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ADIS DRUG EVALUATION

Nusinersen: A Review in 5q Spinal Muscular Atrophy

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Abstract

Survival motor neuron 1 (*SMN1*), located on chromosome 5q, encodes the survival motor neuron (SMN) protein. A deletion or mutation in *SMN1* results in a rare neuromuscular disorder: 5q spinal muscular atrophy (SMA). In such patients, SMN protein production relies solely on *SMN2*. Nusinersen (Spinraza®) is a modified antisense oligonucleotide approved for the treatment of 5q SMA. Administered intrathecally, it modifies *SMN2* pre-messenger RNA splicing, thereby increasing full-length SMN protein levels. Interim analyses from an ongoing phase II study suggest substantial clinical benefits with nusinersen initiation in presymptomatic patients. In phase III studies, nusinersen achieved significant and/or clinically relevant improvements in motor function in symptomatic patients with infantile- and later-onset 5q SMA, and significantly improved event-free survival and overall survival in patients with infantile-onset 5q SMA. Longer term (up to a median of ≈ 6 years of available data), motor function was maintained or improved in symptomatic patients. Nusinersen had a favourable safety profile in clinical studies in presymptomatic and symptomatic patients. Real-world experience supports the effectiveness, safety and tolerability of nusinersen in symptomatic patients of all ages. Thus, nusinersen remains an important treatment option among a broad range of 5q SMA patients.

Plain Language Summary

5q spinal muscular atrophy (SMA) is a rare disease most commonly caused by a defect in the *survival motor neuron* (*SMN*) *1* gene, which in a healthy individual produces a protein [spinal motor neuron (SMN) protein] critical to maintaining the nerves that control muscles. Individuals with 5q SMA do not produce this protein in sufficient levels, resulting in muscle weakness and wasting (including the muscles involved in general movement, breathing and swallowing), so increasing the amount of SMN protein by modifying a nearly identical, but low functioning, gene (*SMN2*) is one way to treat the disease. Nusinersen (Spinraza®) is a treatment that targets *SMN2*. It is administered via lumbar puncture and is approved for use in presymptomatic and symptomatic individuals with 5q SMA. In both groups of patients, nusinersen increases the amount of SMN protein necessary for the muscles and nerves to work normally, improving motor function. This benefit persists over the longer-term (up to a median of ≈ 6 years of available data), and is well tolerated. Nusinersen continues to be an important treatment option among a broad range of 5q SMA patients.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.16571555.

Nusinersen: clinical considerations in 5q SMA

Modifies *SMN2* pre-messenger RNA splicing, thereby increasing full-length SMN protein levels
Improves motor function in presymptomatic and symptomatic patients, and event-free survival and overall survival in symptomatic patients with infantile-onset disease
Improvements seen in all age groups, with greater benefits in those receiving earlier treatment
Most reported adverse events were related to the disease itself or the lumbar puncture procedure

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1 Introduction

Spinal muscular atrophy (SMA) is a rare (incidence of 1 in 8000 to 10,000 individuals [1]) neuromuscular disorder most commonly resulting from a homozygous deletion or mutation in the *survival motor neuron 1* (*SMN1*) gene located on chromosome 5q [1, 2]. *SMN1* encodes survival motor neuron (SMN) protein, which is crucial for the maintenance of motor neurons; insufficient levels of SMN protein lead to motor neuron death and subsequently the signs and symptoms of 5q SMA [atrophy and weakness of the skeletal muscles (including those involved in general movement and breathing) and impaired bulbar function (characterized by difficulties in mouth opening, chewing and swallowing)] [1, 3]. Five 5q SMA types have been identified (based on age of symptom onset and maximal acquired motor function) [1, 2, 4, 5]. Type 0, the most severe form, results in death within weeks of birth even with intensive respiratory support. In patients with type 1 (infantile-onset 5q SMA; the most common form of the disease), symptoms are evident at birth or within the first few months of life, individuals are unable to sit independently, and death usually occurs within the first 2 years. Those with type 2 have symptom onset between 6 and 18 months of age. Affected individuals can sit independently but not walk; most live into adulthood with substantial disability. Type 3 is characterized by symptom onset after 18 months of age. Affected individuals can stand and walk independently and have a normal life expectancy, although these abilities will deteriorate over time. Type 4 is the mildest and rarest form of the disease and symptoms often develop in early adulthood. Affected individuals have mild to moderate disability and a normal life expectancy [1, 2, 4, 5].

