Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2401

risdiplam 0.75mg/mL powder for oral solution (Evrysdi®)

Roche Products Limited

14 January 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan process

risdiplam (Evrysdi®) is accepted for use within NHSScotland.

Indication under review: for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or with one to four SMN2 [survival of motor neuron 2] copies.

Evidence from two phase II/III studies has indicated that risdiplam improves motor milestones and motor function in patients with type 1, 2 and 3 SMA.

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.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or with one to four SMN2 copies.[1]

Dosing Information

The recommended dose of risdiplam is determined by age and body weight and is taken orally once daily after a meal at approximately the same time each day:

- Age 2 months to <2 years: 0.20mg/kg
- Age ≥2 years (<20kg): 0.25mg/kg
- Age ≥2 years (≥20kg): 5mg

Treatment with a daily dose above 5mg has not been studied.

The patient should drink water after taking risdiplam to ensure the medicinal product has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube in situ, risdiplam can be administered via the tube. The tube should be flushed with water after delivering risdiplam. In infants who are breastfed, risdiplam should be administered after breastfeeding. Risdiplam should not be mixed with milk or formula milk.

Treatment with risdiplam should be initiated by a physician with experience in the management of SMA.[1]

Product availability date

21 June 2021.

Risdiplam received a positive scientific opinion (EAMS number 00031/0011) under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency (MHRA) on 17 September 2020. The indication was for the treatment of type 1 and type 2 SMA in patients 2 months and older who are not suitable for authorised treatments. The EAMS scientific opinion expired on 1 July 2021.

Risdiplam meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Spinal muscular atrophy (SMA) is a genetic neurodegenerative disorder resulting from deletions or mutation in the gene (SMN1) that codes for the SMN protein. The loss of SMN can be partially compensated by a second SMN gene (SMN2), which produces a shortened and less functional SMN protein. However, the reduced levels of the SMN protein lead to a loss of spinal motor neurons, progressive muscle weakness and atrophy. The severity of SMA is highly variable. Increasing severity is linked to fewer numbers of survival motor neuron 2 (SMN2) gene copies and a younger age of symptom onset. SMA is considered a spectrum but five clinical subtypes (type 0,

1, 2, 3, and 4) have been classified according to age of onset and the patient's maximal functional status prior to degeneration. Prognosis worsens the earlier the age of onset of symptoms. Without treatment, patients with SMA type 1 who have onset of symptoms in the first 6 months of life never achieve independent sitting. Without respiratory support and tube-feeding, these patients are unlikely to survive past 2 years of age. Patients with type 2 SMA present between 6 and 18 months and are able to sit and possibly stand but never walk independently due to weakness in their lower limbs. Patients with type 3 SMA present between 18 and 36 months and are able to sit, stand, and walk independently. Patients with type 2 and type 3 SMA experience a decline in motor function over time as well as declining pulmonary function and may need non-invasive ventilation support. Patients with type 1, 2 and 3 SMA are associated with having two, three and three to four SMN2 copies respectively.

Risdiplam is a SMN2 pre-mRNA splicing modifier designed to treat SMA by increasing and sustaining functional SMN protein levels.[1,2]

Evidence comes from two key studies (FIREFISH and SUNFISH) both of which comprised a part 1 dose-escalating phase and a part 2 confirmatory phase. Parts 1 and 2 were independent of each other and can be considered as separate studies: only part 2, which is most relevant to the efficacy and safety of risdiplam, will be discussed here.

FIREFISH is an ongoing open-label, single-arm, phase II/III study to evaluate the efficacy and safety of risdiplam in patients with type 1 SMA. Forty-one patients, aged between 2.2 and 6.9 months with a confirmed diagnosis of 5q-autosomal recessive SMA and two SMN2 gene copies, as confirmed by central testing, were enrolled in part 2. They received oral risdiplam once daily at the following starting doses according to age at enrolment: 0.04 mg/kg for age >1 month and <3 months; 0.08 mg/kg for age ≥3 months and <5 months; and 0.2 mg/kg for age ≥5 months. Dose levels were modified and adapted according to individual patient's pharmacokinetic data to a final dose of 0.2mg/kg which was continued up to 24 months. This was followed by an open-label extension which is ongoing.[2,3]

