnosed with SMA, they cannot be classified as having SMA type 1, 2, or 3 (as the severity of symptoms has yet to clinically present). However, to enable categorisation of patients, clinicians have suggested grouping patients by functional stages describing the highest motor milestone achievable: non-sitter, sitter, and walker (21, 32, 33). Novartis Gene Therapies suggests replacing this wording with: **Approximately 60% of all new diagnoses of SMA would become non-sitters if left untreated.** 8. Novartis Gene Therapies believes that the population definition from the draft scope is misleading and should be replaced: *'This evaluation will consider onasemnogene abeparvovec use in people with pre-symptomatic SMA'* As described above, it is theoretically possible for infants to have symptoms of SMA that are unobserved at the time of screening, meaning the term 'presymptomatic' does not fully capture and typify the patient population (1). **Novartis Gene Therapies suggests replacing this wording with:** This evaluation will consider onasemnogene abeparvovec use in babies with a confirmed genetic diagnosis of 5q SMA who have been identified through screening at birth.	

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	Spinal Muscular Atrophy UK	The explanation of the 'type' classification does not make it clear that the symptoms of the disease are on a spectrum, there are overlaps between the 'types.' The beginning of the second paragraph could read: '5q SMA is a heterogenous condition (with the exception of rare cases caused by a mutation, a new gene change in the individual) which, despite the symptoms clearly being on a spectrum, is often clinically classified into 5 main types which reflect the potential severity of its impact. For children and adults, the severity of the condition varies from person to person both within and between 'types'. Each adult and child is affected differently.	Comments noted. The draft scope now states **"***SMA is a heterogeneous condition, with a range of severity, which is often grouped into 5 main types, based on the age of onset of symptoms and how much motor function the person has."* The committee will consider the heterogeneity of the condition within the evaluation. No further action required.
	Genetic Alliance UK	We have been informed by SMA UK that the condition presents more as a spectrum of severity and that each 'type' overlaps with one another.	Comment noted. The background section is intended to give a brief overview of the condition and currently refers to SMA as a heterogeneous condition. No action required.

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	Muscular Dystrophy UK	The explanation of the 'type' classification does not make it clear that the symptoms of the disease are on a spectrum and that there are overlaps between the 'types.' The beginning of the second paragraph could read: '5q SMA is a heterogenous condition (with the exception of rare cases caused by a mutation, a new gene change in the individual) which, despite the symptoms clearly being on a spectrum, is often clinically classified into 5 main types which reflect the potential severity of its impact. For children and adults, the severity of the condition varies from person to person both within and between 'types'. Each adult and child is affected differently.'	Comments noted. The draft scope now states states "SMA is a heterogeneous condition, with a range of severity, which is often grouped into 5 main types, based on the age of onset of symptoms and how much motor function the person has." The committee will consider the heterogeneity of the condition within the evaluation. No action required.
The technology/ intervention	Novartis Gene Therapies (company)	Onasemnogene abeparvovec is a one-time therapy delivered by IV infusion. For clarity, Novartis Gene Therapies suggests replacing the wording with: Onasemnogene abeparvovec delivered via a single-dose IV infusion.	Thank you for your comment. The draft scope has been updated to state onasemnoegene aberparvovec is a single dose treatment.

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Population	Novartis Gene Therapies (company)	The population being considered in this submission is described by NICE as: 'People with presymptomatic 5q spinal muscular atrophy and up to three copies of the SMN2 gene.' Novartis Gene Therapies has conducted a UK advisory board in which clinical experts highlighted that it is theoretically possible for infants to have symptoms of SMA that are unobserved at the time of screening, meaning the term 'presymptomatic' does not fully capture and typify the patient population (1). Therefore, Novartis Gene Therapies suggests replacing the wording of the population in the draft scope with: Infants with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene identified through screening.	The population described in the draft scope reflects that of the HST15 recommendations (section 1.3). The company can submit further comments on this in its submission. No changes required.
	Spinal Muscular Atrophy UK	The number of SMN2 copies is an indicator but not a predictor of severity. Given this and the significant disabilities children with 1-3 copies of SMN2 live with, it is important that they are all considered equally.	Comment noted. The draft scope highlights that increased SMN2 copy numbers may lead to less severe disease. The committee will consider the entire pre-symptomatic population (1-3 SMN2 copies). If evidence allows, consideration by SMN2 copy number may be considered. The scope has been updated to reflect this.

