National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nusinersen for treating spinal muscular atrophy

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Biogen Idec	Yes, it is appropriate to refer this topic to NICE for appraisal. However, based on correspondence to the Topic Selection team via letter on 24/10/2016 and 04/11/2016, Biogen's view is that it would be more appropriate to assess nusinersen via the Highly Specialised Technology (HST) pathway. The rationale for this is the unlikelihood that a Single Technology Appraisal (STA) could capture the full clinical benefit for patients with Spinal Muscular Atrophy (SMA) who would be suitable for treatment with nusinersen (see below).	Comment noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as a Single Technology Appraisal (STA). No action required.
	British Paediatric Neurology Association (Muscle Interest Group)	It is appropriate. This is relevant to a population of children with a life-limiting disorder. This is a proiority area of Rare diseases and published evidence suggests this may significantly improve the health of this population (Finkel et al Lancet doi.org/10.1016/50140-6736(16)31408-8	Comment noted. No action required.
	Genetic Alliance UK	Spinal muscular atrophy (SMA) is a rare condition causing debilitilitating symptoms and frequently very early death. There is currently no treatment which addresses underlying cause of SMA, and this significant unmet need has been recognised by the European Medicines Agency who have granted	Comment noted. Following extensive discussion, it was agreed that this topic is

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		the medicine orphan designation and accelerated assessment. As such, it is appropriate for the medicine to be considered by NICE. However, based on current best estimates of incidence and prevalence, it appears that the population of children who would benefit from treatment may be approximately 900. We understand from our member, SMA Support UK that a significant number of families would choose not to use this treatment. This population size makes the treatment eligible for consideration through the HST programme. Since the NHS England specialised commissioning process, which is supposed to fill the gap between the NICE HST and STA routes is functioning extremely poorly and slowly at present, and nusinersen meets several of the other criteria for the HST programme (the target patient group is so small that treatment will usually be concentrated in very few centres in the NHS; the condition is chronic and severely disabling; the medicine is likely to require life long use and national commissioning), it would be appropriate for this treatment to be considered in the HST programme, which should have its capacity expanded to permit all new medicines which meet the topic selection criteria to be evaluated by this route. We believe the HST Evaluation process is more appropriate for this treatment than the Single Technology Appraisal process.	appropriate for consideration as an STA. No action required.
	Muscular Dystrophy UK	Nusinersen has been shown in clinical trial to have a clinically significant impact upon motor function in patients with SMA Types 1 and 2. These are life-limiting and devastating conditions. SMA Type 1 is exceptionally severe, with 95% of children having a life expectancy of less than 18 months. As noted in the draft scope, there are no active treatments for the condition. Nusinersen provides a hugely valuable opportunity to treat the disease, and represents a significant medical breakthrough.	Comment noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as an STA. No action required.

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		It would be appropriate to refer this topic to NICE. However, in the view of Muscular Dystrophy UK the drug should be appraised via the Highly Specialised Technologies route, rather than the proposed Single Technology Appraisal. There are around 440 patients with SMA Types 1 or 2 in England and Wales. This falls below a patient population of 500 - which Muscular Dystrophy UK understands is the upper-limit for a drug to be considered under the HST programme. It is this patient group - SMA Types 1 and 2 - for which cliical trial data on efficacy exists. Moreover, the expertise and capacity to deliver this treatment exists at a very limited number of centres (due to the way the drug is administered via intrathecal injection). Besides Great Ormond Street and Newcastle - the two PI sites for the clinical trial - not all specialist centres with SMA Type 1 or 2 patients under active follow up will be able to administer the drug. It is therefore likely that the number of centres involved will fall far below that of administering centres for ataluren (the last drug for a neuromuscular condition to be appraised by NICE). Muscular Dystrophy UK believes that an HST review would give greater opportunity to consider the impact of SMA on the infant child and their family. In the case of SMA Type 1 especially, life expectancy is very limited. It is therefore challenging to develop a QALY measure for the condition and we are concerned that a simple cost effectiveness analysis through an STA would not give sufficient scope to consider disease impact.	
	Spinal Muscular Atrophy Support UK	The clinical trials for this treatment have been followed keenly by families affected by SMA. We understand that the latest results are extremely positive (Science Magazine 6/12/16 “In their November announcement about the second trial’s halt, Ionis and Biogen, which has licensed nusinersen and has dubbed it Spinraza, said the treated children experienced a “highly statistically significant improvement” in motor function compared to untreated children. The companies had used an established, widely used test of motor	Comment noted. No action required.

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		movements that monitors actions like sitting, standing, putting the hands on the head and taking steps. Stanley Crooke, the CEO of Ionis, is bluntly enthusiastic. “The babies [with the severest disease] are alive and the longer we treat the better they seem to get,” he says. “It’s a miracle.”) There has been much social media activity and speculation within the SMA community, both within the UK and internationally, as to which children, when and how may have access to the treatment. We are very aware of lobbying activity by groups such as the Fast Movement (in the US) and the hopes that are pinned on this treatment. In view of this environment we consider an appraisal now would be highly appropriate.	
	SMA Trust	There are currently no treatments for the genetic, progressive neuromuscular condition, spinal muscular atrophy (SMA). Nusinersen has the potential to address an urgent unmet medical need for people living with this condition. Slowing the progression of SMA could reduce care costs, as well as other financial aspects associated with the disease. It also has the potential to improve the quality of life of those with the condition, as well as their family members and/or carers. Both of the two clinical trials were closed following interim analysis, having met their primary endpoint (a highly statistically significant improvement in motor function). All of which evidence leads us to the conclusion that it would be highly appropriate to refer this topic to NICE.	Comment noted. No action required.
Wording	Biogen Idec	The wording does not capture the recognised orphan status of this product and the rare disease status of SMA. Biogen is of the opinion that the wording of the remit does not reflect adequately the inherent complexity in measuring meaningful clinical effectiveness and cost-effectiveness. Furthermore, given	Comment noted. The remit is a brief statement outlining the overall objective of the appraisal, and does not

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		the nature of the condition and the paediatric population which it affects, the issue of generating quality of life data is not raised.	discuss further details of the content of the appraisal. No action required.
	British Paediatric Neurology Association (Muscle Interest Group)	*Does the wording of the remit reflect the issues of clinical and cost effectiveness about this technology that NICE should consider?"* Yes	Comment noted. No action required.
	Genetic Alliance UK	The wording of the remit matches the standard format.	Comment noted. No action required.
	Muscular Dystrophy UK	We do not propose alternative wording. However, it is essential that in any appraisal of the drug, NICE considers the unmet medical need and exceptional severity of the condition. The appropriate route through which to do this would be the HST process.	Comment noted. The remit is a brief statement outlining the overall objective of the appraisal, and does not discuss further details of the content of the appraisal. Following extensive discussion, it was agreed that this topic is appropriate for consideration as an STA. No action required.

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	Spinal Muscular Atrophy Support UK	Given there are other rarer forms of SMA with other underlying genetic causes, does it need to state that it is only targeting childhood onset forms of SMA caused by a fault/mutation in the SMN1 gene ?	Comment noted. Nusinersen will be appraised within its marketing authorisation: that is, for 5q-SMA. This is discussed in the Background and Population sections of the scope.
	SMA Trust	We do not propose alternative wording. However, it is essential that in any appraisal of the drug, NICE considers the costs of the treatment in relation to the unmet medical need and severity of the condition as well as the costs of care and wider economic costs of Spinal Muscular Atrophy.	Comment noted. The remit is a brief statement outlining the overall objective of the appraisal, and does not discuss further details of the content of the appraisal. No action required.
Timing Issues	Biogen Idec	SMA affects patient survival and is one of the leading causes of infant genetic death and disability. Type I patients have a life expectancy of less than 2 years and there are currently no approved treatments for SMA. The interim data for nusinersen were so compelling that the sham control arm in the studies was discontinued early for active drug and the regulatory process was expedited. This demonstrates the unprecedented potential for nusinersen. There is a clinically urgent need for the product in this area of high unmet need which should be reflected in the urgency of the appraisal.	Comment noted.
	British Paediatric Neurology	This is relatively urgent. Treatment is to be offered under an Extended Access Programme (EAP) but there are significant difficulties in achieving	Comment noted.

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	Association (Muscle Interest Group)	equity of access to the EAP across the country, already causing pressures of referrals to some paediatric clinical neuromuscular centres.	
	Genetic Alliance UK	Currently there are no treatments available for the condition and significant unmet need. SMA is the most common genetic cause of infant mortality in the UK. The evaluation is of particular urgency due to the speed at which the condition progresses particularly in SMA type 1, with only months from onset of symptoms to likely death. For this reason it is important that patients in England are able to access the treatment as soon as possible after a license is granted, which we understand is likely to be in early 2017.	Comment noted.
	Muscular Dystrophy UK	Given the very limited life expectancy of these children and the promising clinical trial data Muscular Dystrophy UK believes the drug should be urgently appraised.	Comment noted.
	Spinal Muscular Atrophy Support UK	For the SMA community, the appraisal is very urgent.	Comment noted.
	SMA Trust	In SMA Type 1 (the most severe and also most common form), progression and loss of function is rapid and most children die within the first 2 years. A licence from the EMA may approve the drug, meaning a swift appraisal would be necessary in order to try and ensure that no eligible patient progresses, loses function or dies before NICE guidance is issued and the drug available in clinic. In addition, pre-clinical studies suggest that early administration of the drug yields most benefit (Duque SI, Arnold WD, Odermatt P, et al. A large animal model of spinal muscular atrophy and correction of phenotype. Annals of neurology 2015; 77:399-414).	Comment noted.