The primary outcome was the ability to sit without support for ≥5 seconds measured by item 22 of the Bayley Scales of Infant and Toddler Development-Third edition (BSID-III) gross motor scale which was videoed and scored by independent central readers. The primary analysis was performed after 12 months of treatment in the intention-to-treat (ITT) population, which included all enrolled patients. Secondary outcomes at 12 months were analysed in a hierarchical order: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score ≥40; CHOP-INTEND scores increase of ≥4 points from baseline; Hammersmith Infant Neurological Examination section 2 (HINE-2) motor milestone responders and proportion of patients alive without permanent ventilation (that is event-free survival). The results for risdiplam are presented in table 1 and were significantly better ($p<0.001$) than pre-defined performance criteria estimated from the natural history of type 1 SMA and were maintained or improved in analyses at 24 months. [1,2,3]

Table 1: Primary and key secondary outcomes of part 2 of the FIREFISH study at 12 months [1,2,3]

	Risdiplam (n=41)	Performance criterion
Primary outcome: sitting without support for ≥5 seconds, n (%), (90% CI)	12 (29%) (18% to 43%)	5%
Key secondary outcomes		
CHOP-INTEND score ≥40, n (%), (90% CI)	23 (56%) (42% to 69%)	17%
Increase of ≥4 points in CHOP-INTEND from baseline, n (%), (90% CI)	37 (90%) (79% to 97%)	17%
HINE-2 motor milestone response, n (%), (90% CI)	32 (78%) (65% to 88%)	12%
Event-free survival, n (%), (90% CI)	35 (85%) (73% to 92%)	42%
Overall survival	38 (93%) (82% to 97%)	60%

CI=confidence interval; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (ranges from 0 to 64 with increasing score indicating better motor skills); HINE-2=Hammersmith Infant Neurological Examination section 2 response (defined as more motor milestones showed improvement than showed worsening. Improvement = at least a 2-point increase in the ability to kick or maximal score or at least a 1-point increase in head control, rolling, sitting, crawling, standing, or walking)

Health Related Quality of Life was assessed using the change from baseline in the Infant and Toddler Quality of Life Short Form 47 (ITQOL-SF47) Questionnaire, which comprised parent-proxy domains of physical abilities, growth and development, bodily pain/discomfort, temperament and moods, behaviour, general health perception, parent emotional impact and parent time impact and single item scores of overall health, change in health and family cohesion. SMC is unable to present the results. [2,4]

SUNFISH is an ongoing randomised, double-blind, placebo-controlled, phase II/III study to evaluate the efficacy and safety of risdiplam in patients with type 2 and type 3 SMA. Eligible patients were aged 2 to 25 years with confirmed diagnosis of 5q-autosomal recessive SMA type 2 or non-ambulant type 3 SMA. They had a Revised Upper Limb Module (RULM) entry item A ≥2 (that is able to raise arms) and were able to sit independently as assessed by Motor Function Measure (MFM) item 9. They were randomised in a ratio of 2:1 to receive oral risdiplam (5mg once daily for patients weighing ≥20kg or 0.25mg/kg for patients weighing <20kg) or placebo for 12 months. Randomisation was stratified according to age groups (2 to 5 years, 6 to 11 years, 12 to 17 years and 18 to 25 years). After 12 months, patients in the placebo group were switched to receive blinded risdiplam for a further 12 months. This was followed by an open-label extension which is ongoing.[1,2,5]

The primary outcome was change from baseline in Motor Function Measure 32 (MFM32) total score at 12 months and was analysed in the ITT population which comprised all randomised patients. MFM32 is the sum of 32 scores assessing physical function in three dimensions (D1 function related to standing and transfer; D2 axial and proximal function; D3 distal motor function) expressed as a total score (range 0 to 100, with higher scores indicating increased motor function). Six secondary outcomes were analysed in a hierarchical order: MFM32 responder (improvement in

MFM32 total score ≥3 points); change in RULM total score; change in Hammersmith Functional Motor Scale Expanded (HFMSE) total score; change in forced vital capacity (FVC) in patients aged 6 to 25 years; change in caregiver-reported SMA Independence Scale (SMAIS) total score and percentage of patients rated by clinicians as improved in the Clinical Global Impression of Change (CGI-C) scale ratings. Risdiplam was significantly better than placebo for the primary and first two secondary outcomes. However, there was no statistically significant difference in the third secondary outcome, change in HFMSE total score from baseline to 12 months, and further formal testing was not performed. [1,2,5] Details are presented in table 2. Some benefits were maintained at 24 months.