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	Muscular Dystrophy UK	Given the significant disabilities children with 1-3 copies of SMN2 live with, it is important that they are all considered equally.	Comment noted. The draft scope highlights that increased SMN2 copy numbers may lead to less severe disease. The committee will consider the entire pre-symptomatic population (1-3 SMN2 copies). If evidence allows, consideration by SMN2 copy number may be considered. The scope has been updated to reflect this.
Comparators	Novartis Gene Therapies (company)	Novartis Gene Therapies agrees that BSC is the correct comparator, as nusinersen and risdiplam are not routinely commissioned for patients identified through screening.	Comment noted. No action required.
	Spinal Muscular Atrophy UK	Best supportive care is outlined in the internationally agreed standards of care for SMA (November 2017) https://smacare.guide/ This is the minimum standard of care anywhere in the world. Though this is the best comparator, the reality is that this would not be achieved for all children who would fall within the scope of this appraisal.	Comment noted. No action required.
	Genetic Alliance UK	It is important to note that despite having guidance on how to deliver best supportive care, consistency in this delivery is not always achieved.	Comment noted. No action required.

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	Muscular Dystrophy UK	Yes, these are the standard treatments currently used.	Comment noted. No action required.
Outcomes	Novartis Gene Therapies (company)	Novartis Gene Therapies recognises that all outcomes in the draft scope are important.	Comment noted. No action required.
	Spinal Muscular Atrophy UK	Yes. We agree with all that are listed	Comment noted. No action required
Economic analysis	Novartis Gene Therapies (company)	No comments	N/A
Equality and Diversity	Novartis Gene Therapies (company)	There are no special considerations regarding equality.	Thank you for your comment. No action required.
	Spinal Muscular Atrophy UK	It is vital to ensure that all who meet the treatment criteria have equal access, no matter where they live. We realise the families will have to travel to their nearest specialist infusion centre. However in view of the fragility of infants with the severest SMA, the risk of respiratory infection and the challenges of travelling for many there should be the option of having the regular follow up blood tests locally or by community nursing teams in the home setting, with good communication between local and specialist centres. With blood tests to check for any side effects at least once every week to begin with, and then every 2 weeks until clinicians are confident that there are no side effects, minimising travelling distance is especially important for families who already have children with SMA in order to enable them to manage treatment follow-up commitments	Comments noted. The committee will consider any relevant equality issues within the evaluation. No action required.

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		alongside complicated schedules and bespoke care needs. We would like to see these tests done as locally as possible with results efficiently and rapidly sent through to the appropriate specialist centre. Other more in depth monitoring tests would still need to be undertaken by the referring / infusion centre	
	Genetic Alliance UK	For those who are eligible for the treatment it is important to ensure equal access across the UK. Some families may have to travel long distances to receive the treatment in a specialist centre however some of the follow up care such as regular blood tests and monitoring could be done more locally to reduce the burden on individuals and families and improve equitable accessibility to treatment.	Comments noted. The committee will consider any relevant equality issues within the evaluation. No action required.
	Muscular Dystrophy UK	It is vital to ensure that all who meet the treatment criteria have equal access, no matter where they live. We recognise and appreciate that families will have to travel to their nearest specialist infusion centre to receive the treatment,but in view of the fragility of infants most severely affected by SMA; the challenges posed of travelling for many families; and the increased risk faced by many of respiratory infection there should be the option of having the regular follow up blood tests locally with good communication between local and specialist centres. This is especially important for families who already have older siblings with SMA in order to enable them to manage treatment follow-up commitments alongside complicated schedules and bespoke care needs.	Comments noted. The committee will consider any relevant equality issues within the evaluation. No action required.
Other considerations	Spinal Muscular Atrophy UK	We wish to ensure that discussion acknowledges the impact of SMA not just on health and social care related ‘costs’ but also in terms of the huge	Comments noted. These considerations