Humans also have *SMN2*, a nearly identical copy of *SMN1* [2]. While *SMN2* also encodes SMN protein, a single nucleotide difference in exon 7 of the gene alters the splicing of most pre-messenger RNA (pre-mRNA) transcripts; consequently, ≈ 90% of the SMN protein produced from *SMN2* mRNA is truncated (i.e. non-functional) and rapidly degraded [1, 2]. An individual's *SMN2* copy number [which can range from one or two copies (typical) to up to eight copies] is the key determinant of 5q SMA disease severity [1, 6]. While patients with 5q SMA type 1 generally have two *SMN2* copies, those with type 2 three copies, those with type 3 three or four copies and those with type 4 four or more copies [1, 6], the number of *SMN2* copies does not always correlate directly with the observed clinical phenotype [2].

Only recently have therapeutic approaches beyond symptomatic and supportive care become available for patients with 5q SMA. One of these is the antisense oligonucleotide (ASO) nusinersen (Spinraza®). This article provides an updated overview of pharmacological (summarized in Table 1), therapeutic efficacy and tolerability data relevant to the intrathecal use of nusinersen in patients with 5q SMA, previously reviewed in *CNS Drugs* [7].

2 Therapeutic Efficacy of Nusinersen

2.1 In Presymptomatic Patients

An open-label, noncomparative, multinational, phase II study (CS5; NURTURE) is evaluating the therapeutic efficacy of nusinersen in preventing or delaying respiratory intervention or death when initiated prior to symptom onset [8, 9]. Eligible patients had a genetic diagnosis of 5q SMA and two or three copies of *SMN2*, were presymptomatic at screening and were aged ≤ 6 weeks at the time of the first dose. Nusinersen (12 mg dose equivalent) was administered intrathecally on days 1, 15, 29 and 64, and then every 119 days thereafter for a total treatment period of 8 years; the median age at first dose was 22.0 days. An interim analysis was conducted at a data cut-off date of 29 March 2019 (median follow-up duration of 2.9 years). At this timepoint, the 25 enrolled patients had a median (range) age of 34.8 (25.7–45.4) months (i.e. they were past the expected age of symptom onset for 5q SMA type 1 or 2) and had been in the study for 33.9 (25.3–45.1) months. At baseline, 15 and 10 patients had two or three copies of *SMN2*, respectively [8, 9].

The early (i.e. immediately after establishing a genetic diagnosis of 5q SMA) initiation of nusinersen in presymptomatic infants was associated with substantial clinical benefits [8]. At the time of the interim analysis, the primary endpoint of median time to respiratory intervention (defined as invasive or non-invasive ventilation for ≥ 6 h/day continuously for ≥ 7 days, or tracheostomy) or death could not be estimated owing to too few events. All 25 patients were alive and were able to sit without support, and none required permanent ventilation. Respiratory support for ≥ 6 h/day for ≥ 7 consecutive days was required by four patients owing to acute, reversible illnesses, but at the last study day prior to the data cut-off date was no longer needed by two patients [8].

All but two patients were able to walk with support and all but three were able to walk independently; patients unable to achieve these milestones had just two copies of *SMN2* [8]. Notably, 84% of patients achieved sitting without support, 65% achieved walking with assistance and 73% achieved walking independently within the window established by the WHO for healthy children (i.e. by the WHO 99th percentile age of achievement). At day 778, all patients could suck and swallow [as assessed by Hammersmith Infant Neurological Examination (HINE) Section 1]. Mean total HINE Section 2 (HINE-2; see Table 2 for definition) scores improved from 2.7 at baseline to 23.9 at the last observed visit (up to and including day