Table 2: Primary and key secondary outcomes in part 2 of the SUNFISH study at 12 months[1,2,5]

Secondary outcomes	**Risdiplam (n=120)**	**Placebo (n=60)**
Primary outcome: Change from baseline in MFM32 total score, LS mean	(n=115) 1.36	(n=59) -0.19
Difference versus placebo (95% CI), p-value	1.55 (0.30 to 2.81), p=0.016	
Secondary outcomes		
Patients with change from baseline in MFM32 total score ≥3, %	38% (44/115)	24% (14/59)
Odds ratio versus placebo (95% CI), p-value	2.35 (1.01 to 5.44), p=0.047	
Change from baseline in RULM total score, LS mean	(n=119) 1.61	(n=58) 0.02
Difference versus placebo (95% CI), p-value	1.59 (0.55 to 2.62), p=0.047	
Change from baseline in HFMSE total score, LS mean	(n=120) 0.95	(n=60) 0.37
Difference versus placebo (95% CI), p-value	0.58 (-0.53 to 1.69), p=0.390	
Change from baseline in FVC in patients aged 6 to 25 years, LS mean	(n=83) -5.2%	(n=40) -3.1%
Change from baseline in caregiver-reported SMAIS total score, LS mean	(n=116) 1.65	(n=60) -0.91
Patients rated by clinicians as improved on from baseline on CGI-C scale rating, %	(n=120) 48%	(n=60) 40%

MFM32=Motor Function Measure 32-item, score ranges from 0 to 100, with lower score indicating more functional impairment; LS=least square; CI=confidence interval; RULM=Revised Upper Limb Module, score ranges from 0 to 37, with higher scores indicating greater upper limb function; HFMSE=Hammersmith Functional Motor Scale Expanded, score ranges from 0 to 66, with higher scores indicating greater functioning; FVC=forced vital capacity; SMAIS=Spinal Muscular Atrophy Independence Scale; CGI-C=Clinicians Global Impression of Change

The company performed a number of indirect comparisons of risdiplam with nusinersen. In patients with type 1 SMA, an unanchored matching-adjusted indirect comparison (MAIC) was performed using pooled data from FIREFISH Part 1 and Part 2 for risdiplam and results from the ENDEAR study for nusinersen. This was supported by a naïve indirect treatment comparison (ITC). The outcomes assessed were event-free survival, overall survival, motor milestone response and achievements (head control, sitting without support, sitting with or without support, rolling and standing), motor function and safety outcomes. The results suggested that risdiplam was better

than nusinersen in event-free and overall survival, motor function and some of the motor milestone outcomes.

In patients with type 2 or 3 SMA, an anchored MAIC and restricted network meta-analysis (NMA) were performed using a restricted subset of the SUNFISH part 2 population for risdiplam (aged ≤9 years, baseline HFMSE score ≥10, and with no severe scoliosis), to adjust for some differences and compare with the CHERISH study for nusinersen. These assessed motor function outcomes, as well as treatment-related adverse events. For all outcomes except one (change in HFMSE total score), there was no evidence of a difference between risdiplam and nusinersen. However, this outcome was not used in the economic analysis.

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

Summary of evidence on comparative safety

There are no comparative safety data.

