NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal

Onasemnogene abeparvovec for treating spinal muscular atrophy type 1 ID1473

Consultee and commentator comment form

Please use this form for submitting your comments on the draft remit, draft scope and provisional matrix of consultees and commentators. It is important that you complete and return this form even if you have no comments otherwise we may chase you for a response.

Enter the name of your organisation here: Spinal Muscular Atrophy UK

Comments on the draft remit and draft scope

The draft remit is the brief for a proposed appraisal. Appendix B contains the draft remit. The draft scope, developed from the draft remit outlines the question that the proposed appraisal would answer.

Please submit your comments on the draft remit and draft scope using the table below. **Please take note of any questions that have been highlighted in the draft scope itself** (usually found at the end of the document).

If you have been asked to comment on documents for more than one proposed appraisal, please use a separate comment form for each topic, even if the issues are similar.

Please complete this form and upload it to NICE Docs by **Wednesday 17 October 2018**. If using NICE docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact Emily Richards, Scoping Project Manager, emily.richards@nice.org.uk (0)161 413 4070

If you do not have any comments to make on the draft remit and draft scope, please state this in the box below.

Comment 1: the draft remit

Section	*Notes*	Your comments
Appropriateness	*It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for*	Yes

Section	*Notes*	Your comments
	appraisal?	
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	Yes
Timing Issues	*What is the relative urgency of this proposed appraisal to the NHS?*	**Very urgent.** Infants with SMA Type 1 have been able to access nusinersen via the Expanded Access Programme. This is due to close at the end of October and, unless a Managed Access Agreement (MAA) is secured, newly diagnosed infants will no longer have access to this treatment. Even if there is an MAA for nusinersen, if this new 'one off' treatment offers equal or better potential for quality of life, parents and clinicians need to have the choice to access it. The length of time the appraisal process for nusinersen in England has taken has created immense distress for families in the SMA community. We urge NICE not to allow this to happen with this treatment
Any additional comments on the draft remit		

Comment 2: the draft scope

Section	*Notes*	Your comments
Background information	*Consider the accuracy and completeness of this information.*	We suggest that this could be clearer and more accurate, as follows: • Refer throughout to **5q SMA.** This is the most common **form** of SMA and includes **Types** 1, 2, 3 and 4 • First paragraph might more accurately read: 'Its most common form, 5q SMA, which includes childhood onset SMA Types 1, 2, 3 and adult onset Type 4, is caused by defects in the gene SMN1, which leads to degeneration of motor neurones in the spinal cord. The motor neurones most affected by this condition are those that allow walking, crawling, arm movement, head and neck movement, swallowing and breathing. SMA Type 1, the most severe of the childhood onset types of 5q SMA typically cause death

Section	*Notes*	Your comments
		before age 2 years. It has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts' **We suggest that, given this treatment is only for SMA Type 1, it may not be relevant to talk about the other types of 5q SMA.** If it is considered relevant, we suggest these descriptions may more accurately continue as follows: • 'SMA Type 2 may shorten life expectancy while life expectancy for SMA Types 3 and 4 is normal.' Also suggest that Type 2 and 3 descriptions should read: • 'In SMA Type 2 the onset of symptoms is between 7 and 18 months of age. People with this condition are often severely disabled **and are unable to stand without support. They are never able to walk unaided.'** • 'Most people with Type 3 SMA **can walk at some point,** but many lose mobility over time.' • **Treatment usually follows guidelines agreed by international experts. These have been most recently documented in the Standards of Care for SMA (November 2017).** (note there is no committee as such) References for this (which you may want at the end of the document?) are: • Mercuri E, et al. **Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care**. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi:10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. http://smasupportuk.org.uk/international-standards-of-care-for-sma (Accessed 29 August 2019) • Finkel RS et al. **Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics.** Neuromuscul Disord. 2018 Mar;28(3):197-207. doi: 10.1016/j.nmd.2017.11.004. Epub 2017 Nov

