SMC2805

nusinersen solution for injection (Spinraza®)

Biogen Idec Ltd

05 September 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the evidence for the above product using the ultra-orphan framework:

Advice: following a reassessment through the ultra-orphan framework

nusinersen (Spinraza®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of 5q spinal muscular atrophy.

SMC restriction: Patients with symptomatic type 2 or type 3 (later-onset) 5q spinal muscular atrophy.

In a double-blind, randomised, controlled phase III study in patients aged 2 to 12 years with later-onset spinal muscular atrophy (SMA), there was a significant improvement in motor function from baseline to 15 months, assessed by the Hammersmith Functional Motor Scale Expanded, in the nusinersen group compared with the sham control group.

Improvements were maintained in an open-label extension study and were supported by real-world evidence.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Nusinersen is an antisense oligonucleotide treatment that modifies pre-messenger ribonucleic acid (pre-mRNA) splicing of the survival motor neuron 2 (SMN2) gene (which otherwise usually produces survival motor neuron [SMN] proteins that are defective and unstable). Translation of the modified pre-messenger RNA produces functional, full-length SMN protein.[1]

The recommended dose of nusinersen is 12 mg on days 0, 14, 28 and 63 by intrathecal injection, then once every 4 months thereafter. Treatment should be started as soon as possible after diagnosis. The need for continuation of nusinersen should be reviewed regularly and based on individual response to treatment.[1]

Nusinersen was validated as an ultra-orphan medicine by SMC and underwent initial assessment using the ultra-orphan framework, with advice published in May 2018 (SMC1318/18). Nusinersen was accepted for restricted use within NHSScotland for patients with symptomatic type 1 (infantile onset) spinal muscular atrophy (SMA). Since July 2019, nusinersen has been available within the new ultra-orphan pathway for symptomatic patients with type 2 or type 3 (later-onset) SMA and this submission supports a reassessment following data collection for this group.

1.2. Nature of condition

Spinal muscular atrophy (SMA) is an inherited, autosomal recessive, neurodegenerative disorder resulting from deletions or mutation in the gene SMN1 that codes for the SMN protein. This reduces levels of the SMN protein leading to a loss of spinal (and in more serious cases lower bulbar) motor neurons and progressive muscle weakness. A second, almost identical, SMN gene (SMN2) produces shorter and less functional SMN protein. Humans may have between 0 and 8 copies of the SMN2 gene. SMA is a clinical spectrum of disease with worsening disease severity being linked to having fewer SMN2 copies and a younger age of symptom onset. SMA is classified into five clinical subtypes (type 0, 1, 2, 3 and 4) according to age of onset and the patient's maximal functional status prior to degeneration.[1-4]

Patients with type 2 SMA develop symptoms between six and 18 months of age and they achieve a maximal motor milestone of sitting independently. Some patients can stand but are not able to walk unsupported. Life expectancy is reduced and this can range from two to over 40 years. Patients can develop proximal weakness, hypotonia and skeletal changes such as scoliosis. Respiratory impairment can occur but it tends to be milder than the impairment seen in type 1 SMA.[2-5]

Patients with type 3 SMA develop symptoms between 18 months and adulthood and it is the least severe of the paediatric subtypes (type 4 SMA manifests in adulthood). Patients have an almost normal life expectancy and reach a motor milestone of being able to walk independently. Motor weakness develops slowly in patients with type 3 SMA. Approximately

half of patients with type 3a (onset between 18 and 36 months) lose ambulation in 10 years, whereas 90% of patients with type 3b (onset >36 months) are still walking 20 years after diagnosis.[2-4]

SMA can negatively impact the quality of life, education and employment of patients. Patients may experience muscle weakness, pain and fatigue. SMA can significantly affect mobility, the ability to undertake daily tasks and limits independence. Patients need to attend frequent medical appointments, and respiratory impairment may affect attendance at school and employment. Additionally, patients may have poor mental wellbeing associated with the burden of disease.[6, 7] SMA also has a significant impact on the wellbeing of carers, who may be unable to work due to caring responsibilities.[8]

Management of patients with SMA can be complex and challenging. Current treatment options in Scotland for patients with type 2 or type 3 SMA include the orally administered SMN2 pre-mRNA splicing modifier, risdiplam (SMC2401), and nusinersen (via the ultra-orphan pathway). Onasemnogene abeparvovec is licensed for patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene however it is restricted by SMC to patients with a diagnosis of type 1 SMA or pre-symptomatic patients who are likely to develop type 1 SMA (SMC2311).