In the FIREFISH part 2 study, after 12 months of treatment, any treatment-emergent adverse event (AE) was reported in all 41 patients. A grade 3 or higher AE was reported in 54% of patients and a serious AE in 59%. A serious AE led to a dose reduction in 2.4% of patients and an AE led to dose interruptions in 4.9% of patients. No patients discontinued therapy due to an AE. The most frequently reported treatment-emergent AEs of any grade were: upper respiratory tract infection (including nasopharyngitis, respiratory tract infection, rhinitis, influenza, pharyngitis, viral respiratory tract infection and viral upper respiratory tract infection: 68%), pneumonia (39%), pyrexia (39%), constipation (20%), diarrhoea (10%) and maculopapular rash (10%). The most frequently reported serious AEs were pneumonia (32%), bronchiolitis (4.9%), hypotonia (4.9%) and respiratory failure (4.9%). Three patients died during part 2 of FIREFISH but these were considered unrelated to risdiplam but related to SMA respiratory complications.[3]

After 12 months of treatment in the SUNFISH part 2, any treatment-emergent AE was reported by 92% (111/120) of risdiplam patients and 92% (55/60) of placebo patients and these were considered treatment-related in 13% and 10% of patients respectively. No patients discontinued therapy due to an AE. The most frequently reported treatment-emergent AEs in the risdiplam and placebo group respectively were: upper respiratory tract infection (32% and 30%), pyrexia (21% and 17%), headache (20% and 17%), diarrhoea (17% and 10%), and nausea (9.2% and 5.0%), [2,6,7]

Pooled safety data are available for 465 SMA patients treated with risdiplam for up to 3 years that indicate a favourable safety profile but longer-term safety data are awaited.

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

Summary of clinical effectiveness issues

Treatment options for SMA are limited and aim to increase survival and improve motor function. Intrathecal nusinersen has been accepted by SMC for restricted use in patients with symptomatic type 1 SMA (infantile onset) and since July 2019 can be prescribed through the ultra-orphan pathway for patients with types 2 and 3 SMA for up to 3 years while further evidence on its effectiveness is generated (SMC1318). Some patients with SMA may develop complications that interfere with the intrathecal administration procedure, thereby restricting continued treatment with nusinersen. Onasemnogene abeparvovec, a gene therapy, was accepted by SMC in February 2021 for restricted use in patients with type 1 SMA or in pre-symptomatic patients with up to 3 copies of the SMN2 gene who are expected to develop type 1 SMA (SMC2311). In line with SMC process, onasemnogene abeparvovec was not considered as a comparator for risdiplam in type 1 patients as the company submission for risdiplam was received within 6 months of publication of the advice for onasemnogene abeparvovec.

SMC clinical expert advice is that in the current context of treatment, the SMA classification will become more difficult to delineate and separation of some of the subtypes, particularly SMA 2 and 3 will become more difficult.

Risdiplam has received marketing authorisation for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or with one to four SMN2 copies. It is administered as an oral solution, which is an advantage for patients and the service as lumbar punctures are required to administer intrathecal nusinersen, and it is a potential alternative for patients with SMA-related complications for whom this route is not suitable. Risdiplam meets SMC orphan criteria.

Key strengths

- Evidence for type 1 SMA patients from the FIREFISH study found that compared to a pre-defined performance criteria estimated from the natural history of type 1 SMA, risdiplam increased the proportion of patients achieving the motor milestone of sitting unsupported for ≥5 seconds. This was achieved by 29% at 12 months and was higher at 24 months. This was supported by relevant secondary outcomes that were greater than historical control rates including neuromuscular function, survival free from ventilation and overall survival rates. The results are consistent with risdiplam slowing the progression of disease and permitting development of motor function in these patients.[2,3]

- Placebo-controlled evidence for type 2 and non-ambulant type 3 SMA patients from SUNFISH found significant improvements in the primary outcome assessing motor function (MFM32) at 12 months. This was supported by significant improvements over placebo in the two key secondary outcomes.[2]

- The EMA noted that there is evidence of a clinically relevant effect for risdiplam, of sufficient magnitude and duration, on development milestones in mild to moderate SMA type 1, and on motor function in SMA type 2 and non-ambulant type 3 patients.[2]

Key uncertainties

- There are no direct comparative data for risdiplam and the submitting company presented indirect comparisons with the first medicine licensed, nusinersen, in two patient populations (type 1 and type 2/3 SMA). A key uncertainty is the robustness of this indirect evidence. These MAIC and ITCs were limited by the small patients numbers (further reduced after matching in the MAIC), potential confounding due to differences in some baseline characteristics that could not be matched, lack of common control arm to anchor analysis in type 1 patients, primary outcomes from risdiplam studies could not be used as not assessed for nusinersen, and immature event-free and overall survival data. Available results suggest that risdiplam may be better than nusinersen in type 1 SMA for event-free and overall survival and some but not all motor milestone and motor function outcomes. However the confidence intervals were wide indicating uncertainty. Not all indirect comparison results were used in the economic analysis.