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Additional comments on the draft remit	Biogen Idec	This is the first breakthrough in 140 years for patients and families living with SMA (since the disease was classified). Strong interim data suggests that this is a potential life-altering and transformational treatment for SMA; and for those children who respond, nusinersen has demonstrated improvement in gross functional motor milestones which has a high impact on quality of life (QoL) for patients and families. Biogen believes that, should the product be assessed via an STA process, the chances of a successful appraisal are remote.	Comments noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Biogen Idec	It should be noted that degeneration of motor neurones will occur in both the spinal cord and the brain stem. It should also be noted that Biogen and Ionis conducted a comprehensive clinical trial programme, primarily in Type I and Type II SMA, of which there are approximately 450 children affected by the condition in the UK. For England and Wales, it has been calculated that the prevalent population of Type I and II patients is c. 380. Moreover, following application of clinical trial inclusion criteria, it is estimated that the eligible patient population estimate will again reduce and that the number of patients well enough to undergo treatment would reduce this figure further again.	Comments noted. The background section has been updated based on consultation comments and discussion at the scoping workshop. Please note that this section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive.
	British Paediatric	This is accurate, although there should be reference to the breathing muscules in the first paragraph as this has the greatest impact in those most	Comments noted. The background section has

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	Neurology Association (Muscle Interest Group)	severely affected infants. The complexity of disabilty means that the level of support required for these children is extremely high and life-long. A treatment which mitigates the severity of the disease will potentially have a significant economic benefit.	been updated based on consultation comments and discussion at the scoping workshop. Please note that this section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive.
	Genetic Alliance UK	We understand that the life expectancy given for SMA type 2 is based on out of date information, and thus shorter than is the case currently. According to our members SMA Support UK, although young people with type 2 do have a shortened life expectancy, improvements in care standards mean that the majority of people can now live long, fulfilling and productive lives. It is also important to emphasise that these disease types are not rigid categories. There is a wide spectrum of severity both between the different types of SMA and between children, young people and adults within each type. The spectra of the types of SMA meet and overlap. Additionally, it should be mentioned that in addition to SMA caused by alterations in the SMN1 gene, there are also rarer forms of SMA with a different genetic basis. These are not treatable with this medicine.	Comments noted. The background section has been updated based on consultation comments and discussion at the scoping workshop. Please note that this section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive.
	Muscular Dystrophy UK	Yes the background is accurate in broadly describing SMA but more detail could be given on the severity of this condition (particularly types 1&2) and the impact it has on parents'/carers' lives. It is worth noting that the quality and availability of supportive care strategies varies between countries but	Comments noted. The background section has been updated based on consultation comments

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		also within regions. The majority of this care, including physiotherapy, respiratory assistance and tube feeding, is adminstered by parents/carers within the home. This can be a full-time job, having huge social, emotional and financial impacts.	and discussion at the scoping workshop. Please note that this section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive.
	Spinal Muscular Atrophy Support UK	Background Information We are concerned that the description of SMA is not completely accurate. In particular, it refers to: SMA causing paralysis; suggests by inference that those with SMA Type 1 and SMA Type 2 are (separately) homogenous groups; that life expectancy for those with SMA Type 2 is usually into adolescence only. SMA Support UK is accredited to the Information Standard and publishes accurate up to date evidence based information for the public. It is carefully peer reviewed. The following, we suggest, is our more accurate summary of the condition reached in consultation with UK consultants and in reference to the International Standards of Care for SMA. It is also referenced by NHS Choices. “Spinal Muscular Atrophy (SMA) is a rare, genetic neuromuscular condition. SMA causes progressive loss of movement and muscle weakness as a result of muscle wasting (atrophy). Due to inheriting two faulty SMN1 genes, only very low amounts of the SMN protein can be produced causing lower motor neurons in the spinal cord to deteriorate resulting in muscle wasting (atrophy). This results in progressive loss of movement which may affect crawling and	Comments noted. The background section has been updated based on consultation comments and discussion at the scoping workshop. Please note that this section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive.

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		walking ability, arm, hand, head and neck movement, breathing and swallowing. SMA does not affect intellectual ability. SMA is often grouped into 'Types'. Types of SMA are based on the age at which symptoms first appear and what physical 'milestones' a baby or child is likely to achieve. Milestones can include the ability to sit, stand or walk. There are four main types of SMA: Types 1, 2, and 3 appear in childhood; Type 4 appears in adulthood and is an adult onset form of SMA. The childhood onset types are as follows: SMA Type 1: This is the most severe form with symptoms usually appearing before a baby is six months old and sometimes before birth. Babies are unable to sit without support. Most children with SMA Type 1 rarely survive beyond two years of age. This is usually due to breathing difficulties. Babies with SMA Type 1 need 24 hour care as due to severe muscle weakness they are unable to sit unsupported, roll, hold their head up. Some babies may initially be able to move their arms and legs a little but they will lose this ability quite quickly. Their respiratory muscles are also severely affected meaning that as the muscles weaken they will be unable to breath without invasive assistance. Difficulty with breathing, coughing and swallowing increases the risk of respiratory infections which can be life-threatening. Due to muscle weakness they will also have difficulty with feeding and weight gain unless they have invasive treatment such as a gastrostomy. Many people care for their child at home which has a huge financial and emotional impact on families. SMA Type 2: The symptoms of SMA Type 2 usually appear between the ages of 7 and 18 months. Children with SMA Type 2 are unable to stand without support or walk. Though life expectancy may be shortened, improvements in care standards mean that the majority of people can live long and fulfilling lives.	

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		Individuals with SMA Type 2 need 24 hour care and assistance. Due to muscle weakness they need a large amount of equipment including for: seating, toileting, eating, bathing, mobility – powered wheelchairs, access equipment such as ramps, wheelchair accessible vehicles and accessible housing. The financial impact of SMA on families and individuals is huge, not only in order to provide all the necessary equipment and adaptations, but also to pay for care and travel to appointments etc. Some individuals have appointments with 12 or more different healthcare professionals. Some parents give up work in order to provide care for their child and this in turn has a financial impact on families. Physically, SMA Type 2 means very restricted mobility, painful muscle contractures, respiratory illness and for some, poor bone density and difficulties with eating and weight gain. Most are also affected by scoliosis, the sideways curvature of the spine. Combined with weak respiratory muscles this can exacerbate breathing difficulties. Spinal surgery might be an option to slow the rate of scoliosis and relieve some of the breathing difficulties, but some individuals are unable to have this surgery. Care is required 24 hours a day with many requiring ventilation at night, while others may also need this during the day and whenever they have a respiratory infection. As individuals with SMA Type 2 are unable to turn themselves at night, they also need to be turned regularly throughout the night which leads to interrupted sleep for them and their parents/carers. SMA Type 3: The symptoms of SMA Type 3 usually appear after 18 months of age. Children are able to stand and walk, although they may need more support with this over time. Life expectancy for children diagnosed with SMA Type 3 is normal*. Most individuals affected by SMA Type 3 gradually lose their ability to walk and experience a reduction in their ability to use other muscles due to muscle	

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		wasting. Over time, their equipment needs will increase with many needing powered wheelchairs and increased care similar to SMA Type 2. These 'types' are not rigid categories. There is a wide spectrum of severity both between the different types of SMA and between children, young people and adults within each type. * Montes, J., Gordon, A.M., Pandya, S., De Vivo, D.C. and Kaufmann, P. (2009) 'Clinical outcome measures in spinal muscular atrophy', Journal of Child Neurology, 24(8), pp. 968-978. In terms of the population, again we suggest reference should be made to the new Standards of Care once published. In the meantime, based on the information we have, we have the following comments: "SMA affects an estimated 1 in 6,000 to 1 in 10,000 births." In 2012, our Research Correspondent confirmed this statistic as follows: "People think that because SMA is a rare disease we should have an accurate record of how many people there are in the UK with the condition, but this isn't the case. The exact number of people with the condition is not known for a number of reasons, including: sometimes children and adults have an incorrect diagnosis; we don't have routine testing of newborn babies; there is currently no programme for testing everyone in the population; there is no central system for collating these statistics. Instead, scientists take small samples of people and use their findings to make estimates about populations as a whole. Although the reported estimates differ from study to study, the numbers tend to agree that approximately 1 in every 6,000-10,000 babies are born worldwide with the condition (1-5)."	