Table 1 Overview of the key pharmacological properties of nusinersen

Pharmacodynamic properties
Modified 2′-*O*-2-methoxyethyl phosphorothioate antisense oligonucleotide that binds to an intronic splice silencing site (ISS-N1) in intron 7 of *SMN2* pre-mRNA, preventing binding of splicing factors and resulting in retention of exon 7 in *SMN2* mRNA and the translation of full-length (i.e. functional) SMN protein [23, 39]; significantly increased full-length *SMN2* mRNA transcripts (2.6-fold; $p = 0.0198$) and SMN protein staining intensity (63.7%; $p < 0.001$) vs no treatment in thoracic spinal cord tissue preparations from pts with infantile-onset 5q SMA [12]
Reduced and then stabilized plasma *pNF*-H levels (which are elevated in pts with 5q SMA) [61–64]
Reduces serum levels of muscle-specific miRNA in type 2 or 3 5q SMA; reduction in miR-133a predicts therapeutic response [65]
Effects on lung function in pts with 5q SMA range from slowing of lung function decline to improvements in lung function [51, 52, 66, 67]
Does not increase the incidence of cardiac adverse reactions associated with delayed ventricular repolarisation [39]
Pharmacokinetic properties
≈ dose-proportional pharmacokinetics (in terms of C_{max} and AUC) up to a dose of 12 mg [23, 39]
Distributed to motor neurons, vascular endothelial cells and glial cells throughout the CNS (including the spinal cord) following intrathecal injection [12, 23, 39], with the mean trough concentrations in the CSF reaching steady state within ≈ 24 months [23]
Achieves concentration (of > 10 µg per gram of spinal cord) in the cervical, lumbar and thoracic spinal cord of pts with 5q SMA that is predicted to produce pharmacological effects. Prolonged CSF and CNS tissue exposure (CSF concentrations quantifiable 15–168 days after dosing) [12]
Clearance from CSF into systemic circulation is consistent with normal CSF turnover [12]; has been identified in the peripheral tissues [12, 23, 39]. Following intrathecal injection, trough plasma concentrations are relatively low compared with trough CSF concentrations; the median time to plasma C_{max} was 1.7–6.0 h and there was no accumulation following multiple doses [23, 39]
Metabolism [predominantly via exonuclease (3′- and 5′)–mediated hydrolysis] is slow; the estimated mean terminal elimination half-life of nusinersen is 135–177 days in CSF and 63–87 days in plasma [23, 39]. Primary route of elimination for the parent drug and its metabolites is thought to be via urinary excretion; 0.5% of the administered dose recovered in the urine at 24 h [23, 39]

AUC area under the concentration–time curve, C_{max} mean plasma maximum concentration, *CSF* cerebrospinal fluid, *mRNA* messenger RNA, *miRNA* microRNA, *pNF-H* phosphorylated neurofilament heavy chain, *pts* patients, *SMA* spinal muscular atrophy, *SMN* survival motor neuron

778) in patients with two copies of *SMN2* and from 3.2 to 26.0 (the scale maximum) in those with three copies of *SMN2*. Mean total Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) scores improved steadily from baseline (values of 47.0 and 51.9) until ≈ day 183, after which they remained stable. At the time of the interim analysis, mean total CHOP-INTEND scores were 62.1 and 63.4 in the subgroups of patients with two or three copies of *SMN2*, with 67% and 100% of patients achieving the maximum score of 64. Protocol-defined symptoms of 5q SMA were reported in 10 patients with two copies of *SMN2* and 2 patients with three copies of *SMN2* at age 13 months and in 7 and 0 patients at age 24 months. The 7 patients with symptoms of 5q SMA at 24 months of age continued to grow and achieve WHO motor milestones inconsistent with both 5q SMA type 1 and untreated siblings with 5q SMA: all 7 were sitting without support, 5 were walking with support and 4 were walking independently [8].

Preliminary data from another interim analysis (data cut-off date of 19 February 2020) support the WHO motor milestone findings of the earlier analysis, with all NURTURE participants ($n = 25$; median age of 3.8 years) alive and without permanent ventilation [10]. All of the participants who achieved the motor milestone of being able to walk independently maintained that ability over the 11 months since the previous data cut-off date [10]. In the overall population, swallowing ability (assessed using the Parent Assessment of Swallowing Ability questionnaire) was maintained in 92% of 25 patients [median age at last visit of 3.8 (range 2.8–4.8) years] and only 2 patients (both of whom had two copies of *SMN2*) required full-time tube feeding [11].

2.2 In Symptomatic Patients

2.2.1 Infantile-Onset 5q SMA

2.2.1.1 In Clinical Studies The potential of nusinersen in patients with infantile-onset 5q SMA was first demonstrated in an open-label, phase II, dose-escalation study (CS3A) [12]. Results from this study supported the selection of a 12 mg dose for further investigation [7] and informed the design of a subsequent randomized, double-blind, sham-controlled, multinational, phase III study (CS3B; ENDEAR) [13]. ENDEAR enrolled 121 patients with a genetic diagnosis of 5q SMA and two copies of the *SMN2* gene who were aged ≤ 6 months at symptom onset and ≤ 7 months at screening [13]. All patients were symptomatic, hypotonic, and weak (features consistent with a phenotype most likely to be 5q SMA type 1). Randomization to nusinersen (12 mg dose equivalent, administered intrathecally on days 1, 15, 29, 64, 183 and 302) or a sham procedure was stratified by disease duration at screening (≤ 12 weeks or > 12 weeks). The median disease duration at screening was 13.1 weeks. Results from the prespecified interim analysis demonstrating a benefit–risk assessment in favour of nusinersen (Table 2)