- FIREFISH is limited by its open-label, single-arm design and relied on predefined performance criteria for the primary and key secondary outcomes based on historical controls. The data are still immature in type 1 SMA patients and longer-term results from the ongoing FIREFISH study are awaited.[2,3]

- The FIREFISH study population was generally considered representative of patients with type 1 SMA with the exception of patients who had the most severe forms and those who were not clinically stable; FIREFISH excluded patients who needed a tracheostomy or invasive ventilation, hypoxemic patients and patients who had recently been in hospital for a pulmonary event.[2,3]

- In SUNFISH, although the difference between risdiplam and placebo for the primary outcome was statistically significant, the absolute difference was modest (1.55-points on a 100-point scale). There was no statistically significant difference between risdiplam and placebo for the third secondary outcome of change in HFMSE total score and further statistical testing was not performed. The clinical benefit of risdiplam in patients with type 2 and non-ambulant type 3 SMA is less clear. Subgroup analysis suggested a lack of treatment effect in patients aged 18 to 25 years. Further longer-term results from the ongoing SUNFISH study are awaited.[2,5]

- SUNFISH included a wide range of type 2 and type 3 patients representing those seen in clinical practice. The majority of patients in SUNFISH (71%) had type 2 SMA and most patients had three copies of the SMN*2* gene (>80%). The median age at screening was 9 years and only 22 patients were aged 18 to 25 years. Study patients had a wide range of disease duration and consequently varying degrees of SMA-related complications. Consequently, the heterogeneous patient population, although reflecting the spectrum of type 2 and 3 non-ambulant patients in practice, may have contributed to difficulty in assessing the type and size of the treatment effect. [2,5]

- The marketing authorisation does not specify line of treatment and FIREFISH and SUNFISH patients had not received previous disease-modifying treatment for SMA. This is currently being assessed in the JEWELFISH study.

- SUNFISH enrolled patients with type 2 or non-ambulatory type 3 SMA. The licensed indication does not specify the ambulatory status of type 3 patients but there is no evidence from SUNFISH part 2 for use in ambulant type 3 patients.
- The licensed indication also includes patients with one to four SMN2 copies; these patients may be pre-symptomatic but there are currently no efficacy and safety data to support use in these patients. The treatment effect is being assessed in these patients in a post-authorisation efficacy study and in RAINBOWFISH. [2]

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 risdiplam, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- SMA is a complex and often severely disabling condition which causes severe muscle weakness affecting all the muscles in the body. The progressive nature of the condition means that patients continuously deteriorate making daily activities difficult. This poses an enormous physical and emotional burden on patients, as well as their families and carers, on whom they become dependent.
- Currently available treatments are nusinersen (which is limited by its intrathecal administration) and onasemnogene abeparvovec (for patients with type 1 SMA). There is an unmet need for an easily administered medicine suitable for a wider patient population to provide choice and an alternative to current treatments when these are not suitable or not working.
- Risdiplam offers the convenience of oral administration, allowing patients to be treated at home and avoiding the distress, risks and complications associated with repeated intrathecal injections of nusinersen. Current problems with service infrastructure stops adult patients having access to intrathecal nusinersen. The availability of an oral medicine would improve access to treatment for patients from all geographical areas.
- Risdiplam distributes evenly across the body including the central nervous system after crossing the blood-brain barrier. This wider distribution may lead to SMN protein increase in the central nervous system and throughout the body.
- The PACE participants fully supported the use of risdiplam in patients with types 1, 2 and 3 SMA. They noted the limitations of outcome measures used in studies but presented evidence of qualitative benefit from experience with risdiplam through EAMS. They emphasised that stabilisation and maintenance of function is itself a sought after and positive outcome in what is a progressive muscle wasting condition. They described how, beyond this, perceived small improvements in the ability to perform daily activities could have a huge and life-changing impact on well-being and quality of life for any non-

ambulant patient. For adult ambulant patients with type 3 SMA, risdiplam may stabilise the condition and this was also considered of major importance by the PACE participants.