These treatments aim to reduce symptoms and slow the progression of disease. Choice of treatment depends on several factors including age, comorbidities, spine anatomy, treatment tolerance and side effects.[9] Patients may also receive supportive management including respiratory and nutritional support, physiotherapy and rehabilitation.[4]

Clinical experts consulted by SMC consider that nusinersen previously filled an unmet need before the introduction of risdiplam. They consider that nusinersen would be used for patients who are unable to tolerate risdiplam.

2. Impact of new technology

Comparative efficacy

Key evidence for nusinersen for patients with type 2 or 3 SMA (relevant to this submission) is from CHERISH.[10-12]

Table 2.1 Overview of relevant study

Criteria	CHERISH
Study design	International, double-blind, randomised, controlled, phase III study
Eligible patients	• Children aged 2 to 12 years of age with a diagnosis of 5q-linked SMA with symptom onset after 6 months of age • Diagnosis was genetically-confirmed (homozygous gene deletion, mutation or compound heterozygote) • Children could sit independently but had never walked independently

	• Estimated life expectancy exceeding two years • HFMSE score between 10 and 54 on screening
Treatments	Patients were randomised to receive nusinersen 12 mg intrathecal injection or a sham control procedure (needle prick to lower back) on days 1, 29 and 85 (loading dose) and 274 (maintenance). Patients were allowed to receive concomitant medication for AEs or to provide adequate supportive care.
Randomisation	Patients were randomised in a ratio of 2:1 to receive nusinersen or sham control. Randomisation was stratified by age at screening (<6 years versus ≥6 years).
Primary outcome	Change from baseline in HFMSE score at 15 months. The HFMSE is a validated measure of motor function for ambulatory children with type 2 or 3 SMA. It comprises 33 items to assess activities of daily living. Each item is scored 0 (no response) to 2 (full response), and HFMSE total score ranges from 0 to 66; higher scores indicate better motor function and a 3-point change is clinically meaningful.
Secondary outcomes	• Proportion of patients with a 3-point or greater increase in HFMSE • Proportion of patients achieving any new WHO motor milestones at 15 months • Number of motor milestones achieved at 15 months • Change from baseline in RULM score at 15 months • Proportion of patients achieving standing alone at 15 months • Proportion of patients achieving walking with assistance at 15 months
Statistical analysis	A hierarchical statistical testing strategy was applied for the primary outcome and the secondary outcomes, in the order specified above, with no formal testing of outcomes after the first non-significant outcome. Therefore, the results reported for these outcomes are descriptive only and not inferential (no p-values reported). Efficacy analyses were conducted in the ITT population, which included all randomised patients who underwent at least one assigned procedure. An interim analysis was planned to occur when all patients had been enrolled for at least 6 months and at least 39 children had completed 15-month assessment; multiple imputation methods were used to account for the children who did not have 15-month data available.

Abbreviations: AE = adverse events; HFMSE = Hammersmith Functional Motor Scale Expanded; ITT = intention-to-treat; SMA = spinal muscular atrophy; WHO = World Health Organisation; RULM = revised upper limb module.

At the interim analysis (data cut-off 31 August 2016), 43% (54/126) patients had completed 15-month assessment and data was imputed for those without. The nusinersen group had a significantly greater improvement in Hammersmith Functional Motor Scale Expanded (HFMSE) score at 15 months compared with the sham control group. The primary outcome was significant at the interim analysis and at the recommendation of the data and safety monitoring board, the study stopped early and all patients who had not had a 15-month assessment had a

visit that represented the end of the double-blind period, where all assessments scheduled for the 15-month assessment were performed. Secondary outcomes were tested at the final analysis.[10] Details of the primary and secondary outcomes are presented in Table 2.2.