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		Importantly, this is a worldwide statistic and we suggest it should be referenced as such. The references used were as follows: 1. Czeizel, A. and Hamula, J. (1989) 'A Hungarian study on Werdnig-Hoffmann disease', Journal of Medical Genetics, 26(12), pp. 761-763. 2. Spiegler, A.W., Hausmanowa-Pertrusewicz, I., Borkowska, J. and Kłopocka, A. (1990) 'Population data on acute infantile and chronic childhood spinal muscular atrophy in Warsaw', Human Genetics, 85(2), pp. 211-214. 3. Burd, L., Short, S.K., Martsolf, J.T. and Nelson, R.A. (1991) 'Prevalence of type I spinal muscular atrophy in North Dakota', American Journal of Medical Genetics, 41(2), pp. 212-215. 4. Ogino, S., Leonard, D.G., Rennert, H., Ewens, W.J. and Wilson, R.B. (2002) 'Genetic risk assessment in carrier testing for spinalmuscular atrophy', American Journal of Medical Genetics, 110(4), pp. 301-307. 5. Prior, T.W., Snyder, P.J., Rink, B.D., Pearl, D.K., Pyatt, R.E., Mihal, D.C., Conlan, T., Schmalz, B., Montgomery, L., Ziegler, K., Noonan, C., Hashimoto, S. and Garner, S. (2010) 'Newborn and carrier screening for spinal muscular atrophy', American Journal of Medical Genetics, 152A(7), pp. 1608-1616. "SMA Type 1 has an incidence of 1 in 25,000 live births in the UK." We are not familiar with this statistic. The information we have that relates to SMA Type 1 incidence is as follows: In 2012, there were 729,674 live births in the UK (Birth Summary Tables, England and Wales - Office for National Statistics www.ons.gov.uk/ons/rel/vsob1/birth-summary-tables--england-and.../index.html). If the worldwide statistics are used: 1 in 6,000 are born with SMA - this is then 122 births /annum (121.6); 1 in 10,000 are born with SMA, this is 73 birth/annum (72.9). This suggests a mean of 97 (97.4)	

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		That same year, we were advised by Professors Muntoni and Talbot that an acceptable statistic to use would be that about 100 children are born with SMA each year, which agrees with the above calculation. Of these, they advised, Type 1 accounts for 50 - 60%., so between 50 and 60 babies are born with SMA Type 1 each year. Using this acceptable estimate, the incidence of babies born with SMA Type 1 in 2012 could be calculated as between 1 in 12,161 (729,674/60) and 1 in 14,593 (729,674/50). We assume then that if the statement '1 in 25,000 babies are born with SMA Type 1' is being used, this means there are now fewer babies born with SMA Type 1 in the UK in 2016 than in 2012. This may be the case. It is likely families who have a familial history of SMA Type 1 are more likely to screen future pregnancies. This will lower the incidence in the UK compared to that in countries where screening is not available. Assuming therefore that the worldwide figures remain correct (a range of 1 in 6,000 to 1 in 10,000 born with SMA), it is reasonable to assume that the lower incidence of 1 in 10,000 for SMA as a whole is relevant to the UK. In 2015 there were 697,852 live births (Birth Summary Tables, England and Wales - Office for National Statistics www.ons.gov.uk/ons/rel/vsob1/birth-summary-tables--england-and.../index.html). This suggests 70 births were affected by SMA. If 50% have SMA Type 1 this is 35 births. If 60% are affected by SMA Type 1 this is 42 births. This gives a potential range of 1 in 16,615 and 1 in 19,939 babies born with SMA Type 1 in 2015 in the UK. "At any one time, it is thought that there are between 2,000 and 2,500 children and adults in the UK living with SMA" Our organisation established this statistic with Professors Talbot and Muntoni in 2012. We published it in our information sheets. It appears again in the publication 'Key Facts about SMA' that we produced with Muscular Dystrophy	

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		UK and The SMA Trust in 2014 http://smasupportuk.org.uk/key-facts-about-sma The calculation behind this was as follows: • There are about 100 children born with SMA each year. • Type 1 accounts for 50 – 60% of all SMA but median life expectancy is 1 year, so it is estimated that there are about 25 children alive in the UK with Type 1 at any one time. • Type 2 median life expectancy then was 25 and 25% of the SMA population had SMA Type 2: 25 x 25 = 625. • Type 3: by the same reasoning 25 x 70 = 1750. • Total = 2,400 • The two professors then felt that the range 2000 – 2500 was the best estimate. Although there is a reduction in the number of births since 2012, which suggests fewer babies born with SMA, there is consensus across the sector that the majority of those with SMA Type 2 live increasingly longer lives and indeed our organisation is both in direct contact with, and aware of, more and more adults with SMA Type 2. This suggests a possible increase in the median life expectancy within this group. Similarly, if those with SMA Type 3 live 'normal' lives, the lifespan of 70 referred to as the median in 2012 may now be longer.	
	SMA Trust	It is important for all the information about SMA to be consistent and based on the same assumptions. We have worked closely with SMA Support UK, Muscular Dystrophy UK, NHS Choices and others to agree key facts and statistics. The following descriptions are based on these agreed key facts, together with some statistical assumptions from SMA Support UK.	Comments noted. The background section has been updated based on consultation comments and discussion at the scoping workshop.

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		We are concerned that the description of SMA is not completely accurate. In particular, there is no reference to it being a rare neuromuscular condition and, although it causes muscle weakness, this would not normally be described as paralysis. SMA Support UK is accredited to the Information Standard and publishes accurate up to date evidence based information for the public. It is carefully peer reviewed. We support the following summary reached in consultation with UK consultants and in reference to the International Standards of Care for SMA. It is also referenced by NHS Choices. "**Spinal Muscular Atrophy (SMA)** is a rare, genetic neuromuscular condition. SMA causes progressive loss of movement and muscle weakness as a result of muscle wasting (atrophy). Due to inheriting two faulty SMN1 genes, only very low amounts of the SMN1 protein can be produced causing lower motor neurons in the spinal cord to deteriorate resulting in muscle wasting (atrophy). This results in progressive loss of movement which may affect crawling and walking ability, arm, hand, head and neck movement, breathing and swallowing. SMA does not affect intellectual ability. SMA is often grouped into 'Types'. Types of SMA are based on the age at which symptoms first appear and what physical 'milestones' a baby or child is likely to achieve. Milestones can include the ability to sit, stand or walk. There are four main types of SMA: Types 1, 2, and 3 appear in childhood; Type 4 appears in adulthood and is an adult onset form of SMA. The childhood onset types are as follows: **SMA Type 1:** This is the most severe form with symptoms usually appearing before a baby is six months old and sometimes before birth. Babies are unable to sit without support. Most children with SMA Type 1 rarely survive beyond two years of age. This is usually due to breathing difficulties. Babies with SMA Type 1 need 24 hour care as due to severe muscle weakness they are unable to sit unsupported, roll, hold their head up. Some	Please note that this section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive.

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		babies may initially be able to move their arms and legs a little but they will lose this ability quite quickly. Their respiratory muscles are also severely affected meaning that as the muscles weaken they will be unable to breath without invasive assistance. Difficulty with breathing, coughing and swallowing increases the risk of respiratory infections which can be life-threatening. Due to muscle weakness they will also have difficulty with feeding and weight gain unless they have invasive treatment such as a gastrostomy. Many people care for their child at home which has a huge financial and emotional impact on families. **SMA Type 2:** The symptoms of SMA Type 2 usually appear between the ages of 7 and 18 months. Children with SMA Type 2 are unable to stand or walk without support. Though life expectancy may be shortened, improvements in care standards mean that the majority of people can live long and fulfilling lives. Individuals with SMA Type 2 need 24 hour care and assistance. Due to muscle weakness they need a large amount of equipment including for: seating, toileting, eating, bathing, mobility – powered wheelchairs, access equipment such as ramps, wheelchair accessible vehicles and accessible housing. The financial impact of SMA on families and individuals is huge, not only in order to provide all the necessary equipment and adaptations, but also to pay for care and travel to appointments etc. Some individuals have appointments with 12 or more different healthcare professionals. Some parents give up work in order to provide care for their child and this in turn has a financial impact on families. Physically, SMA Type 2 means very restricted mobility, painful muscle contractures, respiratory illness and for some, poor bone density and difficulties with eating and weight gain. Most are also affected by scoliosis, the sideways curvature of the spine. Combined with weak respiratory muscles this can exacerbate breathing difficulties. Spinal surgery might be an option to	

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		slow the rate of scoliosis and relieve some of the breathing difficulties, but some individuals are unable to have this surgery. Care is required 24 hours a day with many requiring ventilation at night, while others may also need this during the day and whenever they have a respiratory infection. As individuals with SMA Type 2 are unable to turn themselves at night, they also need to be turned regularly throughout the night which leads to interrupted sleep for them and their parents/carers. **SMA Type 3:** The symptoms of SMA Type 3 usually appear after 18 months of age. Children are able to stand and walk, although they may need more support with this over time. Life expectancy for children diagnosed with SMA Type 3 is normal*. Most individuals affected by SMA Type 3 gradually lose their ability to walk and experience a reduction in their ability to use other muscles due to muscle wasting. Over time, their equipment needs will increase with many needing powered wheelchairs and increased care similar to SMA Type 2. These 'Types' are not rigid categories. There is a wide spectrum of severity both between the different types of SMA and between children, young people and adults within each type." * Montes, J., Gordon, A.M., Pandya, S., De Vivo, D.C. and Kaufmann, P. (2009) 'Clinical outcome measures in spinal muscular atrophy', Journal of Child Neurology, 24(8), pp. 968-978. We believe additional information may be necessary in order to capture more detail on the financial impact/burden of the condition, particularly in relation to Type 1. For example, overnight ventilation necessitates 24 hour care, which increases the cost burden. Respiratory weakness places patients at risk of hospitalisation and of sudden death. Patients can also undergo scoliosis surgery (the insertion of iron rods into the back) which is risky and can require a lengthy stay in hospital.	