- Through their experience, the PACE participants highlighted the health benefits associated with risdiplam including reduced fatigue and improvements in energy levels, swallowing, strength of voice, sleep, mobility and upper body motor function. These improvements may allow patients to be less dependent on family and carers in many ways, including needing assistance with activities of daily living and self-caring and for support during the night.

Additional Patient and Carer Involvement

We received patient group submissions from SMA UK and MDUK, both organisations are registered charities. SMA UK has received 4.2% pharmaceutical company funding in the past two years, including from the submitting company. MDUK has received 1.53% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented two cost-utility analyses to evaluate risdiplam for (i) type 1 SMA patients (clinically diagnosed or having two SMN2 copies) and (ii) type 2 or 3 SMA patients (clinically diagnosed or having two to four SMN2 copies). In both analyses risdiplam with best supportive care (BSC) is compared against nusinersen with BSC. BSC has been defined as services associated with a multidisciplinary approach involving the input of neurologists, respiratory specialists, dietitians, gastroenterologists, geneticists, palliative care physicians, and orthopaedic surgeons in the management of SMA patients.

De novo Markov models were developed separately for type 1 and type 2/3 SMA. The patient population in the type 1 model mirrored that of the FIREFISH phase 2/3 clinical study for risdiplam, which included infants with symptomatic type 1 SMA aged 2–7 months. The type 2/3 model patient population mirrored the SUNFISH phase 2/3 clinical study for risdiplam but included both ambulant and non-ambulant patients aged 2–25 years.

Both type 1 and type 2/3 analyses adopted a six-state Markov model including death. The common motor milestone health states between the two models were: not sitting, sitting, standing and walking. However, in the case of type 2/3 the 'sitting' health state was split into sitting 'with' and 'without support' to represent the clinical significance for patients with type 2/3. In the type 1 model an additional permanent ventilation (PV) state was included to reflect the greater severity and poorer prognosis of SMA type 1 patients. In both models, patients could transition to consecutive progressive or regressive health state, and can transition to death state from any of the states. Both models had a cycle length of one month and a lifetime horizon was used.

Clinical evidence used in the economic evaluation primarily came from the FIREFISH (type 1 SMA) and SUNFISH (type 2/3 SMA) studies for risdiplam, and the ENDEAR (type 1 SMA) and CHERISH (type 2/3 SMA) studies for nusinersen.[2, 3] Due to lack of direct comparative clinical evidence available for risdiplam vs. nusinersen, an ITC was required to demonstrate the relative treatment effect. For type 1 SMA, due to the evidence network being disconnected an unanchored MAIC was used, whereas for type 2/3 SMA an anchored MAIC was used for relative effect estimation in the comparison of risdiplam to nusinersen.

Transition probabilities between motor milestone health states for the risdiplam arm in both models were derived from the clinical data of patients who received the final dose of risdiplam in the FIREFISH and SUNFISH studies and had at least 52 weeks follow-up, whereas for the nusinersen arm these were estimated using the results from the appropriate ITC. For type 1 SMA, the transition from 'not sitting' to 'sitting' and 'sitting' to 'standing' were informed by the assessment of motor milestones using the HINE-2. For type 2/3 SMA, the transitions for nusinersen arm were informed by the RULM score. Backward transitions to worse health states for both risdiplam and nusinersen-treated patients can happen at any time until 66 months in the type 1 model and 26 months in the type 2/3 model. From this point onward a plateauing of treatment effect is assumed, and patients remain in their motor milestone health states for the remaining time horizon.