Table 2.2: Primary and secondary outcomes from CHERISH at 15 months in the ITT population [10]

	Nusinersen (n=84)	Sham control (n=42)	Difference (95% CI)
Primary outcome (interim analysis, data cut-off 31 August 2016)			
LS mean change from baseline in HFMSE score to 15 months	4.0	-1.9	5.9 (3.7 to 8.1), p<0.001
Secondary outcomes (final analysis, data cut-off 03 March 2017)			
Proportion of patients with a clinically significant improvement in HFMSE total score from baseline (≥3 points)	57%	26%	Odds ratio: 6.0 (2.0 to 15.0), p<0.001
Proportion of patients that achieved any new WHO motor milestone	20%	6%	14% (-7.0 to 34.0), p=0.08
Change from baseline in number of WHO motor milestones achieved per child	0.2	-0.2	0.4 (0.2 to 0.7)
LS mean change from baseline in RULM test score	4.2	0.5	3.7 (2.3 to 5.0)
Proportion of patients achieving standing alone	2%	3%	-1% (-22 to 19)
Proportion of patients achieving walking with assistance	2%	0	2% (-19 to 22)

Abbreviations: CI = confidence interval; HFMSE = Hammersmith Functional Motor Scale Expanded; ITT = intention-to-treat; LS = least squares; RULM: Revised Upper Limb Module; WHO = World Health Organisation.

Health related quality of life was assessed using three questionnaires: Clinical Global Impression of Change (CGI-C), Paediatric Quality of Life Inventory (PedsQL) and Assessment of Caregiver Experience with Neuromuscular Disease (ACEND). At each visit, greater proportions of patients in the nusinersen group compared with the control group were judged to having improvement in CGI assessments. Improvements in physical functioning were observed in both treatment groups assessed by PedsQL. Carer burden was reduced for several domains including feeding, grooming, dressing, transfer and mobility in the nusinersen group, while carer burden increased in these domains in the sham control group.[11]

2.1. Indirect evidence to support clinical and cost-effectiveness comparisons

Clinical experts consulted by SMC consider that risdiplam is the only relevant comparator for this submission. In the absence of direct evidence comparing nusinersen with risdiplam, the submitting company submitted five matching adjusted indirect comparisons (MAIC) and two simulated treatment comparisons (STC) to highlight comparative efficacy between nusinersen and risdiplam. None of the comparisons were used in the economic case.

MAICs were performed for outcomes including the Hammersmith Infant Neurological Examination (HINE-2) at 24 months, permanent ventilation at 12 months and overall survival at 12 months in patients with type 1 SMA and therefore were not examined in detail. MAIC adjustments tended to lack significance and tended to revise the proportion of difference favouring risdiplam.[13]

MAICs were not always possible and two outcomes were assessed using an STC: HFMSE and RULM score, change from baseline to 12 months in type 2 and type 3 SMA. In both cases the crude estimate favoured nusinersen, and the adjusted estimate favoured risdiplam.[13]

Additional evidence on reassessment

From July 2019 nusinersen could be prescribed for patients with type 2 or 3 SMA within the ultra-orphan pathway. Following this the submitting company had the opportunity to collect additional data to support its reassessment submission. This included information from studies as well as real-world data.

SHINE was an international, open-label, extension study which evaluated the efficacy and long-term safety of nusinersen in patients with symptomatic SMA who had participated in previous nusinersen studies (including CHERISH). Of the 126 patients in CHERISH, 83/84 patients in the nusinersen group and 42/42 patients in the sham control group enrolled in SHINE, where all patients received nusinersen. Patients who had previously received nusinersen in CHERISH received 12 mg nusinersen on days 1 and 85, with a sham procedure on day 29 followed by a maintenance dose of nusinersen once every 4 months thereafter. Patients who had previously received sham control in CHERISH received 12 mg nusinersen on days 1, 29 and 85 and then once every 4 months thereafter. From initiation of nusinersen in CHERISH including extension of treatment in SHINE, the median duration of treatment was 7.2 years (range 1.3 to 8.4 years) in the nusinersen group and from initiation of nusinersen in SHINE, the median duration of treatment was 5.8 years (range 2.7 to 6.7 years) in the previous control group. The most common reason for discontinuation in both groups was voluntary withdrawal.[1, 14]