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		In addition to the practical impact and cost of care, it is also important to capture some of the other ways in which SMA impacts both the patient and his/her family: **Financial:** for example, through the cessation of employment to fulfil caring responsibility, or additional cost burdens such as specialist adaptations to the home. **Emotional:** parents worry about whether children will live or die and future loss of function. Stress can be high, often exacerbated by lack of sleep due to night-time care requirements **Social:** parents and children's social activities are severely restricted, with an effect on friendships and peer groups. We agree with the estimation that 1 in 6,000 to 10,000 births is affected by SMA. This is a widely referenced, worldwide statistic. However, we do not recognise the quoted statistic that Type 1 has an incidence of 1 in 25,000 live births in the UK. The NICE quoted source for this statistic is our own website, which is puzzling as this is not a figure we have ever used. Instead we concur with the extrapolation used by SMA Support UK, based on their own information, as follows: "In 2012, there were 729,674 live births in the UK (Birth Summary Tables, England and Wales - Office for National Statistics www.ons.gov.uk/ons/rel/vsob1/birth-summary-tables--englandand.../index.html). If the worldwide statistics are used: 1 in 6,000 are born with SMA - this is then 122 births /annum (121.6); 1 in 10,000 are born with SMA, this is 73 birth/annum (72.9). This suggests a mean of 97 (97.4) That same year, we were advised by Professors Muntoni and Talbot that an acceptable statistic to use would be that about 100 children are born with SMA each year, which agrees with the above calculation. Of these, they advised,	

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		Type 1 accounts for 50 - 60%., so between 50 and 60 babies are born with SMA Type 1 each year. Using this acceptable estimate, the incidence of babies born with SMA Type 1 in 2012 could be calculated as between 1 in 12,161 (729,674/60) and 1 in 14,593 (729,674/50). We assume then that if the statement '1 in 25,000 babies are born with SMA Type 1' is being used, this means there are now fewer babies born with SMA Type 1 in the UK in 2016 than in 2012. This may be the case. It is likely families who have a familial history of SMA Type 1 are more likely to screen future pregnancies. This will lower the incidence in the UK compared to that in countries where screening is not available. Assuming therefore that the worldwide figures remain correct (a range of 1 in 6,000 to 1 in 10,000 born with SMA), it is reasonable to assume that the lower incidence of 1 in 10,000 for SMA as a whole is relevant to the UK. In 2015 there were 697,852 live births (Birth Summary Tables, England and Wales - Office for National Statistics www.ons.gov.uk/ons/rel/vsob1/birth-summarytables--england-and.../index.html). This suggests 70 births were affected by SMA. If 50% have SMA Type 1 this is 35 births. If 60% are affected by SMA Type 1 this is 42 births. This gives a potential range of 1 in 16,615 and 1 in 19,939 babies born with SMA Type 1 in 2015 in the UK." We agree with the estimation that at any one time, there are likely to be between 2,000 and 2,500 children and adults in the UK living with SMA. This is based on collaboration with Professors Talbot and Muntoni in 2012, resulting in the 'Key Facts about SMA' which were produced by ourselves, SMA Support UK and Muscular Dystrophy UK in 2014 and which we all quote in our public information. Although there is a reduction in the number of births since 2012, which suggests fewer babies born with SMA, there is consensus across the sector that, as a result of improvement in care standards, the majority of those with	

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		SMA Type 2 live increasingly longer lives. This suggests a possible increase in the median life expectancy within this group. Similarly, if those with SMA Type 3 live 'normal' lives, the lifespan of 70 referred to as the median in 2012 may now be longer.	
The technology/ intervention	Biogen Idec	It should be noted that the technology causes an increase in the production of functional SMN protein by altering splicing of SMN2 gene. It should be noted that there is no planned pivotal trial in Type III patients and that data for a limited number of these patients is only available from Phase I and II trials. It should also be noted that a Marketing Authorisation Application for the technology has been filed (10/10/2016) and has been accepted for accelerated assessment by the European Medicines Agency (EMA) with Commission Decision expected towards the middle of 2017.	Comment noted. This section provides a brief overview of the technology; further details may be considered during the appraisal if appropriate. No action required.
	British Paediatric Neurology Association (Muscle Interest Group)	Nusinersen is administered by mulitple intrathecal injections: regimens comprise loading doses (e.g.4 doses over 2 months) followed by maintenance doses (e.g. every 4 months) depending on the age of the child and severity of the disease.	Comment noted. This section provides a brief overview of the technology; further details may be considered during the appraisal if appropriate. No action required.
	Muscular Dystrophy UK	Yes, we believe the description is accurate.	Comment noted. No action required.
	Spinal Muscular Atrophy Support UK	We believe the description is accurate.	Comment noted. No action required.

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	SMA Trust	Yes, we believe the description is accurate.	Comment noted. No action required.
Population	Biogen Idec	Biogen considers that the HST appraisal route is the most appropriate mechanism for assessing the value of this product to patients in light of its orphan status and restricted use. As stated via previous correspondence, assessment is currently ongoing to determine whether a positive benefit: risk profile has been established in each SMA sub-type based on trial data. There are a number of possible permutations for the Committee for Medicinal Products for Human Use (CHMP) approval so the degree of uncertainty to make any formal decisions is very high at this point in time – a premature decision could potentially underestimate the clinical benefit of the product and deny patients of the first breakthrough therapy for the treatment of SMA. It is expected that a degree of clarity will be gleaned regarding the ultimate label following the Rapporteur's initial assessment report that is due in late December (although, it is worth noting that ultimately the final CHMP decision is expected towards the middle of 2017).	Comment noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as a Single Technology Appraisal (STA). The population has been updated in line with the marketing authorisation. No action required.
	British Paediatric Neurology Association (Muscle Interest Group)	This should include all infants and children with Spinal Muscular Atrophy, with types 1,2 and 3 considered. Later consideration may need to be given to the inclusion of adults with SMA types 2 and 3.	Comment noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration

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			may be given to subgroups if evidence allows.
	Muscular Dystrophy UK	We believe it is important to focus on SMA Types 1 and 2 given that clinical trial data is available for these two patients groups.	Comment noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration may be given to subgroups if evidence allows.
	Genetic Alliance UK	Like many rare conditions, the incidence and prevalence of spinal muscular atrophy is not known with certainty or precision. Our members SMA Support UK that they estimate that there are about 100 children born with SMA each year. Based on the approximate proportion of these births affected by each of the types and the estimated life expectancy, they have come up with approximate numbers of individuals affected by each type of SMN1 SMA alive in the UK at any time: - 25 children with type 1 - 625 children and adults with type 2 - 1750 children and adults with type 3	Comment noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration may be given to

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		However, due to increasing life expectancies, these numbers should probably be revised upward. It should also be considered that if nusinersen increases the life expectancy of affected children as has been seen in the clinical trials, this will also increase these numbers. It is not clear at this stage what exactly the licensed indication for the treatment will be, and therefore which ages and types will be included. The clinical trials have investigated the treatment in children with types 1, 2 and 3 and from birth to age 18. Therefore we think it likely that nusinersen will be used to treat all children with SMA due to SMN1 mutations. As such, it may be appropriate to consider subgroups based on age, time since diagnosis and/or severity of symptoms.	subgroups if evidence allows.
	Spinal Muscular Atrophy Support UK	Currently within the age range 0 – 12 years there are considered to be sub groups according to Type of SMA, though again it is important to remember that within and between types there is a wide spectrum of ability and severity. We hear that a critical factor in terms of positive outcomes may be timing the treatment to be started as early as possible following diagnosis. This may suggest a need to consider treatment targeted at the different sub groups, bearing in mind the usual age of diagnosis as follows: Infants 0 – 6 months diagnosed with SMA Type 1 Infants 7 – 18 months diagnosed with SMA Type 2 Children > 18 mths months diagnosed with SMA Type 3 Based on the incidence statistics above, there are 100 such diagnoses each year. Again, it is possible that the revised Standards of Care will amend this commonly understood classification.	Comment noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration may be given to subgroups if evidence allows.

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	SMA Trust	Please see previous comments on Population in the Background section of this form. In addition it's worth highlighting the considerable differences that exist between life expectancy/symptoms in Type 1 and those in Type 2. Broad label marketing approval is being sought and, in due course, it is hoped it will also be appropriate to consider children with SMA Type 3, as well as adults living with SMA when appraising Nusinersen.	Comment noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration may be given to subgroups if evidence allows.
Comparators	Biogen Idec	There is no approved treatment for SMA. Current standard of care is variable based on the relevant sub-group. However, it should be noted that in more severely affected patients, such as Type I patients, supportive care is essentially palliative with a focus on non-invasive procedures. This is a challenging starting point when attempting to demonstrate cost effectiveness and suggests that a purely cost per QALY-based assessment would be problematic for these patients. For Type I patients, standard of care is palliative, with patients expected to worsen in prognosis following treatment onset until death (with a median life expectancy of <2 years). For Type II patients, standard of care involves multidisciplinary medical support to manage substantial disability during their lifetimes, relying on respiratory equipment such as suction machines and ventilators (CPAP/BiPAP with/without tracheostomy) and other orthotic/therapy equipment such as wheelchairs, supportive seats, braces and sleep systems,	Comment noted. No action required.