Section	*Notes*	Your comments
		23. http://smasupportuk.org.uk/international-standards-of-care-for-sma (Accessed 29 August 2019) We note the remit references our website as the source of population stats – thank you. Just to say we updated all our information sheets in September so the actual link to this information is now: http://smasupportuk.org.uk/what-is-spinal-muscular-atrophy . Just a small note of concern, that the remit quotes SMA Support UK as the source of the statistics, rather than pinpointing the information sheet / link which identifies these two publications as the source of the incidence and prevalence of 5q SMA data: • Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, Cook SF, Lochmüller H (2017) **Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy –a literature review**. *Orphanet J Rare Dis* 12: 124. • Verhaart IEC, Robertson A, Leary R, McMacken G, König K, Kirschner J, Jones CC, Cook SF, Lochmüller H. (2017) **A multi-source approach to determine SMA incidence and research ready population.** *J Neruol* 264: 1465-1473. And these as the source of the England & Wakes population statistics: • Office of National Statistics (2018) '**Births in England and Wales: 2017'.** Available at: • www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytables englandandwales/2017 (Accessed:26 August 2018) • Office for National Statistics '**Overview of the UK Population: July 2018.'** Available at www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2017#main-points (accessed 26 August 2018) Would readers need to know this so that they can confirm / dispute what has been said?

Section	*Notes*	Your comments
The technology/ intervention	*Is the description of the technology or technologies accurate?*	Yes, as far as we are aware
Population	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*	We understand this is the correct population for this intravenous treatment which is not possible for children diagnosed later with SMA Type 2 or 3.
Comparators	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*	If nusinersen is recommended for funding by NHS England we suggest that: • Nusinersen alone is not the 'best alternative care' comparator. In most cases, the 'best alternative care' comparator would be: • Nusinersen in conjunction with adherence to supportive care as outlined in the internationally agreed standards of care for SMA (November 2017) However, a family may not wish to embark on long-term intrathecally administered nusinersen treatment, or there may be a clinical reason why nusinersen is not recommended for a particular child. In this case, the 'best alternative care' comparator would be: • Adherence to supportive care as outlined in the internationally agreed standards of care for SMA (November 2017)
Outcomes	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	This appears to be a comprehensive list. We strongly suggest, however, that health-related quality of life should be of both the patient and parent / carers / family. Due to their children's care or needs, parents/carers of children with SMA Type 1 often struggle with lack of sleep, emotional distress and mental health challenges. The impact on siblings and grandparents can also be significant, affecting their emotional / mental health quality of life.

Section	*Notes*	Your comments
Economic analysis	*Comments on aspects such as the appropriate time horizon.*	Please see comments in answer to questions posed in the Innovation section
Equality	*NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* • *could lead to recommendations that have a different impact on people protected by the*	We understand from Avexis and clinicians that, if access is agreed, due to the specialist nature of the treatment and method of delivery, it would be likely to be limited to the two treatment Centres currently engaged in related clinical trials. It would be important to ensure that all families with a child meeting the treatment criteria have equal access, no matter where they live. To ensure this, assistance with travel and accommodation for those needing it would be essential.

Section	*Notes*	Your comments
	equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*	
Other considerations	*Suggestions for additional issues to be covered by the proposed appraisal are welcome.*	
Innovation	*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)? Do you consider that the use of the technology can result in any potential*	**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)?** A 'one-off' intravenous treatment leading to improvements in the outcomes listed would be a step-change in the treatment and management of the condition. To quote Professor Kevin Talbot DPhil FRCP, Head of the Division of Clinical Neurology, Nuffield Department of Clinical Neurosciences, University of Oxford, this gene therapy, 'is a remarkable development and a historic landmark' The treatment uses harmless, genetically-engineered viruses to increase SMN protein levels and in late 2017, received "Breakthrough Therapy" status in the USA to facilitate its development. It is most definitely innovative in its approach endeavouring to address the fundamental cause of 5q SMA Type 1.