Table 2 Efficacy of nusinersen in patients with infantile-onset 5q spinal muscular atrophy in ENDEAR [13]

Endpoint[a]	% of pts (total no. of pts)		HR (95% CI)
	Nusinersen	Sham control	
Interim analysis			
Motor milestone response rate[b]	41** (51)	0 (27)	
Final analysis			
Motor milestone response rate[b]	51** (73)	0 (37)	
EFS rate[c]	61 (80)	32 (41)	0.53 (0.32–0.89)*
CHOP–INTEND response rate[d]	71** (73)	3 (37)	
Overall survival rate	84 (80)	61 (41)	0.37 (0.18–0.77)*
Proportion of pts not requiring permanent assisted ventilation	78 (80)	68 (41)	0.66 (0.32–1.37)
CMAP response rate[e]	36**[f] (73)	5 (37)	
EFS rate in pts with a disease duration of ≤ 13.1 weeks at screening	77 (39)	33 (21)	0.24 (0.10–0.58)**[f]
EFS rate in pts with a disease duration of > 13.1 weeks at screening	46 (41)	30 (20)	0.84 (0.43–1.67)

Additional information has been obtained from the EU summary of product characteristics [23] and the US prescribing information [39]

CHOP-INTEND Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease, *CMAP* compound muscular action potential, *EFS* event-free survival, *HINE-2* Hammersmith Infant Neurological Examination Section 2, *HR* hazard ratio, *pts* patients

*$p \leq 0.005$, **$p < 0.001$ vs sham contro

[a]Endpoints were assessed in a hierarchical manner in the intention-to-treat population

[b]Co-primary endpoint; proportion of patients achieving an improvement in ≥ 1 of 7 HINE-2 categories [i.e. a ≥ 1-point increase in the head control, rolling, sitting, crawling, standing or walking categories or a ≥ 2-point increase (or a maximal score) in the ability to kick category] and achieving improvement in more categories than worsening. HINE-2 scores range from 0 to 26, with higher scores indicating better motor function

[c]Co-primary endpoint; avoidance of death or permanent assisted ventilation (defined as tracheostomy or ventilatory support for ≥16 h per day for > 21 continuous days in the absence of an acute reversible event)

[d]Proportion of pts achieving a ≥ 4-point increase from baseline in the CHOP-INTEND total score (scores range from 0 to 64, with higher scores indicating better motor function)

[e]Proportion of pts with a peroneal CMAP amplitude increasing to or maintained at ≥ 1 mV compared with baseline

[f]Nominal p-value

prompted the early termination of ENDEAR, with patients invited to complete an end-of-study visit (used in the final analysis) ≥ 2 weeks after receiving their most recent dose of nusinersen or sham control and transition into an open-label phase III extension study (SHINE; CS11) [13].

Nusinersen improved motor function in patients with infantile-onset 5q SMA, as demonstrated by a significantly higher motor milestone response rate relative to sham control at the time of both the interim and final analyses (co-primary endpoint) (Table 2). At the final analysis, 22% of nusinersen recipients had achieved full head control, 10% were able to roll over, 8% were able to sit independently and 1% were able to stand [13]. Nusinersen also improved the likelihood of event-free survival (EFS) at the time of the final analysis, as indicated by the significant 47% reduction in the risk of death or permanent assisted ventilation in nusinersen compared with sham control recipients (co-primary endpoint) (Table 2). At this timepoint, the median duration of EFS had not yet been reached in the nusinersen group (and was 22.6 weeks in the sham control group) [13].

At the final analysis, nusinersen was associated with a significantly higher CHOP-INTEND response rate than sham control (Table 2). An improvement from baseline in the CHOP-INTEND score of ≥ 1 point was achieved by 73% of nusinersen recipients and 3% of sham control recipients; 7% and 49% of patients demonstrated a worsening from baseline of ≥ 1 point and 3% and 46% demonstrated a worsening from baseline of ≥ 4 points [13]. While the risk of death was significantly reduced (63%) with nusinersen compared with sham control, there was no significant between-group difference in the proportion of patients not requiring permanent assisted ventilation (Table 2) and all subsequent endpoint analyses in the hierarchical testing strategy were considered exploratory. It is worth noting that as data for patients who had died were censored, the effect of nusinersen on the use of permanent ventilation may have been masked by the twofold higher proportion of deaths in the sham control group compared with the nusinersen group. In the subgroup of patients with a disease duration of ≤ 13.1 weeks at screening, the median time to death or permanent assisted ventilation had not yet been reached in nusinersen recipients, but was 25.4 weeks in sham control recipients [13].