Parametric survival analysis was used to estimate long-term survival for type 1 and type 2 SMA patients, whereas general population mortality was assumed for type 3 SMA patients. Additionally, a hazard ratio of 0.75 informed by NICE TA588 was further applied for type 2 SMA patients to reflect the anticipated reduced likelihood of mortality associated with the treatment with disease-modifying therapies compared to BSC.

Patient and caregiver utility data for all motor milestone health states in both type 1 and type 2/3 model have been derived from literature sources or via a previous NICE submission TA588.[8] The company has included caregiver utilities alongside patient utilities within the base case for both models given the substantial extent of care required for SMA patients from family members or carers. Scenario analyses using alternative utility values have been conducted.

Drug acquisition, administration and resource use costs for risdiplam and nusinersen were included in the analysis. Health-state unit and resource use costs were estimated separately for risdiplam and nusinersen using real world studies conducted by the respective companies.[8,9] Due to the difference in administration between the two medicines, the company justified applying different resource use costs in the model. Adverse events have not been included in either model due to their low incidence in the SUNFISH and FIRESFISH studies.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. A PAS discount is in place for nusinersen and this was included in the results used for decision-making by using estimates of the comparator PAS price. The results presented do not take account of the PAS for nusinersen or the PAS for risdiplam but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for nusinersen due to commercial confidentiality and competition law issues.

The base case results with list prices with key scenario analyses are presented in table 3 below.

Table 3: Base case and scenario analysis results for the type 1 and type 2/3 SMA models (List price)

	Scenario	ICER
	type 1 SMA	
0	**Base case**	Dominant*
1	HCRU costs - UK BOI study values for both arms	Dominant
2	HCRU costs - TA588 BOI study values for both arms	Dominant
3	Source of caregiver utilities UK BOI study	Dominant
4	Source of nusinersen efficacy- naïve HINE	Dominant
5	PV health state costs: More optimistic 250% increase from the "Not Sitting" health state	Dominant
6	PV health state costs: 175% increase from "Not sitting" health state in both arms	Dominant
7	EFS extrapolation Best statistical fit – Gompertz	Dominant
8	OS extrapolation Best statistical fit – Gen Gamma	Dominant
9	Caregiver utilities excluded + scenario 2 + scenario 6	Dominant
10	Caregiver utilities excluded + scenario 1 + scenario 6	£22,053
11	Time horizon : 80 years	Dominant
12	Time horizon: 50 years	Dominant
13	Time horizon: 30 years	Dominant
	type 2/3 SMA	
0	**Base case**	Dominant
1	Source of patient utility values: SUNFISH	Dominant
2	Exclusion of intrathecal disutility (nusinersen)	Dominant
3	Source of caregiver utilities UK BOI study	Dominant
4	HCRU costs - UK BOI values for both arms	Dominant
5	HCRU costs - TA588 BOI values for both arms	Dominant
6	OS extrapolation best statistical fit – Gen Gamma	Dominant
7	Caregiver utilities excluded + scenario 4	Dominant
8	Caregiver utilities excluded + scenario 5	Dominant
9	Time horizon : 80 years	Dominant
10	Time horizon: 50 years	Dominant
11	Time horizon: 30 years	Dominant

HCRU = healthcare resource use, BOI = burden of illness, PV = permanent ventilation, EFS = event-free survival, OS = overall survival,

*Dominant = risdiplam is estimated to be more effective and less costly than nusinersen at list prices.