Results from SHINE suggests that World Health Organisation (WHO) motor milestones were more likely to be achieved in the nusinersen group compared with patients in the previous control group. Improvements in mean HFMSE total scores were observed initially in both groups (nusinersen and previous control groups). In all participants mean HFMSE total scores were maintained above CHERISH baseline up to day 1,710, then decreased below baseline from day 2,430 onward. Most type 2 or type 3 patients treated with nusinersen experienced

stabilisation or improvement in motor function and the greatest benefit was observed in patients who initiated treatment earlier. PedsQL scores increased in the CHERISH and SHINE study period for patients in the nusinersen treatment group in terms of both the patient and parent-rated inventory total score and neuromuscular score. In the previous control group, there were decreases in the patient-rated inventory total score and the parent-rated neuromuscular score. Conversely, there were increases in the patient-rated neuromuscular score and the parent-rated inventory total score. ACEND total scores in feeding, grooming, dressing, transfers and mobility domains were higher for previous nusinersen patients compared with previous control patients.[1, 14, 15]

The submitting company provided supportive real-world data for up to 4 years on the use of nusinersen (licensed dose) in adult and paediatric patients with later-onset SMA from two UK based registries; SMA Research and Clinical Hub (REACH) UK (paediatric patients) and Adult SMA REACH (≥16 years). Data from the adult registry were collected from treatment centres in England only. There were 82 children and 12 adults with type 2 SMA, and 57 children and 82 adults with type 3 SMA. Primary outcomes included the proportion of patients who maintained baseline WHO motor milestone or attained a new WHO motor milestone. Results suggest that most adult and paediatric patients were stable and remained in the same WHO motor milestone category. At the end of the data cut-off periods, 4.3% patients had discontinued nusinersen treatment in the adult group and 24% in the paediatric group. The most common reason for discontinuation in the paediatric group was switching to risdiplam. Reasons for switching treatment included increased difficulty with performing lumber puncture, spinal surgery, and patients' preference.[16, 17]

*Other data were also assessed but remain confidential.**

Comparative safety

The regulator concluded that nusinersen has demonstrated a favourable safety pattern in the treatment of SMA.[4] Evidence from CHERISH supports the relative safety of nusinersen compared with sham control for the treatment of patients with type 2 or type 3 SMA.

In the CHERISH study at the final analysis (data cut-off 03 March 2017), patients reporting any serious adverse event (AE) were 17% (14/84) in the nusinersen group and 29% (12/42) in the sham control group. Serious treatment-emergent AEs in the nusinersen group versus the sham control group were: pneumonia (2% versus 14%) and respiratory distress (2% versus 5%). Treatment-emergent AEs with incidence at least 5% higher in the nusinersen group than in the control group were: pyrexia (43% versus 36%), headache (29% versus 7%), vomiting (29% versus 12%), back pain (25% versus 0) and epistaxis (7% versus 0).[10]

Nusinersen was considered to be well tolerated and no new safety concerns were identified in SHINE.[14] Adverse events including headache, vomiting and back pain are considered to be associated with the lumbar puncture procedure. These are most likely to occur within 72 hours of the procedure.[1, 10]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- In the key phase III study, CHERISH, patients in the nusinersen group had statistically significant and clinically meaningful improvements in motor function, as assessed by HFMSE at 15 months, compared with those in the sham control group. Improvement was maintained up to 4.7 years in the extension study, SHINE.[10, 14]
- Significant improvements with nusinersen versus sham control were observed for the secondary outcome in CHERISH, proportion of patients with a clinically significant improvement in HFMSE score, and there appeared to be numerical benefit with nusinersen in others including achievement of new WHO motor milestones and improvements in RULM scores. [10]
- Additional real-world data were provided to support maintenance of motor function outcomes in children and adult patients with type 2 or 3 SMA following longer-term treatment (up to 4 years).[16, 17]
- Clinical experts consulted by SMC were mixed in their views that nusinersen is a therapeutic advancement and considered that nusinersen has a limited role for patients with type 2 or 3 SMA since the introduction of risdiplam. Clinical experts consider that it is useful to have additional treatment options for patients with type 2 or 3 SMA.