Section	*Notes*	Your comments
	significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*	**Do you consider that the use of onasemnogene abeparvovec can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** We note the significant difficulties there have been with the economic analysis for nusinersen and that the NICE committee's consultation paper (August 2018) raised concerns that identifying robust utility values in babies and young children is exceptionally challenging. We draw attention to the flaws the measures present as summarised by **Griebsch, I *et al*. Quality-Adjusted Life-Years Lack Quality in Pediatric Care: A Critical Review of Published Cost-Utility Studies in Child Health** Pediatrics May 2005, VOLUME 115 / ISSUE 5 : • Children undergo dramatic changes in growth and function (e.g., mobility, self-care) at different rates, difficulties may arise to attribute improvements to health care interventions rather than to normal development. There is no methodologic guidance about how this should or even might be dealt with. • All current generic measures (with the exception of the Health Utility Index Mark 2) are derived from adult populations, and additional attributes that are particularly relevant to child health, including, for example, autonomy, body image, cognitive skills, and family relationships, may not be captured by these measures. Furthermore, no generic instrument for children and infants **younger than 5 years** is available. • Children, particularly young children do not have the cognitive ability to comprehend and complete valuation or even measurement tasks. The implication is that, for very young children, some form of proxy inevitably will be used for measurement tasks, whether this be the clinician or the parent. Although parents may be perceived by economists as the more appropriate source of measurement and/or valuation, the potential for interaction between the utility function of the parent and the proxy (their child) for whom he or she is making the measurement/valuation may lead researchers to choose to use clinician judgment to avoid this problem. The issues with this are that: clinicians only see and record a 'snapshot' which may not truly represent the changes taking place and impact on daily living for both child and parents; measurement tools are insufficiently subtle and limited in their measurements.

Section	*Notes*	Your comments
		This last point is confirmed in many studies that show this, for example, Srikrishna S, *et al.* **(**2009*)* **Is there a discrepancy between patient and physician quality of life assessment?** Neurourol Urodyn. 2009;28(3):179-82. doi: 10.1002/nau.20634. The NICE nusinersen committee (August 2018) further concluded that quantifying carer -related disutilities was extremely difficult. We are concerned that an economic analysis should cover all direct health and personal health and social services costs including: • **mental health:** • **equipment costs and housing adaptations**: • **emergency hospital stays, surgery and clinic time:** • **continuing health care (CHC) cost:** Though we accept that, due to the length of time the treatment has been trialled, there will be uncertainty as to future long-term outcomes for those treated with this gene therapy, the evidence to date clearly indicates that these wider costs will potentially reduce significantly. We consider it vital that this potential is adequately reflected in the ICER. We are also concerned that any model needs to reflect that the health impact is not only on **one** carer but also on the many e.g. grandparents often play a key role. Also, that due to the 'carer burden' of caring for someone with SMA, that it impacts on other caring responsibilities of the carer e.g. a parent who is unable to care for a sick or elderly relative such that their care needs fall to health and personal social services. However much effort is made to adjust the ICERs to better reflect evidence and address shortcomings, we suggest that NICE's economic analysis remains fundamentally flawed as it does not reflect the much wider impact in the 'real world' of the costs of the condition and potential benefits of treatment. From our perspective there needs to be a much more holistic approach as only then can the ICERs really begin to reflect the true potential value of this and any treatment. As examples of this 'real world' wider impact of 5q SMA, there are:

Section	*Notes*	Your comments
		• **education costs**: requiring Teaching Assistants, school adaptations • **work costs:** carers (parents and grandparents) who have to give up work to care for their child, and in the long term the child – loss of potential productivity and contribution to the economy through work / taxes • **health and social care costs borne by families:** interventions and support paid for by health and social services and included in NICE's model are insufficient for families to manage and are 'topped up' either formally or informally by the family e.g. care hours • **many equipment and housing adaptation costs are borne by families** **In summary: we strongly suggest that NICE adopts an economic analysis that includes:** • **all these 'real-world' costs that are currently not included in their model** • **all aspects of the health and personal health and social services required to support a child with SMA Type 1 and their family** • **the impact of SMA affecting more than one carer.** **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Avexis Clinical Trial data will in due course also include Phase 3 trial results STRIVE1-EU.
Questions for consultation	*Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the*	**How many people have SMA type 1 in England, and how many would be offered onasemnogene abeparvovec therapy?** Population statistics (see references above and England & Wales live births 2017 = 679,106), suggest that the incidence of SMA Type 1 in England and Wales = 60% x 68 = **41 infants born with SMA Type 1 each year.** We assume that potentially all these infants would be offered this therapy though it may not be clinically indicated for a very few extremely weak infants with SMA Type 0. If nusinersen is at this stage being funded by NHS England for infants with SMA Type 1, this may be an alternative choice. Both treatments would be offered in combination

Section	*Notes*	Your comments
	planned time lines).	with best supportive care as outlined in the SoC with a further alternative of best supportive care only. **How will people with type 1 SMA be identified for treatment with onasemnogene abeparvovec?** Infants may be diagnosed in hospital shortly after birth, following admission with a respiratory crisis or in the community following concerns of muscle weakness reported / observed by parents / health visitor / community nurse / GP. Diagnosis can be quickly confirmed via an SMN1 gene deletion blood test which is usually available within 2 – 4 weeks. Given the clinical trial findings are strongly indicating that the earlier the intervention the better the potential outcome, it is essential that this path to diagnosis is as rapid as possible. Any health practitioner potentially making this diagnosis must be both aware of and able to offer a rapid path to this treatment. Communication and referral paths from the community, neuromuscular centres and specialist treatment centres must be first rate and seamless. A diagnosis of SMA Type 1 is devastating for parents and families who often describe their shock, numbness, disbelief and emotional turmoil. It is a hugely difficult time for them to make any decisions and yet the timing of any potential drug treatment may well be critical. Not only would they have to decide on whether to agree to a drug treatment, they would now potentially be having to decide which of two options to choose. It is essential that these options are discussed fully and carefully with them by clinical experts, that expectations are appropriately managed and that they are supported emotionally and practically during this time and that this support continues **How is onasemnogene abeparvovec expected to be used in clinical practice? At what point in the treatment pathway would it be considered?** We understand the earlier the intervention the better the potential outcomes and that therefore treatment should be considered and delivered as soon after diagnosis as is practically possible. **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** The NICE committee appraisal of nusinersen has already compiled significant data on the impact of SMA Type 1 on

Section	*Notes*	Your comments
		families and data on the clinical effectiveness of nusinersen. It has already explored current economic models and deliberated over their limitations. It will be aware of new data on nusinersen via 'real-world' studies of those enrolled in the global EAP for SMA Type 1 and any new reports by Biogen of further clinical trial /other data following licencing in other countries. NICE will be aware of other ongoing trials being conducted by Biogen and Novartis/Avexis. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Both Great Ormond Street Hospital (GOSH) and the John Walton Muscular Dystrophy Centre for Research in Newcastle will be delivering the Phase 3 trial of the therapy. There should therefore be no practical barrier to the administration and delivery of the treatment. SMA REACH is already mapping outcomes of the natural history of children with 5q SMA and the outcomes for children with SMA Type 1 treated with nusinersen. The infrastructure is therefore there for the monitoring of outcomes with this therapy. Outcomes that have every day clinical meaning and don't create an extra burden for clinicians need to be recorded. Administrative support / funding for this needs to be in place and, we understand, is underway. There need to be easy ways for parents to report the impact treatment has on their child and their health-related quality of life. We understand there are already significant developments for this via the global TREAT-NMD SMA Patient Registries, which include the UK SMA Patient Registry. Work to streamline the interface between SMA REACH and other SMA Patient Registries needs to continue such that outcomes for nusinersen, this treatment and any future treatments are captured and can be compared via one database. Clinicians will need to have available clear accessible user-friendly information about the treatment options that families will face. They will need to be given time to deliver this information and to either provide or set up appropriate ongoing support. Patient groups will also need this information so that, when asked, they can support parents / families with accurate