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		with patients expected to worsen in prognosis following symptom onset until death.	
	British Paediatric Neurology Association (Muscle Interest Group)	Standard treatment within the NHS is supportive, following international standards of care (Wang J Child Neurol. 2007 Aug;22(8):1027-49. Currently being updated)	Comment noted. No action required.
	Muscular Dystrophy UK	Yes, the only comparator is current standards of care. This usually involves coordinated, individualized, multidisciplinary care from neurologists, pulmonologists, orthopaedic surgeons, gastroenterologists, dieticians, and physical, occupational and speech therapists.	Comment noted. No action required.
	Spinal Muscular Atrophy Support UK	We suggest this should be referenced to the best standard of care for the different Types of SMA as defined by the current International Standards of Care for SMA (www.treat-nmd.eu/downloads/file/standardsofcare/sma/english/ sma_soc_brochure_en.pdf), and if possible to the new standards as soon as they are published. This work started at the 218th ENMC International Workshop February 19th - 21st 2016 (www.enmc.org/publications/workshop-reports/revisiting-consensus-statement-standards-care-sma/) with the ongoing work led by Richard S. Finkel, Thomas Sejersen and Eugenio Mercuri.	Comment noted. The International Standards of Care Committee for Spinal Muscular Atrophy are referenced in the background section. No further action required.
	SMA Trust	Yes and they include multidisciplinary care such as regular specialist physiotherapy, salbutamol treatment, nutritional management, gastrostomy tube placement and in later stages of the condition respiratory assistance may be needed, such as cough assist machines or other invasive/ non-invasive forms of ventilation. We suggest referencing the International	Comment noted. The International Standards of Care Committee for Spinal Muscular Atrophy are referenced

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		Standards of Care for SMA (www.treatnmd.eu/downloads/file/standardsofcare/sma/english/sma_soc_brochure_en.pd)f New Standards of Care are currently being finalised and were the subject of an ENMC International Workshop in February 2016. We suggest that the new version is used as soon as it becomes available.	in the background section. No further action required.
Outcomes	Biogen Idec	Biogen broadly agrees with the outcome measures stated in the draft scope. However, it is noted that there were differences in the pivotal trials regarding motor function endpoints and these differences need to be considered during the appraisal process. There were no quality of life measures included in the ENDEAR study (for patients with symptoms consistent with Type I SMA). This was primarily due to the age range of trial patients, inclusion criteria were infants under 7 months old. It is our understanding that, in line with this study, there are no validated health-related quality of life measures for this patient population and a cost per QALY assessment is therefore extremely challenging. To note, the EQ-5D is not validated in infants. PedsQoL was included as a quality of life measure in the CHERISH study (later onset disease, consistent with Type II) so a degree of flexibility needs to be considered when setting the problem statement to account for these differences. However, it should be noted that no validated means for mapping this score to a measure such as the EQ-5D currently exists. Biogen worked in collaboration with the FDA to design a primary outcome measure for the ENDEAR pivotal Phase III trial. This was due in part to there being no established outcome measure to score Type I patients, given no improvement is typically seen in this patient population following onset of disease. The creation of this measure is testament to the innovative nature of the medicine and step-change in treatment, given improvement in patient symptoms is seen whilst receiving nusinersen.	Comment noted. The outcomes have been updated based on consultation comments and discussion at the scoping workshop.

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		Compound Muscle Action Potential (CMAP) amplitudes correlate with clinical severity, age, and function. Increases in CMAP amplitudes would indicate whether there is any increase in electrically excitable muscle	
	British Paediatric Neurology Association (Muscle Interest Group)	Outcomes should include the need for non-invasive ventilation as well as invasive ventilation.	Comment noted. The outcomes have been updated based on consultation comments and discussion at the scoping workshop; non-invasive ventilation has been added.
	Genetic Alliance UK	The outcomes listed are appropriate, however we would also suggest adding more specific information on the differen complications of SMA (eg scoliosis, muscle contractures, heart failure). We also consider it important that in addition to the standardised scales used to measure general motor and respiratory function, the committee also consider specific milestones and symptoms which impact on the patient and carers qaulity of life, such as ability to cough and to use their fingers.	Comment noted. The outcomes have been updated based on consultation comments and discussion at the scoping workshop; motor function in relation to age-appropriate milestones has been added.
	Spinal Muscular Atrophy Support UK	Due to the complexity of the condition, the difference between Types of SMA, and bearing in mind the wide spectrum of severity and ability between and within the types, we assume the outcome measures within each heading will be more detailed such that the health related benefit of the treatment will be evident when the below either do not occur or occur later than expected:	Comment noted. The outcomes have been updated based on consultation comments and discussion at the scoping workshop. Further details of the components of each

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		Motor function - outcomes without treatment: SMA Type 1: Physio & OT for positioning and to relieve discomfort due to inability to raise arms, reach for toys, roll over, sit unaided SMA Type 2: Physio, OT and aids to support standing; use of mobility aids/ powerchair from as early as age 14 months SMA Type 3: Physio and self-management exercises to maintain posture, movement and mobility, may over time need walking frame/ wheelchair Respiratory function - outcomes without treatment: SMA Type 1: Early chest physiotherapy; suction & medications to remove secretions; cough assist; pain relief to reduce respiratory distress. The majority of babies do not live beyond 2 years of age due to respiratory difficulties SMA Type 2: Chest physiotherapy, cough assist at times of infection Complications - outcomes without treatment: SMA Type 1: due to swallowing difficulties/choking, feeding through a nasogastric tube, a nasojejunal tube or a gastrostomy tube. SMA Type 2: due to swallowing difficulties/choking can require nasogastric tube, a nasojejunal tube or a gastrostomy tube; often develop scoliosis requiring spinal brace / jacket / surgery Invasive ventilation - outcomes without treatment: SMA Type 1: would be required to maintain life	outcome may be considered during the appraisal if appropriate.

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		SMA Type 2: at times e.g. for respiratory infection Mortality - outcomes without treatment: SMA Type 1: Due to respiratory difficulties, the majority of babies do not live beyond 2 years of age SMA Type 2: The majority can live long lives SMA Type 3: Life expectancy normal The stark differences between mortality outcomes do not reflect the reality of the spectrum from more severe SMA Type 1 through to Type 3. This uncertainty may be reflected, for example, in that some families who seek our support have received a diagnosis for their child of SMA Type 1 / 2. Also, given the advances in standards of care, we have asked the ENMC reviewers to advise in the new guidance if these are still regarded as reasonable statements of life expectancy. Health related quality of life - outcomes without treatment: SMA Type 1: enormous impact on health and well -being of parents – full time day and night care (turning and respiration); equipment (lie flat car seats, respiratory equipment); financial impact; impact on siblings and extended family - need for ongoing emotional support SMA Type 2: frequent hospital admissions disrupt life for all family; access to equipment (power chair), housing adaptations, ongoing challenges relating to physical disability – access to school, community and work; need for ongoing financial and emotional support of child and parents – hidden costs of disability. Adults need access to physio, equipment for mobility and daily living	

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		SMA Type 3: impact of loss of strength e.g. previous ability to walk - emotional and physical, need for equipment and housing adaptations. Need for ongoing financial and emotional support of child and parents – hidden costs of disability. Adults need access to physio, equipment for mobility and daily living.	
	Muscular Dystrophy UK	Yes, though perhaps more detail could be included under 'complications of SMA'.	Comment noted. The outcomes have been updated based on consultation comments and discussion at the scoping workshop.
	SMA Trust	These outcomes capture important health-related benefits. However, whilst the focus is on improvement, it is crucial that any technology appraisal is also mindful of the fact that to patients and their families, stabilisation of their clinical state is just as much a priority as improvements in motor function/other scores.	Comment noted. The outcomes have been updated based on consultation comments and discussion at the scoping workshop. If appropriate, consideration may be given to either improvement or stabilisation of outcomes.
Economic analysis	Biogen Idec	It is Biogen's view that nusinersen would be best assessed via the HST route. Should nusinersen be referred to STA assessment, the criteria against which the product will be assessed, as required by the NICE reference case, will be unable to be met. This is due primarily to quality of life data paucity, caused by paediatric data elicitation limitations, particularly for SMA Type I. Furthermore, there are currently no validated mapping measures based on	Comment noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as an

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		endpoints in the pivotal nusinersen clinical trials, which could be used to establish credible quality of life data. This means that it would not be possible to inform the quality-adjusted life year element of the incremental cost-effectiveness ratio equation with robust data. Such an approach would be detrimental in establishing and demonstrating the important clinical value of nusinersen treatment. Additionally, the current cost-effectiveness threshold for STA analyses is not set for the assessment of orphan products. This issue has been flagged through the ongoing NICE and NHS England consultation. It follows, therefore, that assessing nusinersen via the STA route based on NICE reference case requirements would not be inappropriate. Biogen proposes that assessment of nusinersen via a cost-consequence analysis, as in line with HST appraisal, would be a more appropriate means of valuing the costs and benefits of the product compared to a conventional cost-effectiveness analysis. The analysis time horizon should be sufficiently long to reflect any differences in costs or outcomes between nusinersen and best supportive care. It should be noted that the life expectancy of Type I and II patients differs significantly, as does the expected timeframe for treatment of patients with nusinersen for each SMA Type. These factors should be taken into consideration when comparison is made versus best supportive care, in addition to how SMA patients have typically been treated until now (i.e. via palliative mechanisms in severely affected patients) given no disease modifying therapy has been available. Biogen would like to highlight the consideration of indirect costs and benefits when assessing nusinersen. The SMA population, particularly in the case of Type I and II patients, are reliant on carers due to the nature of the disease and the age at which patients are affected. By not taking into consideration the wider societal and economic impact of a disease modifying therapy it is likely that not all benefits of nusinersen will be captured.	STA. The economic evidence requirements and reference case are described in the Guide to the methods of technology appraisal 2013. No action required.