Key uncertainties:

- Clinical experts consulted by SMC consider that risdiplam is the only relevant comparator for type 2 and type 3 SMA patients in Scotland. No direct comparative evidence was available and indirect treatment comparisons were performed comparing nusinersen with risdiplam. The submitting company considered that the indirect treatment comparisons had several limitations, introducing high levels of bias and therefore did not use them to inform the economic analysis. The MAICs included patients with type 1 SMA which is not relevant to this submission. Limitations also included variation in patient characteristics, treatment doses and treatment durations which is likely to contribute to substantial bias. No safety outcomes were included.[13] Overall, due to the rarity of the condition, substantial differences between studies and difficult outcomes to measure the results of the comparison are uncertain.
- There were some differences in the CHERISH study population compared with the licensed population: SMC clinical experts consulted for the initial assessment (SMC1318/18) considered that CHERISH represented a predominately type 2 SMA patient population, only 16% of patients were ≥6 years and patients with respiratory impairment, and patients with severe contractures or scoliosis were excluded.[10] Therefore, efficacy is less certain in patients with type 3 SMA and older children. Some real-world data has been provided for

older children, adults and type 3 SMA patients, however this data is uncontrolled.[16, 17]

- During the SHINE extension period, many patients developed scoliosis and contractures and this may have impacted their ability to complete HFMSE assessments. Therefore, limited HFMSE data were collected from SHINE and this should be interpreted with caution.[14]

3. Impact beyond direct health benefits and on specialist services

Treatment with nusinersen could lead to an improvement in motor function, potentially a decline in symptoms such as muscle weakness, pain, fatigue and the need for orthopaedic surgical interventions. This could have a positive impact on patients' wellbeing, attendance and performance at school or employment. Patients may require less care, be able to retain their independence, mobility and continue to undertake normal daily tasks, thereby reducing the impact on families and carers. Additionally, carers may be more likely to stay in employment.

The introduction of nusinersen for patients with type 2 or type 3 SMA will have significant service implications. Currently, there are no adult nusinersen services in Scotland, therefore introduction of an adult service would require additional resource, significant time and planning. Eligible patients require hospital admission and younger patients may require general anaesthesia. Additionally, the administration of nusinersen may require theatre time, a trained specialist doctor to administer the dose and in more complex cases may require availability of several members of the multidisciplinary team including anaesthetists, neurologists and spinal surgeons. There are also risks associated with intrathecal procedures. Preparation of nusinersen requires resource from pharmacy aseptic services.

4. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of nusinersen, as an ultra-orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Spinal muscular atrophy (SMA) is an inherited, neurodegenerative disorder characterised by progressive muscle weakness. It presents as a clinical spectrum of disease with worsening disease severity linked to fewer survival motor neuron 2 gene copies and a younger age of symptom onset. SMA significantly affects mobility, independence and ability to undertake daily tasks and has other physical impacts including contractures, pain, bone fractures, scoliosis, fatigue, choking and constipation.
- Currently, SMA is defined by type which is based on the timing and severity of clinical presentation. PACE participants raised that the clinical distinction between types, most notably, type 1 and type 2, may not be clear cut. Newborn screening for SMA will also mean that diagnosis of SMA will no longer be by clinical presentation.

- Nusinersen is currently available within the ultra-orphan pathway in NHS Scotland for patients diagnosed with type 2 or 3 SMA, and was viewed by PACE clinicians as standard of care for patients with SMA. The availability of treatment options for patients diagnosed with type 2 or type 3 SMA is imperative and ensures that individual patient needs are considered.
- Nusinersen offers significant, life-changing benefits to individuals diagnosed with SMA types 2 and 3 and appears to offer similar benefits in clinical outcomes to other disease modifying treatments for SMA. It slows disease progression, stabilises or improves motor function and enhances quality of life. It allows patients to maintain education or work, independence, can reduce care needs and improves daily functioning.
- Some patients prefer the less frequent administration of nusinersen over daily oral alternatives, and the treatment frequency can offer flexibility to patients and carers. The infrequent administration of nusinersen allows patients to live a normal life, travel and attend school. Hospital visits help to ensure continuous multidisciplinary input and this is valued by patients and carers on nusinersen currently. The intrathecal delivery of nusinersen offers peace of mind to families.
- Treatment with nusinersen offers hope to patients and carers, it may help to reduce the burden of care, reduce psychological strain and impact on finances.
- PACE participants support the procedural flexibility of the administration of nusinersen in Scotland and highlighted the need for alternatives to general anaesthesia for nusinersen administration in Scotland.