Section	*Notes*	Your comments
		information about treatment and processes which enable parents / families to make their own very personal and individual choices. **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).** We strongly urge NICE to appraise this technology via the HST route as it meets the criteria for this route, namely: • Clinical trial evidence suggests that there is likely to be significant benefit to patients in terms of efficacy and administration. This is a 'one off' intravenous treatment • Though the price will be high, due to its being 'one off' the price will be known • There is appropriate clinical trial evidence, such as would enable evaluation. This is either available or anticipated to be available in the near future • The timing is right. There has not yet been an application to EMA, but we understand this is imminent. NICE has already collected a significant amount of evidence of the impact of SMA and the urgent need for treatment and is aware of economic models and their limitations. There is therefore a huge inroad already into the information required for this appraisal. This should allow NICE to include a plan for an HST of this treatment in its workload timeline now and publish timely guidance within six months of the marketing authorisation • Given the information available, the relevant clinical question(s) could be addressed by the application of the highly specialised technologies evaluation methodology **Additionally:** • The target patient group for the technology in its

Section	*Notes*	Your comments
		licensed indication is of an absolute maximum of 40 children a year. The numbers are so small and the technology so specialised that it will be concentrated in very few centres in the NHS – likely to be only the two named above • The target patient group is distinct for clinical reasons: though there is some blurring between types of SMA as there is a continuum of severity, we understand this intravenous treatment has to be delivered by age 6 months. Only children with SMA Type 1 show symptoms and are diagnosed by this age • The condition is chronic and severely disabling – this is clearly evidenced and well known to NICE via the EAP for SMA Type 1 and its nusinersen appraisal • The technology is expected to be used exclusively in the context of a highly specialised service: though the prevalence of all Types of 5q SMA exceeds the 'usual' 500 limit for specialised services, in view of the population incidence, services for SMA Type 1 would meet this criterion • The technology is likely to have a very high acquisition cost • The technology has the potential for life long impact • The need for national commissioning of the technology is significant.
Any additional comments on the draft scope		

Comment 3: provisional matrix of consultees and commentators

The provisional matrix of consultees and commentators (Appendix C) is a list of organisations that we have identified as being appropriate to participate in this proposed appraisal. If you have any comments on this list, please submit them in the box below.

As NICE is committed to promoting equality and eliminating unlawful discrimination Please let us know if we have missed any important organisations from the lists contained within the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

If you do not have any comments to make on the provisional matrix of consultees and commentators, please cross this box: ☐x

Comments on the provisional matrix of consultees and commentators

Comment 4: regulatory issues (to be completed by the company that markets the technology)

Section	*Notes*	Your comments
Remit	*Does the wording of the remit reflect the current or proposed marketing authorisation? If not, please suggest alternative wording.*	
Current or proposed marketing authorisation	*What are the current indications for the technology?*	
	What are the planned indications for the technology?	
	FOR EACH PLANNED INDICATION:	
	Which regulatory process are you following?	
	What is the target date (mm/yyyy) for regulatory submission?	
	What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable)	
	What is the anticipated date (mm/yyyy) of regulatory approval?	
	What is the anticipated date (mm/yyyy) of UK launch?	
	Please indicate whether the information you provide concerning the proposed marketing authorisation is in the public domain and if not when it can be released. All commercial in confidence	

Section	*Notes*	Your comments
	information must be highlighted and underlined.	
Economic model software	*NICE accepts executable economic models using standard software, that is, Excel , DATA, R or WinBUGs. Please indicate which software will be used. If you plan to submit a model in a non-standard package, NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non – standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software*	

Please complete this form and upload it to NICE Docs by **Wednesday 17 October 2018**. If using NICE docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact Emily Richards on (0)161 413 4070 or at above the email address.