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		adjustment for the individual and their families on all aspects of their quality of life, mental health, future work opportunities and finances.	may be included in the evaluation as part of the HST methods. No action required.
	Muscular Dystrophy UK	Though the application is only for those with 1 – 3 *SMN2* copies, we would like to clarify/draw attention to the position of babies with 4 copies of SMN2. 3 *SMN2* copies are 'usual' for children who develop SMA Type 2 or SMA Type 3a – both of which result in significant disabilities. However, children clinically classified as having SMA Type 2 may have a range of 2 – 4 SMN2 copies; children clinically classified as having SMA Type 3a may have a range of 3 – *5 SMN2* copies. If then pre symptomatic treatment is restricted to those with 1 – 3 *SMN2* copies, some children will miss out on the optimum delivery of treatment. We suggest that 'watch and wait' for symptoms in these children is unacceptable. We wish to ensure that discussion acknowledges the impact of SMA not just on health and social care related 'costs' but also in terms of the huge adjustment for the individual and their families on all aspects of their quality of life, mental health, future work opportunities and finances.	Comments noted. Onasemnogene aberparvovec has a license for "5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene". The technology will be evaluated within its license. No action required. These suggested considerations may be included in the evaluation as part of the HST methods. No action required.

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Innovation	Novartis Gene Therapies (company)	Onasemnogene abeparvovec is a gene therapy delivered via a single-dose IV infusion that is designed to address the genetic root cause of SMA in the screened population, replacing the missing or non-functional *SMN1* gene before SMA symptoms are observed. In the SPR1NT clinical trial, patients treated with onasemnogene abeparvovec soon after genetic diagnosis achieved age-appropriate motor milestones within normal WHO developmental windows, indicating that treatment may have halted the course of the disease (7). These results reinforce the transformational nature of onasemnogene abeparvovec given that, when managed with BSC only, at best, patients with two or three copies of *SMN2* will either never walk unaided or eventually become wheelchair bound (12), and those with two copies of *SMN2* will typically have a life expectancy of less than two years. **Expert recommendations and consensus statements recognise that the early initiation of treatment, ideally before symptoms become apparent, is associated with markedly better outcomes compared with later initiation of treatment and support immediate treatment following genetic diagnosis (6, 17-21).**	Thank you for your comment. Innovation will be considered in more detail as part of the evaluation. No action required.
	Spinal Muscular Atrophy UK	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* A 'one-off' intravenous treatment available pre-symptomatically would lead to not only improvements but an end to the outcomes listed and would be a step-change in the treatment and management of the condition. The opportunity for a family with a medical history of SMA for their newborn child to receive a one off pre-symptomatic treatment has life transforming implications for future generations and family planning decisions. *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*	Thank you for your comment. Innovation will be considered in more detail as part of the evaluation. No action required.

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		We understand that the QALY calculation will take into account health related benefits related to both the patient and the carer including: • mental health • equipment, aids and housing adaptations: • emergency hospital stays, surgery and clinic time • Continuing Health and Social Care costs *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits*	
	Muscular Dystrophy UK	A 'one-off' intravenous treatment available pre-symptomatically would lead to not only improvements but an end to the outcomes listed and would be a step-change in the treatment and management of the condition. The opportunity for a family with a medical history of SMA for their newborn child to receive a one off pre-symptomatic treatment has life transforming implications for future generations and family planning decisions	Comment noted. Innovation will be considered in more detail as part of the evaluation. No action required.
Questions for consultation	Novartis Gene Therapies (company)	**Where do you consider onasemnogene abeparvovec will fit into the existing care pathway for pre-symptomatic SMA?** Onasemnogene abeparvovec is already routinely commissioned for patients clinically diagnosed as SMA type 1. Patients from the screened population will be given a single-dose IV infusion of onasemnogene abeparvovec before symptoms are observed. Diagnosis of SMA in the screened population in the UK is currently through genetic testing referrals due to a sibling history of SMA or a parent with confirmed carrier status. Diagnosis is confirmed by genetic testing of *SMN1/SMN2*.	Comments noted. Please see relevant sections of this document for related response.