Additional Patient and Carer Involvement

We received a joint patient group submission from SMA UK and Muscular Dystrophy UK, which are both registered charities. SMA UK has received 13% pharmaceutical company funding in the past two years, including from the submitting company. Muscular Dystrophy UK has received 1.32% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both patient groups participated in the PACE meeting. The key points of the joint submission have been included in the full PACE statement considered by SMC.

5. Value for money

5.1. Economic case

An overview of the economic analysis is presented in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (95 years), with a mean patient starting age of 4.54 years
Population	Patients with later-onset (type 2 and 3) SMA
Comparators	Risdiplam (main comparator in Scotland), best supportive care (BSC)
Model description	Markov model with 5 health states, reflecting WHO motor milestones (not sitting, sitting without support, standing with support, walking independently) and death. Model cycle length was 4 weekly. Patients could stay in the same health state per cycle or move a maximum of one milestone per cycle.
Clinical data	The CHERISH study provided the milestones transition probabilities data for type 2 SMA for nusinersen to 15 months, with SHINE providing further transition probability data for nusinersen to 96 months.[10, 14] BSC type 2 SMA transition probabilities were based on the sham control arm of CHERISH to 15 months.[10] The transition probabilities for the type 2 population were adjusted so that any sham control (BSC) patients (n=2) who were in the walking independently state by the end of the CHERISH clinical study were assumed to be in the standing with support state, on the grounds that it would not be feasible for type 2 patients to be walking independently over the clinical study timeframe. The same adjustment was made for nusinersen patients (n=4). There were limited data available for type 3 SMA, so it was assumed that all type 3 patients in the analysis would start and finish in the walking independently state over the duration of the clinical trial evidence for nusinersen and BSC, supported by evidence from a published natural history study showing type 3 patients lose the ability to walk at much later ages.[18] Real-world UK registry data (REACH) were used to estimate nusinersen treatment discontinuations by health state, applied to all later-onset SMA patients (type 2 and 3 combined).[16, 17] For a comparison with risdiplam, the submitting company assumed equal motor milestone effectiveness for nusinersen and risdiplam. A relative risk of discontinuation for risdiplam vs nusinersen of 0.44 was estimated from a study reviewing UK persistence rates for the two treatments and applied to the nusinersen discontinuation rates based on real-world evidence.[19]
Extrapolation	Beyond the clinical trial evidence, a rate of motor milestone decline was estimated for BSC based on natural history evidence. This was applied to BSC from 15 months onwards.[18] The relative risk of decline for nusinersen was based on nusinersen vs sham control analysis of the proportion of patients who had lost at least one motor milestone at 15 months using the CHERISH final analysis dataset (relative risk estimate of 0.34). This was applied to the nusinersen data per cycle from 96 months.

	Transitions to the death state from the most severe health states (not sitting, and sitting without support) were based on survival data from a large natural history study, with general population mortality (pre COVID) assumed for the standing with support and walking states.[20]
Quality of life	Health state utilities for patients were derived from a previous NICE technology appraisal for onasemnogene abeparvovec (HST24), estimated to be 0.19 not sitting, 0.60 for sitting with support, 0.77 for standing without support, and general population utility for walking independently.[21] Caregiver utilities (one carer assumed) were also included based on a Spanish study using the EQ 5D in SMA carers, with estimated utilities per health state of 0.484 not sitting, 0.628 for sitting with support, 0.771 for standing without support, and general population utility for walking independently.[22] An additional on-treatment utility increment of 0.10 was also applied for nusinersen patients which was stated to be for the milestone benefits not captured by the 4 gross motor milestone states in the model, such as head control, rolling and crawling. The estimate was stated to be based on similar increments included in the US Institute for Clinical and Economic Review economic assessment of nusinersen and onasemnogene abeparvovec in SMA, supported by clinical expert opinion.
Costs and resource use	Medicine acquisition costs have been estimated for nusinersen, and risdiplam. Nusinersen intrathecal lumber puncture drug administration costs were included. No drug administration costs were assumed for risdiplam due to its oral administration. Health state costs for disease management for later-onset SMA are based on costs used in previous technology appraisal for onasemnogene abeparvovec (HST24).[21] No adverse event costs were estimated.
PAS	A Patient Access Scheme (PAS) was submitted by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for risdiplam and this was included in the results used for decision-making by using estimates of the comparator PAS price.