Key weaknesses

- The Committee discussed the cases presented for SMC type 1 and type 2/3 patients and agreed it was appropriate for the company to present the results for these groups separately given the different clinical and economic cases for each group. The Committee also considered the views of patient groups and clinical experts who highlighted the challenges with differentiating the SMA types across the spectrum of the condition. Given these clinical challenges, the Committee concluded it would make a judgment on the case as a whole.
- Due to the lack of direct comparison between risdiplam and nusinersen and shorter duration of trial data, there is a considerable amount of uncertainty around the long-term relative effectiveness of risdiplam vs. nusinersen. This is especially true in case of type 2/3 model where clinical benefits observed were minimal or not significant.
- Utility data for all motor milestone health states in both type 1 and type 2/3 model have been derived from literature sources directly or via previous NICE submission TA588. Caregiver utility data have also been included in the base case for both models. When these are removed QALY gains from risdiplam decrease considerably indicating their proportionately larger contribution to the overall QALYs used in the model. Scenario analyses were also conducted to test alternative patient utility values, which did not alter the results significantly.
- Healthcare resource use costs have been obtained from real world studies conducted by the companies themselves and then applied to each medicine separately: the Roche study results applied to risdiplam and the Biogen study results applied to nusinersen. While recognising the higher costs associated with an intrathecal treatment, the differences were felt to lack face validity. This approach increases the likelihood of inherent bias, which is also evident from the significant impact on the ICERs observed in the scenario analyses when the same healthcare resource use study is selected for both arms in the model. These scenarios reduced the cost-effectiveness of risdiplam, with a substantial impact in type 2 and 3 SMA.
- PV health state costs were applied differently to the nusinersen arm in the type 1 model. Combined scenario analyses 9 & 10 showed that when PV health state costs are assumed to be the same across both treatment arms a change in ICER value occurs.

The Committee considered the benefits of risdiplam in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as risdiplam is an 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 risdiplam for use in NHSScotland.

Additional information: guidelines and protocols

In July 2020, a European ad-hoc consensus statement on gene replacement therapy for SMA was published.[10] This consensus statement notes that nusinersen was the first medicine to be approved by the EMA for the treatment of SMA and that onasemnogene abeparvovec has recently been approved. Nusinersen is an antisense-oligonucleotide that increases SMN protein concentration by modifying the splicing of the SMN2 gene. Onasemnogene abeparvovec is an adeno-associated viral vector-based gene therapy designed to deliver a functional copy of the SMN1 gene to the motor neurons. Some key points from the consensus statement are summarised below:

- In symptomatic patients, age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to gene therapy treatment. SMA types (type 0, 1, 2, 3, 4) alone are not sufficient.
- In presymptomatic patients, SMN2 copy number is the most important predictor of clinical severity and age of onset.
- If onasemnogene abeparvovec is given after 6 months of age and/or in advanced stages of the disease, parents or patients should clearly be made aware that there are so far no published data on efficacy and safety and the risk/benefit should be carefully considered.
- In patients with symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.
- Patients weighing >13.5kg should only receive treatment in specific circumstances as the risk of gene therapy increases with dose. For these patients, treatment with other disease modifying therapies or future intrathecal administration of nusinersen should be considered as an alternative.
- At the time of publication of the consensus statement there is no published evidence that combination of gene therapy and nusinersen is superior to any single treatment alone.

Early initiation of treatment, preferably in the pre-symptomatic stage of the disease, is associated with notably better outcome than starting treatment later. In newly diagnosed patients treatment delays should be avoided. This guidance pre-dates the availability of risdiplam.

In 2007, an International Conference on the Standard of Care for SMA published a consensus statement on SMA standard of care, this was updated in November 2017. [11,12] All care considerations should start with a focus on a patient's clinical symptoms, signs and risk factors. In type 1 patients (infants unable to sit unsupported) supportive care includes rehabilitation (involving positioning, stretching and mobility), nutritional and hydration management, swallowing (short-term nasogastric or nasojejunal tube then long term gastrostomy tube) and pulmonary management (airway clearance with chest physiotherapy and oral suctioning, non-invasive ventilation, nebulised bronchodilators, and antibiotics if required). The consensus

statement notes that nusinersen has received a licence in Europe and USA. This guidance pre-dates the availability of onasemnogene abeparvovec and risdiplam.

Additional information: comparators

The main comparator is nusinersen.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Risdiplam	Up to 5mg orally daily	Up to 239,633

Costs from eMC Dictionary of Medicines and Devices Browser on 1 September 2021. The dose is calculated according to age and weight to a maximum of 5mg daily. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 22 patients eligible for treatment with risdiplam in year 1 rising to 63 patients in year 5 to which confidential uptake figures were applied.

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.

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

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12. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M*, et al.* Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular disorders : NMD. 2018;28:103-15.

This assessment is based on data submitted by the applicant company up to and including 19 October 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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 Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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 SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice 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 in determining medicines for local use or local formulary inclusion. 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.