Section	Consultee/ Commentator	Comments [sic]	Action
		A single-dose IV infusion of onasemnogene abeparvovec would be administered as soon as possible after the genetic diagnosis of SMA is confirmed. Treated patients would be expected to achieve age-appropriate milestones that would never be achieved in untreated patients and may not have been achieved if treatment had been delayed until symptoms developed. **Would any additional tests be required in clinical practice with the use of onasemnogene abeparvovec in this population?** The screened population will have had their diagnosis confirmed with genetic testing of *SMN1/SMN2*. Prior to treatment with onasemnogene abeparvovec, the patient must be checked for symptoms of active infectious disease of any nature. Before administration of onasemnogene abeparvovec, baseline laboratory testing is required, including (3): • AAV9 antibody testing using an appropriately validated assay • Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin • Creatinine • Complete blood count (including haemoglobin and platelet count) • Troponin-I **Do you consider onasemnogene abeparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes – see Innovation section above.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Are there any subgroups which should be considered separately? For example, should subgroups by *SMN2* gene copy number be considered? There are no subgroups of people within the screened population in whom onasemnogene abeparvovec should be examined separately. Onasemnogene abeparvovec is indicated for patients with 5q SMA with a bi allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene (3). The SPR1NT trial was designed with two cohorts of patients with up to three copies of *SMN2* that represent the population in the MAA (11) The *SMN2* two-copy and *SMN2* three-copy cohorts have different efficacy outcomes and length of time followed in the trial. SMA exists on a broad spectrum, and although patients with different *SMN2* copy numbers are genetically distinct, there is overlap in clinical symptoms and disease severity. For example, although in general, fewer copies of *SMN2* may result in a more severe disease phenotype, some patients with three copies of *SMN2* will develop a severe form of SMA (12). Considering subgroups of patients with differing numbers of *SMN2* separately may exclude some patients with severe disease from early treatment. **Do you consider that the use of onasemnogene abeparvovec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** An important benefit provided by onasemnogene abeparvovec that will not be captured by the quality adjusted life years measure of health benefit is benefit to caregivers (34).	

Section	Consultee/ Commentator	Comments [sic]	Action
		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. In a recent survey, caregivers of non-sitters in the UK reported a substantial burden on their time, employment status, and income, with the majority either changing their working hours or stopping work entirely (35). Although caregivers in the UK did not incur out-of-pocket expenses for respiratory support, mobility equipment, wheelchairs or nutrition support, they did incur substantial out-of-pocket expenses for home adaptations, home healthcare and other ongoing expenses. **Treatment with onasemnogene abeparvovec soon after genetic diagnosis may alleviate the burden that comes with caring for a child with SMA, as demonstrated by the achievement of age-appropriate motor milestones within normal WHO developmental windows and the ability to thrive by patients in the SPR1NT trial (7).**	
	Muscular Dystrophy UK	From observations and discussions with families, we consider that onasemnogene abeparvovec would be the first choice of families with a child with pre-symptomatic/screening detected SMA Early symptoms of SMA may not be immediately obvious. It may be necessary to define 'pre-symptomatic', especially with a comparator of best supportive care. Some babies may have mild symptoms at birth, for example, tongue fasciculation, quiet voice, abdominal breathing, minor feeding issues amongst others. A muscle stimulation test or similar may be required to allocate a pre or post symptomatic treatment pathway. Yes, compared to best supportive care, onasemnogene abeparvovec is a life-giving technology. For those who already have SMA in the family it is an opportunity to see their children follow normal developmental patterns compared to life limiting disabilities or in the more severe cases death. It will also transform the family planning decision making process.	Comments noted. Please see relevant sections of this document for related response