5.2. Results

The base case results are presented in Table 5.2. With equal effectiveness at achieving motor milestones assumed for the comparison of nusinersen vs risdiplam, nusinersen was estimated to be associated with lower quality adjusted life years (QALYs) than risdiplam and a higher rate of treatment discontinuation.

For the comparison with BSC the QALY gains are driven by patients with nusinersen spending more time in the standing with support and walking states. There are net disease management cost offsets for nusinersen associated with BSC patients spending greater time in the more severe and higher cost health states of not sitting and sitting without support. Net incremental

costs for nusinersen are due to the acquisition and administration costs for nusinersen vs none for BSC.

Table 5.2 Base case results for nusinersen vs. comparators

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
nusinersen versus:	CIC	23.10	14.74	-	-	-	-
risdiplam	CIC	23.47	15.92	CIC	-0.37	-1.18	CIC
BSC	CIC	22.82	12.04	CIC	0.28	2.70	CIC

Abbreviations: CIC = commercial-in-confidence; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years; BSC = best supportive care

In addition, the results of sub-group analysis for type 2 and type 3 SMA separately for the comparison with BSC are presented in Table 5.2a and b. The lower QALYs for type 2 SMA sub-group is due to nusinersen patients spending a longer time in the more severe health states relative to the overall later-onset population (Table 5.2a). The results generated for the type 3 SMA sub-group are presented in Table 5.2b.

Table 5.2a Sub-group analysis Type 2 SMA

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
nusinersen versus:	CIC	21.77	10.87	-	-	-	
BSC	CIC	21.52	9.43	CIC	0.25	1.45	CIC

Abbreviations: CIC = commercial-in-confidence; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years; BSC = best supportive care

Table 5.2b Sub-group analysis Type 3 SMA

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
nusinersen versus:	CIC	25.60	22.34	-	-	-	

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	CIC	25.45	19.55	CIC	0.15	2.79	CIC

Abbreviations: CIC = commercial-in-confidence; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years; BSC = best supportive care

5.3. Sensitivity analyses

One way sensitivity analysis varied various input parameters by their 95% confidence intervals, or if not available by ±20% range. The most impactful parameters on the ICER for the comparison with BSC when varied were caregiver utilities, patient health state utilities and sitting without support and not sitting health state costs. There was some sensitivity to varying discontinuation rates in some of the health states (sitting without support).

A range of scenario analysis were conducted for the comparison with BSC and risdiplam in the submitting company submission and economic model, with results of selected key scenarios presented in Table 5.3. The ICER vs BSC was improved with the inclusion of caregiver utilities (scenario 1). There is ICER uncertainty associated with the inclusion of an additional on-treatment utility for nusinersen (scenario 2), to a lower rate of BSC motor milestones decline (scenario 4), source of health state costs and a shorter time horizon (scenarios 5 and 6). Inclusion of a disutility for nusinersen administration increases the ICER (scenario 7). For the comparison with risdiplam, uncertainty over relative discontinuations (scenario 8) and including a disutility for nusinersen administration (scenario 7) has an impact on relative costs and QALYs despite the assumption of equal effectiveness in achieving motor milestones.