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	British Paediatric Neurology Association (Muscle Interest Group)	Consideration should include subgroups by age at onset (i.e. SMA type). The published evidence suggests that the time horizon to demonstrate a difference between the technology and supportive care is relatively short (within 12 months)	Comment noted. The 'Other considerations' section has been updated to specify that, if evidence allows, consideration will be given to subgroups based on severity of disease (including considerations such as age of SMA onset).
	Spinal Muscular Atrophy Support UK	We are aware from our contact with families caring for babies with SMA Type 1, that the 'benefits' to a family of their baby with SMA Type 1 living longer and achieving new milestones would be immeasurable. For babies with SMA Type 1, we hear that results are indicating that early treatment could be transformative. This would reduce concerns over the ongoing needs for costs of supportive equipment and care as well as the hidden costs to the family of caring for a disabled child (see publications by Genetic Alliance UK, Contact a Family, Scope) and the impact/costs for any family that would still face the loss of their child. For children with SMA Type 2 or 3 with longer life expectancy, the family would anyway have been caring for their disabled child and have in place health and social care support. These costs would decrease as would the hidden costs for the family. In the very long run, there would be an expectation that the child would become a more independent adult than they would have been without treatment.	Comments noted. No action required.
Equality	Biogen Idec	Please refer to Biogen's comments below regarding a potential HST appraisal and the design of a route to reimbursement that considers the geographical	Comment noted. Access to specialist centres is an

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		spread of centres likely to use the technology as a means to facilitate equity of access.	implementation issue; it is not an equality issue to be considered by the committee, and cannot be addressed in technology appraisal guidance. No action required.
	British Paediatric Neurology Association (Muscle Interest Group)	This technology requires expertise to administer (intrathecal injections) and significant support resources) to achieve safe procedures (with sedation or anaesthesia of vulnerable infants). The econmic analysis needs also to consider the resources required to deliver the treament (including anaesthetic time, theatre time, potential PICU bed days). There needs to be consideration of how to achieve equity of access across the country, whilst maintaining expertise by a minimum threshold number of procedures undertaken.	Comment noted. Access to specialist centres is an implementation issue; it is not an equality issue to be considered by the committee, and cannot be addressed in technology appraisal guidance. No action required.
	Spinal Muscular Atrophy Support UK	If this treatment can only be offered at specialist centres this creates an issue in terms of equality of access. This, we suggest, would need to be addressed via the provision of travel grants and free accommodation options.	Comment noted. The reference case specifies that costs included in the analyses should relate to resources that are under the control of the NHS and personal and social services. Access to specialist centres is an implementation

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			issue; it is not an equality issue to be considered by the committee, and cannot be addressed in technology appraisal guidance. No action required.
	SMA Trust	The medically invasive administration method required for Nusinersen would make it likely that the drug would only be available at specialist centres which could have the effect of limiting access among certain population groups, either because of geographic or financial constraints. Travel and accommodation options would need to be considered	Comment noted. The reference case specifies that costs included in the analyses should relate to resources that are under the control of the NHS and personal and social services. Access to specialist centres is an implementation issue; it is not an equality issue to be considered by the committee, and cannot be addressed in technology appraisal guidance. No action required.

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Innovation	Biogen Idec	Nusinersen is a definitive step-change in the management of SMA. It is the first breakthrough treatment for SMA in 140 years. In the UK, treatment of patients has been primarily through palliative care for Type I patients and supportive care for Type II patients; given patients with disease will continually worsen following disease onset until death. However, based on interim analysis of nusinersen trial data improvement in patient motor milestone attainment, motor function, and survival (in Type I patients) has been seen. For example, results from the primary endpoint of the pre-specified interim analysis of CHERISH demonstrated a difference of 5.9 points (p= 0.0000002) at 15 months between the treatment (n=84) and sham-controlled (n=42) study arms, as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). It is widely acknowledged that a 3 point difference on the HFMSE equates to a clinically significant improvement for the patient. In CHERISH, the interim data showed a 4.0 point improvement from baseline and a 5.9 point difference between the active drug and SHAM control group. It is therefore evident that nusinersen has a significant and substantial impact on health-related benefits across SMA types, with the potential to drastically alter the disease course and current treatment practice. The interim analysis primary endpoint in the ENDEAR study was the proportion of motor milestone responders using modified section 2 of the Hammersmith Infant Neurological Examination (HINE; defined as more HINE categories improving than worsening [≥2-point increase/maximal score in kicking ability, or ≥1-point increase in head control, rolling, sitting, crawling, standing, or walking]. This endpoint was designed specifically for the nusinersen clinical trials, given that to date there have been no treatment options. This alone indicates the perceived value of nusinersen to SMA patients. As discussed previously, it is highly unlikely that the benefit of nusinersen would be captured by standard QALY calculation. This is primarily due to data paucity and the lack of a mapping measure allowing for trial endpoint data to be converted to quality of life data. Furthermore, there are benefits to patients	Comments noted. No action required.

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		and wider society (in particular family members whose lives are drastically changed when caring for an SMA patient) which would likely not be captured by a standard utility elicitation measure. Biogen therefore recommends that the focus of analysis be on cost-consequence and additionally takes into consideration value of the product to wider society, in particular carers.	
	British Paediatric Neurology Association (Muscle Interest Group)	This is potentailly has a very significant impact with benefit for children with SMA - definitely a "step-change" in its management If benefit in terms of ventilation-free survival are confirmed then there will be a reduction in the need for complex health care support for these children. Improvements in motor function are confirmed there will be a significant impact on the QALY assessment.	Comments noted. No action required.
	Genetic Alliance UK	Yes. As yet very few antisense oligonucleotides have been licensed in the EU, and this treatment also represents a stepchange in the management of the condition, as the first medicine which treats the underlying cause of the disease	Comments noted. No action required.
	Muscular Dystrophy UK	Yes, the technology is the first drug to treat SMA to be considered for a licence by the European Medicines Agency. Clinical trial results and reported outcomes show a clinically significant benefit for patients with SMA Types 1 or 2. As noted in Comment 1, Muscular Dystrophy UK believes that an HST review would give greater opportunity to consider the impact of SMA on the infant child and their family. In the case of SMA Type 1 especially, life expectacy is very limited. It is extremely challenging to develop a QALY measure for the condition and we are concerned that a simple cost effectiveness analysis through an STA would not give sufficient scope to consider disease impact.	Comments noted. No action required.

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	Spinal Muscular Atrophy Support UK	We understand this technology could offer a 'step-change' in that SMA is a condition for which there is currently no drug treatment.	Comments noted. No action required.
	SMA Trust	Yes, the technology represents a “step-change” in the management of SMA as it is the first to target its underlying genetic cause. The use of antisense oligonucleotides is an innovative technology. Phase 2 clinical trials on infants showed acceptable safety and tolerability, pharmacology consistent with its intended mechanism of action and encouraging clinical efficacy. We understand that Phase 3 results are available but have not yet been published.	Comments noted. No action required.
Other considerations	Biogen Idec	Please see Biogen’s response to the ‘questions for consultation’ section below.	Noted
	Spinal Muscular Atrophy Support UK	If early treatment is critical this makes rapid access to diagnosis essential. This is not happening uniformly across the country. There would need to be a big push to ensure community health professionals recognise symptoms and that referral and diagnosis is fast and streamlined, also that access to this treatment option was well known. In our view, it would be vital that any family considering treatment receives full information about what the maximum outcome might be for their child, based on time since diagnosis, SMA Type and the age of their child. We also consider it essential that parents and children have emotional support throughout and after treatment – especially if outcomes aren’t as they expected. We are concerned for those who would need to travel long distances to receive treatment – the logistics, costs and stress of such arrangements, particularly for those travelling with poorly infants. We would not wish to see	Comments noted. Diagnosis of SMA is not within the scope of this appraisal. The reference case specifies that costs included in the analyses should relate to resources that are under the control of the NHS and personal and social services. No action required.

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		the option of treatment denied to families and consider it vital that there is sufficient financial and emotional support to make this manageable.	
	SMA Trust	There are two other issues that could potentially have an impact on the proposed evaluation: 1. Diagnosis of SMA can be patchy and sometimes takes longer than it should. Given that drug efficacy appears greater the earlier it is administrated, it will be important to ensure that 'front-line' clinicians have access to full information about SMA and Nusinersen. 2. If an effective treatment becomes available, there will be pressure to review the position on genetic testing for SMA, especially newborn screening.	Comments noted. Diagnosis of SMA and newborn screening are not within the scope of this appraisal.
Questions for consultation	Biogen Idec	**Is the definition of the population appropriate? Will nusinersen be used to treat infants and children or just infants?** Biogen considers that nusinersen has a place in the treatment of both infants and children who have the greatest unmet need and in whom clinical benefit has been established. A clear understanding of what this might be is yet to emerge pending the availability of the full clinical trial results from the pivotal studies (ENDEAR [consistent with Type I SMA] and CHERISH [consistent with Type II SMA]). However, interim analysis has demonstrated the potential for patients with high unmet need to benefit from treatment. It is therefore vital to ensure the correct assessment is undertaken to allow timely access to a product that could meet such a high unmet need. **Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom nusinersen is expected to**	Comments noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration may be given to subgroups if evidence allows. Following extensive discussion, it was agreed that this topic is

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		be more clinically effective and cost effective or other groups that should be examined separately? Given the accelerated regulatory assessment for nusinersen and the fact that there has been no prior HTA in this patient group, it is extremely difficult to suggest subgroups in which a greater clinical effectiveness and cost-effectiveness argument may be seen. Presently, Biogen does not have access to all patient level data sets (as the CHMP approval was expedited based on the significant results observed in the interim data readout) and so cannot make a judgement based on analysis with regards to subgroups. It should be noted that Type I and II patients are subgroups of the total SMA population, with pivotal phase III trials consistent with these subgroups. Based on epidemiology estimates, there are c. 380 Type I and II patients in England and Wales, with this figure reduced further when factoring in patients who would be eligible and also well enough to receive treatment with nusinersen. **Would it be appropriate to consider subgroups based on severity of symptoms or time since diagnosis?** Biogen supports the proposal in 'other considerations' that 'Guidance will only be issued in accordance with the marketing authorisation'. It is suggested that focussing NICE's efforts on those populations for whom clinical efficacy has been established in Biogen's pivotal studies (i.e. in accordance with the details of the marketing authorisation) rather than restricting consideration to the indication is important for this appraisal, in light of the established epidemiology of the different subgroups and the risk of an inappropriate appraisal route.	appropriate for consideration as an STA. No further action required.