A ≥ 5-point increase in the HINE-2 total score was achieved by 28% of 58 nusinersen recipients and 5% of

20 sham control recipients who were alive at the end of ENDEAR and who had been enrolled for ≥ 6 months (prespecified analysis) [13]. Patients receiving nusinersen who achieved HINE-2 or CHOP-INTEND response criteria earlier in ENDEAR generally demonstrated greater overall improvements at the last visit [14]. Among 51 HINE-2 and 71 CHOP-INTEND responders, the respective response criteria were met by 62% and 83% of patients by day 183, by an additional 27% and 13% by day 302 and by an additional 11% and 4% by day ≥ 395 [14].

Interim results (data cut-off date of 27 August 2019) from SHINE (in which all patients were receiving nusinersen) demonstrated improvements in motor function outcomes in both patients originally treated with nusinersen and those originally treated with sham control in ENDEAR, with the greatest benefits seen in patients with earlier treatment initiation [15, 16]. In patients originally treated with nusinersen in ENDEAR, the mean change from baseline in the CHOP-INTEND score at day 1058 was + 19.8 points in those aged ≤ 5.5 months ($n = 32$) and + 13.1 points in those aged > 5.5 to ≤ 8 months ($n = 26$) at their first dose of nusinersen [15]. In those originally treated with sham control in ENDEAR who commenced nusinersen therapy in SHINE aged ≥ 14 to ≤ 23 months ($n = 11$), the mean change from baseline in the CHOP-INTEND score at day 1058 was + 5.1 points [15]. At this timepoint, 40% of 105 ENDEAR/SHINE participants were able to sit independently [16]. Sitting independently was first achieved by 1, 2, 3 or 4 years of age, respectively, by 37%, 10%, 10% and 2% of patients aged 1.7 to ≤ 5.5 months at their first dose ($n = 41$) and by 8%, 10%, 23%, and 3% of those aged > 5.5 to ≤ 8.0 months at their first dose ($n = 40$). Only one of the 24 patients aged > 8.0 to ≤ 23.0 months at their first dose achieved sitting independently at 4 years of age. Walking independently was achieved by one patient (aged 1.7 to ≤ 5.5 months at their first dose) at 3 years of age [16]. In a multivariate analysis, weight-by-age percentile (≥ 5% vs < 5%), baseline CHOP-INTEND score and disease duration were identified as prognostic for independent sitting [17].

2.2.1.2 In Real-World Studies Real-world experience supports the effectiveness of nusinersen in improving motor function in patients with infantile-onset 5q SMA. In the largest ($n = 104$) real-world study in this patient population, nusinersen for 6 months was associated with significant ($p < 0.001$) changes from baseline in both CHOP-INTEND and HINE-2 scores [18]. Patients in this study were aged 0–19 years, had mean baseline CHOP-INTEND and HINE-2 scores of 15.08 points and 0.82 points, and were enrolled in the Italian expanded access programme (EAP). Improvements did not appear to be related to the number of *SMN2* copies, with significant changes ($p < 0.001$) in these endpoints seen in both patients with two and three *SMN2* copies ($n = 65$ and 24). At month 6, 55.7% and 20.2% of patients achieved improvements from baseline of > 2 points in CHOP-INTEND and HINE-2 scores, respectively; such improvements occurred in 36.6% of 71 patients aged > 2 years and 35.0% of 20 patients aged > 10 years [18]. No significant change from baseline in body mass index was seen at month 6 ($n = 84$) [19]. Among patients in the Italian EAP cohort with 12-month follow-up data (mean baseline CHOP-INTEND and HINE-2 scores of 15.66 points and 0.69 points) [20], there were significant ($p < 0.05$) improvements from baseline in both the CHOP-INTEND and HINE-2 scores for the entire cohort ($n = 85$), and for the subgroups with two and three *SMN2* copies ($n = 61$ and 18). Significant ($p < 0.05$) improvements from baseline at month 12 were also seen in both scores in patients aged < 210 days ($n = 6$) and those aged < 2 years ($n = 23$) at baseline, and in the CHOP-INTEND score in those aged 2–4 years at baseline ($n = 20$); improvements from baseline at month 12 were not significant in either score in patients aged > 5 years [i.e. 5–11 years and > 12 years ($n = 29$ and 5)] at baseline [20].