Table 5.3 Scenario Analyses for nusinersen vs comparators

	Parameter	Base case	Scenarios
1	Caregiver utilities	Excluded	Included
2	On-treatment utility increment	0.10 increment for additional motor benefits	Excluded
3	Health state utilities	From NICE HST24	NICE TA755/TA588
4	BSC rate of motor milestone decline	Estimated as per Wadman et al	Rate halved
5	Health state costs	From NICE HST24	NICE TA588 source
6	Time horizon	Lifetime	30 years

7	Nusinersen intrathecal administration	No disutility applied	Apply a disutility (0.071 from Lo et al)
8	Treatment discontinuations	Relative risk of 0.44 for risdiplam vs nusinersen	Same discontinuation
			Relative risk of 0.22

5.4. Key strengths:

- Appropriate and transparent economic model.
- Use of longer-term clinical follow-up data to 96 months from SHINE for estimating nusinersen motor milestone outcomes, and use of natural history data to estimate a long-term rate of decline for BSC motor milestone outcomes beyond the clinical study data.
- REACH registry real-world data provided useful UK evidence on nusinersen discontinuation rates by health state for use in the economic analysis.
- Availability of health state cost and utility data for the model from prior technology appraisals of late-onset SMA therapies.
- Good range of scenario analyses for the comparison with BSC to explore uncertainty in the base case ICER.

5.5. Key uncertainties:

- No comparison was initially provided versus the main comparator used in Scottish clinical practice, risdiplam due to concerns from the submitting company that the limitations with the ITCs mean this would not be robust. SMC clinical experts have confirmed that risdiplam is the main treatment used for later-onset SMA in Scotland. The economic analysis provided on request by the submitting company assumed equal effectiveness between treatments, which is uncertain, and only took account of estimated relative discontinuation rates for nusinersen and risdiplam. The assumption of equal effectiveness and the cost-effectiveness results produced are associated with high uncertainty. However, SMC clinical expert feedback confirmed it is reasonable to assume comparable effectiveness between these treatments. An exploratory scenario analysis setting discontinuation rates the same between treatments (hence zero differences in QALYs) enabled a comparison of the relative drug costs for nusinersen and risdiplam with both PASs considered.
- There are limitations with the clinical evidence with which to assess the relative effectiveness of nusinersen vs BSC for use in the economic analysis. There is a particular lack of evidence for the effectiveness of nusinersen in type 3 SMA, making the cost-effectiveness results for this sub-group and the overall later-onset population uncertain. Further, for type 2 SMA there was limited CHERISH control arm data and

follow-up relative to nusinersen to determine motor milestone transition probabilities for BSC.

- The cost-effectiveness results for nusinersen vs BSC were upwardly sensitive to a number of parameters and data uncertainties. There was ICER sensitivity to the BSC rate of motor milestone decline, the source used for health state costs, and shorter time horizon (Scenarios 4-6, Table 5.3).
- The inclusion of an arbitrary additional on-treatment utility benefit for nusinersen for motor functions not captured by the model health states is highly uncertain for inclusion in the base case. Scenario analysis excluding it has an upward impact on the ICER (Scenario 2, Table 5.3).
- Disutility related to the administration of nusinersen (intrathecal lumber puncture procedure) was not included in the base case, with scenario analysis including it demonstrating lower cost-effectiveness vs the comparators (Scenario 7, Table 5.3).
- The sub-group analyses of type 2 and 3 SMA demonstrates a higher ICER than for the total later-onset SMA population. However, the type 3 SMA analysis appears unreliable (with large differences in the deterministic and probabilistic ICERs) hence cost-effectiveness in this sub-group is highly uncertain.

6. Conclusion

The Committee considered the benefits of nusinersen in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as nusinersen is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted nusinersen for restricted use in NHSScotland.

7. Costs to NHS and Personal Social Services

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

8. Guidelines and protocols

In March 2018, the SMA care group published a guideline for the diagnosis and management of spinal muscular atrophy.[24]

9. Additional information

9.1. Product availability date

30 May 2017

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
nusinersen	**12 mg loading dose on days 0, 14, 28 and 63 followed by 12 mg maintenance dose every 4 months by intrathecal injection**	**Year 1 450,000 Subsequent years 225,000**

Costs from BNF online on 22 May 2025. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 11 July 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial-in-confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.