Section	Consultee/ Commentator	Comments [sic]	Action
	Spinal Muscular Atrophy UK	*Where do you consider onasemnogene abeparvovec will fit into the existing care pathway for pre-symptomatic SMA?* From observations and discussions with families, we consider that onasemnogene abeparvovec would be the first choice of families with a child with pre-symptomatic SMA *Would any additional tests be required in clinical practice with the use of onasemnogene aberparvovec in this population?* Early symptoms of SMA may not be immediately obvious. It may be necessary to define 'pre-symptomatic', especially with a comparator of best supportive care. Some babies may have mild symptoms at birth, for example, tongue fasciculation, quiet voice, abdominal breathing, minor feeding issues amongst others. A muscle stimulation test or similar may be required to allocate a pre or post symptomatic treatment pathway if the options are different. *Do you consider onasemnogene abeparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Yes, compared to best supportive care, onasemnogene abeparvovec is a life-giving technology. For those who already have SMA in the family it is an opportunity to see their children follow normal developmental patterns compared to life limiting disabilities or in the more severe cases death. It will also transform the family planning decision making process.	Comments noted. Please see relevant sections of this document for related response.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are there any subgroups which should be considered separately? For example, should subgroups by SMN2 gene copy number be considered? For the reasons given above we would **not** want to see *SMN2* sub-groups within the grouping of 1 – 3 *SMN2* copies for this treatment.	
Additional comments on the draft scope	Spinal Muscular Atrophy UK	Any additional comments on the draft scope Though the application is only for those with 1 – 3 SMN2 copies, we would like to see a discussion about the position of babies with 4 copies of SMN2. 3 SMN2 copies are 'usual' for children who develop SMA Type 2 or SMA Type 3a – both of which result in significant disabilities. However: • children clinically classified as having SMA Type 2 may have a range of 2 – 4 SMN2 copies; • children clinically classified as having SMA Type 3a may have a range of 3 – 5 SMN2 copies. If then pre symptomatic treatment is restricted to those with 1 – 3 SMN2 copies, some children will miss out on the optimum delivery of treatment. We suggest that 'watch and wait' for symptoms to appear in these children, which means the disease has progressed is unacceptable. We are aware that the comparator here is best supportive care, but the reality is that pre-symptomatic children who have 4 SMN2 copies may only at the moment have access to risdiplam via the MAA once they are 2 months old and that there is a possibility that this timing may in due course be addressed and be earlier. Though this is a positive possibility, from a family perspective access to a one-off gene therapy may well be the preferred option.	Comments noted. Onasemnogene aberparvovec has a license for "5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene". The technology will be evaluated within its license. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		We suggest that there needs to be a discussion with clinical experts so that recommendations made by NICE about access to the range of possible treatments for children who are pre-symptomatic are aligned with international consensus and best practice. We suggest that the NICE discussion should also include the impact of copy number restrictions on access to treatment in terms of who would and would not have access to treatment if there were population screening. This will be an important consideration for the NSC's review and recommendation process. We suggest access needs to be assured for all those who are at risk of developing early onset childhood onset SMA	
	Muscular Dystrophy UK	The community would want assurance that there will be immediate post diagnosis access to a bridging treatment that would be prescribed during the time that pre-administration assessments for onasemnogene abeparvovec are taking place. Blood tests, administration and logistics can take a significant amount of time during which the baby could potentially develop symptoms.	Comments noted. This evaluation will focus on the clinical and cost-effectiveness of onasemnogene aberparvovec. The evaluation will consider the current treatment pathway for SMA. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Neonatal and Paediatric Pharmacists Group (NPPG)

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