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		With regard to subgroups, Biogen considers that this is currently difficult to answer. Whilst the inclusion/ exclusion criteria in the pivotal studies were based on age of onset, it is possible that there may be overlap in terms of disease severity. A degree of flexibility should be reserved so that this issue can be explored further during the appraisal process. **Is genetic testing for SMA part of routine clinical practice in the NHS?** Biogen understands that genetic testing for SMA is part of routine clinical practice when SMA is being considered as a potential diagnosis. **Do you consider that the use of nusinersen can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** It is highly probable that a QALY calculation would not capture the significant and substantial health-related benefits associated with nusinersen treatment. It is also likely that the calculation of a robust QALY will not be possible, due primarily to the paediatric populations enrolled in the pivotal nusinersen trials. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Biogen proposes that nusinersen be assessed via a HST appraisal route, employing cost-consequence analysis. This would reduce uncertainty associated with decision making whilst enabling the clinical value of the product to be evaluated given that calculation of a QALY(s) would not be	

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		necessary and the ambiguity associated with producing a value(s) of this nature given data paucity would not be introduced into the decision problem.	
	British Paediatric Neurology Association (Muscle Interest Group)	Q: Will nusinersen be used to treat infants and children or just infants? Nusinersen will be used for both children and infants Q How should best supportive care be defined?. By reference to the international standards of care (see reference above): Q. Are electromyographic measures of muscle function, such as motor unit number estimation (MUNE) and compound muscle action potential (CMAP), relevant outcomes for patients with spinal muscular atrophy? These are relevant outcomes in research studies. They are not currently used in routine clinical practice. Q.Would it be appropriate to consider subgroups based on severity of symptoms or time since diagnosis? By severity of symptoms - i.e. by type of SMA (type 1,2, or 3) also defined by SMN2 copy number. Q. Is genetic testing for SMA part of routine clinical practice in the NHS? Yes SMA diagnosis is confirmed by SMN1 gene testing and laboratories now also report SMN2 copy number.	Comments noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration may be given to subgroups if evidence allows. Attendees at the scoping workshop agreed that electromyographic measures of muscle function were not relevant outcomes for patients with SMA. No further action required.

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	Spinal Muscular Atrophy Support UK	Is the definition of the population appropriate? We presume that, though the study did not take place with children aged between 7 months and 2 years, they would be included in the proposed population. We imagine there will be significant questioning from parents with children age over 12 years, and indeed from young people and adults who themselves have SMA, as to whether or not this treatment could work for them. We would envisage potential lobbying to extend the age range upwards, though the method of delivery and time commitment required for the treatment programme may diminish demand. It will be vital to clarify at what stage of the condition treatment is effective. Would it be appropriate to consider subgroups based on severity of symptoms or time since diagnosis? Families of all children with SMA, no matter the type, would want to know the benefits and at what stage the treatment is effective. They would want equitable access for all. Is genetic testing for SMA part of routine clinical practice in the NHS? Only where there is a history of SMA in the family. We hear research may be indicating that pre-symptomatic treatment is leading to transformational results. This raises the question of the need to consider a national screeening programme for newborns which would identify all babies with SMA. This would then increase equality of access to the treatment. We welcome comments on the appropriateness of evaluating this topic through the HST process. What evidence is there that this technology is suitable for HST evaluation, and that it meets the prioritisation criteria for this programme?	Comments noted. The population has been updated in line with the marketing authorisation. Attendees at the scoping workshop agreed it was not appropriate to restrict the population to particular subtypes of SMA, but consideration may be given to subgroups if evidence allows. Following extensive discussion, it was agreed that this topic is appropriate for consideration as an STA. No further action required.

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		We understand that for this to be considered, NICE's commonly accepted threshold is of fewer than 500 patients in England and Wales with the condition. As outlined in our response re population, the exact number of infants, children, young people and adults living with SMA is unknown. We suggest one source of such information would be the SMA Patient Registry. People registering are interested in clincial trials which would seem to indicate a willingness to take part in innovative treatments. On December 12th, we were advised by the Registry that: "In England and Wales, there are currently within the age range 0-12 years: SMA Type 1: 49 SMA Type 2: 79 SMA Type 3: 21 There are 9 patients that fall within this age group whose SMA Type hasn't been stated." Our recent database search of those diagnosed with SMA with whom SMA Support UK has contact (as of Dec 10th 2016) gave details of 869 children, young people and adults with SMA in the UK. We had not been notified of the deaths of any of these people, though families with very short term contact with us may not let us know. This suggests we may be in touch with 35% – 43% of the SMA population. As our services are more heavily used by families who have just received a diagnosis and we then commonly have contact at times of transition and change in their lives (going to pre-school, primary, secondary school etc.), we suspect we are in touch with a higher percentage of the population that is aged under 12 years of age.	

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		Our records of those with whom we are currently in contact for England and Wales give numbers according to age as follows: Type 1 age 0 - 12 years = 68 Type 1 / 2 age 0 - 12 years = 5 Type 2 age 0 - 12 years = 84 Type 3 age 0 - 12 years = 35 Total number age 0 - 12 years = 192 Type 1 child, age unknown = 14 Type 1 / 2 child, age unknown = 0 Type 2 child, age unknown = 21 Type 3 child, age unknonw = 3 Total number children age unknown = 38 This suggests a population well below the 500 threshold. The population may well be further reduced for the following additional reasons: - we understand the treatment itself is seven intrathecal treatments per annum for as long as it is beneficial/ clinically safe. This is a commitment some families may decide not to make -at present the treatment is only available in two specialist centres. Though this may be increased it necessarily has to be offered by a multi-disciplinary team including an anaesthetist. We imagine this will mean the number of sites will remain restricted which, due to the travel involved, may influence a family's decision -not all these infants and children will be clinically well enough to undergo treatment procedures and not all families will want the treatment	

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		-if treatment as close as possible to the time of diagnosis is indicated, many in this 0 - 12 year age group would be excluded -family choices are affected by personal circumstances, beliefs, culture and values which may impact on their decision about participation This creates a picture of a population actually wanting the treatment as likely to be substantially fewer than 500, which suggests the technology would be appropriate for an HST evaluation. As an organisation, based on this, we consider the appraisal should be an HST. We also consider this to be the most likely option that will lead to this drug being licensed and available with full information to those who meet appropriate criteria and wish to access it as quickly as possible.	
	SMA Trust	**STA or HST Appraisal?** We understand that NICE intends to appraise this technology through its standard Single Technology Appraisal (STA) process. We believe that it would be more appropriate for this technology to be considered under the Highly Specialised Technologies (HST) programme for rarer conditions because: □ Nusinersen was given an orphan drug designation by EMA and granted accelerated assessment status by EMA's Committee for Medicinal Products for Human Use (CHMP) □ Of the number of SMA patients in England and Wales: prevalence of ~440 patients with Type 1 and II SMA, which falls beneath NICE's commonly accepted threshold of 500 as the upper limit for selection by HST. Whilst Biogen has filed for a broad indication, the patients who have the greatest unmet need should be the priority (Type I and II).	Comments noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as an STA. The population has been updated in line with the marketing authorisation. No further action required.

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		□ The drug would be administered through a small number of specialist centres of excellence because it is administered intrathecally. requiring the involvement of a multi-disciplinary team including a paediatric anaesthetist. □ There are major challenges to producing the type of data NICE would need for an STA process (e.g. capturing quality of life data in paediatric populations or demonstrating a meaningful quality adjusted life year (QALY) for this patient population. The HST would allow wider discussion on the consequences of SMA both on the patients and those caring for them. This allows for a more representative view of the disease and treatment than a narrow cost effectiveness analysis. **Definition of Patient Population** In Appendix B, the population is summarised as 'Children with Spinal Muscular Atrophy', whereas the two clinical trials actually limited the age range from 3 weeks to 7 months in the Type I study and 2 to 12 years in the Type II study. It is very much hoped that the term 'children' will accommodate the full age range rather than just the specific ages included in clinical trials.	
Additional comments on the draft scope	Biogen Idec	Biogen welcomes NICE's indication that this technology might be considered for evaluation through the Highly Specialised Technologies (HST) Programme. It is Biogen's firm belief that this is the most appropriate route for appraisal and that the technology meets the eligibility criteria that NICE has set out. The eligibility against the established criteria is discussed below. **The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS** The UK epidemiology of spinal muscular atrophy (SMA) is relatively well-established and has been previously discussed in Roche's horizon scanning	Comments noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as an STA. No action required.

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		submission. In summary, evidence shows a broad prevalence of c. 440 patients with Types I and II in the UK. For England and Wales, it has been calculated that the prevalent population of Type I and II patients is c. 380. It is expected that the patient population who will be eligible for treatment, as in line with clinical trial criteria, will be smaller still. Furthermore, without analysis of patient level data it is currently unknown as to which patients benefit most from treatment. Establishing the potential number of centres in which nusinersen is likely to be used is challenging given the rarity of the condition and relatively conservative current approach to treatment in the UK. It is understood that currently, in the absence of any efficacious therapies, very few Type I patients are offered the use of life-extending interventions, such as tracheostomy/breathing support. The current UK treatment paradigm is essentially palliative for those patients who are severely affected. Projecting the clinical uptake of a product such as nusinersen is therefore problematic and reference to precedent cases is considered an appropriate starting point. NICE has established precedence in this complex area of rare disease where it acknowledged the complexity of evaluating the true value of the therapy in pioneering areas of high unmet need. Translarna (ataluren) is a therapy indicated for the treatment of Duchenne muscular dystrophy (DMD). The Managed Access Agreement implemented during the HST appraisal of this product requires that patients be treated at one of the 16 specialist tertiary centres across England that constitutes the NorthStar Network. It is understood that outcome data to support ongoing reimbursement for Translarna is collected by the clinicians in these centres and is owned by the Network. NorthStar Network centres are also involved with the SMArtNet disease registry that allows for the collection of data on SMA patients. Biogen considers that this precedent is important and will work with NICE to explore	

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		all relevant learnings from this and other cases to ensure that Nusinersen receives a fair and appropriate evaluation and that NICE is comfortable that patients will receive the benefit demonstrated in the clinical trials at a fair price, in line with other therapies in this space of rare disease. Unlike Translarna, however, there are additional nuances associated with nusinersen that are worth considering as they suggest that it may be more appropriate for the use of the product to be restricted to a smaller subset of specialist centres with an appropriate geographical spread (to ensure equitable access). For example, nusinersen is administered via intrathecal (IT) injection. This is necessarily more complicated than the administration of Translarna (oral therapy). Biogen's internal research with UK sites suggests that sedation (such as general anaesthesia) may be required before administration of the IT injection. These restrictions mean that a subset of centres within the Network that are able to administer the product is potentially foreseen and may form part of the negotiations Biogen foresees with NICE, NHSE, clinicians and patient groups. Finally, it is also worth noting that Biogen has recently initiated an Expanded Access Programme (EAP) for patients with Type I SMA in the UK. Biogen is supporting clinicians who request access to the product by allowing free-of-charge supplies during regulatory/ reimbursement assessment. This EAP is in the process of being initiated at two sites in England (Institute of Human Genetics, Newcastle, and Dubowitz Neuromuscular Centre, London). These sites were involved in Biogen's pivotal studies resulting in these two highly specialised centres gaining the most experience with the product to-date and hence why Biogen has made the EAP programme available to these sites. It is possible that the number of sites could be expanded during the EAP but, as above, this expansion would be limited to a subset specialist centres in England to ensure appropriate use of the product balanced with equitable	

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<tr><td></td><td></td><td>access. It is hoped that the experience gained through the EAP would facilitate smooth transition of patients following a successful appraisal process.

The target patient group is distinct for clinical reasons

SMA is a rare, autosomal recessive neuromuscular disease that affects the survival of motor neurons of the spinal cord. It is characterised by symmetrical weakness and atrophy of the proximal voluntary muscles of the legs, arms, and eventually of the entire trunk during disease progression. These clinical manifestations are the result of progressive loss of alpha motor neurons in the anterior horn of the spinal cord[4] .

SMA is caused by a mutation that results in absence of the survival motor neuron 1 (SMN1) gene . All SMA patients have at least one copy of a ‘back-up’ gene (SMN2). The SMN2 gene is able to generate some functional SMN protein that partially compensates for the loss of SMN1 gene allowing most cells to function. However, there is insufficient SMN protein for motor neuron survival leading to progressive muscle weakness and atrophy . As an aside, nusinersen targets the splicing of the SMN2 gene to enhance the production of SMN protein.

Broadly, the number of SMN2 gene copies that a patient has correlates with onset and severity of disease; Type I patients tend to have 2 or 3 copies only (correlating with earlier onset and more severe symptoms). The disease (and sub-group) classification can therefore be summarised as [7,8,9,] ,

<table>
<tr><th>SMA Type</th><th>Age of Onset</th><th>SMN copies</th><th>Motor function achieved</th><th>Life expectancy</th></tr>
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<tr><td>Type I</td><td>0-6 months</td><td>2-3</td><td>May never sit; sits with support only</td><td>Less than 2 years of age</td></tr>
<tr><td>Type II</td><td>7-18 months</td><td>3</td><td>Independent sitting; may never stand</td><td>Approximately 70% alive at age</td></tr>
<tr><td>Type III</td><td>>18 months</td><td>3-4</td><td>Independent stand and walk</td><td>Normal life expectancy</td></tr>
</table>

In summary, the condition is well-characterised with generally clear clinical distinctions between sub-groups. As outlined in Biogen’s previous discussions with NICE, Biogen recently completed its pivotal sham-controlled study in infants with infantile-onset SMA (consistent with Type I) [ENDEAR]. The regulatory filing will be supplemented with data from a second pivotal sham-controlled trial in children with later-onset SMA (consistent with Type II) [CHERISH]. Open-label data from other Phase 1 and 2 studies were also included with the filing, including data from the NURTURE study, a phase 2, open-label study in pre-symptomatic infants with genetically diagnosed SMA.
</td><td>25</td></tr>
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		The condition is chronic and severely disabling
		
		SMA disease progression can be divided into three phases:
		
		• Preclinical phase
		  • Infants appear normal.
		  • Motor unit loss is progressing but has not reached a critical threshold.
		  • Preclinical phase will be very short in the most severe form of the disease (Type I) but may extend for several months or years in later-onset SMA.
		• Subacute phase
		  • Motor unit loss reaches a critical threshold.
		  • Ongoing motor unit loss is fairly rapid and can be exacerbated by stressors such as illness, nutritional compromise or growth.
		  • Clinical symptoms evolve, ranging from severe weakness and progressive paralysis in Type I, loss of ability to sit or roll in more severe Type II, or to a more obvious slowing of acquisition of expected gross motor milestones in less severe later-onset SMA sub-types.
		• Chronic phase
		  • Motor unit loss appears to plateau.
		  • Some re-innervation may occur but denervation generally progresses with age.
		
		SMA is a chronic condition. There are currently no treatments available so patients with Type I SMA generally receive palliative care in the UK	

		(experiencing significant levels of disability during their short life expectancy). Patients with Type II SMA will experience substantial disability during their lifetimes, relying on respiratory equipment such as suction machines and ventilators (CPAP/BiPAP with/without tracheostomy) and other orthotic/therapy equipment such as wheelchairs, supportive seats, braces and sleep systems. Whilst Type III patients may experience lower levels of disability, it is expected that support from the multi-disciplinary team will be required with varying degrees of intervention required. **The technology is expected to be used exclusively in the context of a highly specialised service** It is understood that, by definition, a paediatric neurology product should be considered highly specialised. However, Biogen recognises the general pressure on NHS budgets and, in particular, the demands on NHS England's Specialised Commissioning budget. Therefore, Biogen is prepared to explore a broad range of options to ensure access to this medicine, including learnings from HST appraisal precedents. We are committed to developing these solutions in partnership with patients, clinicians, NHS England and NICE to ensure that equitable access is available to those with the greatest need. **The technology is likely to have a very high acquisition cost** Biogen is not yet able to confirm the proposed list price for this product, which will be made available as part of ongoing reimbursement activities. However, on 2nd April 2015, "orphan designation (EU/3/12/976) was granted by the European Commission to Isis USA Ltd for antisense oligonucleotide targeted to the SMN2 gene for the treatment of 5q spinal muscular atrophy". At the time of designation, SMA affected less than 0.4 in 10,000 people in the European Union (equivalent to a total of fewer than 20,000 people). This product was fully acquired by Biogen in August 2016. Given SMA is a rare orphan disease, it is expected that acquisition costs are likely to be high and comparable to other pharmacological interventions in rare diseases. **The technology has the potential for life long use**	

		Currently, long-term data on SMA patients treated with nusinersen are extremely limited. The data generated in the ENDEAR study (infantile onset of SMA less than 6 months of age) found that infants receiving nusinersen demonstrated a statistically significant improvement in the achievement of motor milestones compared to those not receiving treatment. Whilst it is difficult to draw firm conclusions on the impact on other outcomes, it is hoped that an improvement in motor function development would also correlate with improved life expectancy. However, this will need to be established through long-term data collection to ensure whether this therapy could stabilise the disease and /or demonstrate maintained efficacy of the product with its impact on morbidity and mortality is fully understood. In addition, the temporal sensitivity of motor neurones to SMN protein is poorly understood. As such, it is possible that high levels of circulating SMN protein are required to ensure the ongoing survival of motor neurones and it is therefore possible that nusinersen will need to be used for the duration of a patient's life. As above, the flexibility that the HST route affords would allow for Biogen to explore a range of options to ensure access to this medicine on an ongoing basis, including learnings from HST appraisal precedents such as those identified during the assessment of Translarna. **The need for national commissioning of the technology is significant** As a treatment for a rare paediatric and neurological disease, nusinersen would be eligible for national commissioning and would fall under specialist commissioning requirements. The technology could not be viably commissioned through other funding or reimbursement routes given the specific clinical requirements described above. Biogen considers that, according to the evidence presented above and through previous discussions with NICE, nusinersen meets the eligibility criteria for assessment via the HST (it is worth mentioning that the Scottish Medicines Consortium recently confirmed that they consider the product to be an orphan drug). Biogen considers that learnings from HST precedents are important and that these should be considered in the context of nusinersen. In particular, the number of centres in which nusinersen will be used is likely to be less than Translarna due to the nature of the product and it may be appropriate to explore these restrictions further as part of the appraisal	

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		process. Finally, we also consider that HST is the most appropriate route for assessment due to the challenges of generating adequate quality of life data in paediatric patient populations such as SMA and to facilitate the detailed discussions associated with designing an appropriate route to reimbursement.	

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

Department of Health