Improvements in motor function may occur beyond the first year of nusinersen treatment, according to 24-month follow-up data from the Italian EAP cohort ($n = 68$), with improvements more obvious in patients younger than 2 years of age [21]. For both CHOP-INTEND and HINE-2 scores, significant ($p < 0.001$) improvements were seen from baseline at 12 months, from baseline at 24 months and from 12 months at 24 months. Patient age (but not *SMN2* copy number) was predictive of changes in both the CHOP-INTEND and HINE-2 scores, with the improvement from baseline to 24 months significant ($p < 0.05$) across all age subgroups (i.e. < 210 days, < 2 years, 2–4 years, 5–11 years and 12–18 years) for the CHOP-INTEND score and for all age subgroups before the age of 4 years for the HINE-2 score [21].

2.2.2 Later-Onset 5q SMA

2.2.2.1 In Clinical Studies The efficacy of nusinersen in 126 patients with later-onset 5q SMA aged 2–9 years was evaluated in a randomized, double-blind, sham-controlled, multinational, phase III study (CS4; CHERISH) [22]. Patients with a genetic diagnosis of 5q SMA who were aged > 6 months at symptom onset (most likely to be classified as 5q SMA type 2 or 3) were eligible [22]. All patients were non-ambulatory and 88% had three copies of the *SMN2* gene [22, 23]. Randomization to treatment arms [nusinersen (12 mg intrathecally on days 1, 29, 85 and 274) or a sham procedure] was stratified by age at screening (< 6 or ≥ 6 years) [22]. CHERISH was terminated early following the results of a prespecified interim analysis, which showed the benefits of nusinersen over sham control (Table 3), with patients who had not already had a 15-month assessment

invited to complete an end-of study visit. Patients who completed CHERISH were invited to enrol in SHINE [22].

Therapy with nusinersen in CHERISH (Table 3) was associated with a statistically significant and clinically meaningful improvement in motor function [as assessed by the total Hammersmith Functional Motor Scale Expanded (HFMSE) score; primary endpoint] compared with sham control [between-group least-squares mean (LSM) difference of 5.9 points] at the time of the prespecified interim analysis [22]. At the time of the final analysis, the LSM between-group difference in this endpoint was 4.9 points (no formal statistical analysis undertaken as significance was established at the time of the interim analysis) [22]. Among nusinersen and sham control recipients with observed values at month 15 ($n = 66$ and 34), 73% and 41% demonstrated an improvement (not specified) while 23% and 44% demonstrated a worsening (not specified) in the total HFMSE score [22, 23].

At the final analysis (Table 3), nusinersen demonstrated a significant advantage over sham control in the proportion of patients achieving a ≥ 3-point increase from baseline in the total HFMSE score, reflecting a six-fold higher likelihood of achieving this endpoint with nusinersen than sham control at month 15 [22]. However, there was no significant between-group difference in the proportion of patients achieving ≥ 1 new WHO motor milestone; all subsequent endpoint analyses in the hierarchical testing strategy were considered exploratory [22].

Interim results (data cut-off date of 27 August 2019) from SHINE (in which all patients were receiving nusinersen) demonstrated improved motor function [as assessed by total HFMSE and Revised Upper Limb Module (RULM) scores] in both patients originally treated with nusinersen and those originally treated with sham control in CHERISH [24]. Greater benefits were seen in patients with earlier treatment initiation (i.e. those who received nusinersen throughout CHERISH and SHINE). The mean change from baseline in the total HFMSE score was 4.6 at day 1650 in patients treated with nusinersen in both CHERISH and SHINE ($n = 20$) and 1.7 at day 930 ($n = 35$) in those who commenced nusinersen in SHINE. In the respective groups, the mean change from baseline in the total RULM score was 6.4 at day 1650 ($n = 20$) and 3.4 at day 930 ($n = 36$). At the time of this analysis, the median time on nusinersen was 4.1 years for patients treated with nusinersen in CHERISH and SHINE and 2.8 years for those receiving sham control in CHERISH and nusinersen in SHINE [24].

These findings are generally supported by data from ≈ 3 years of nusinersen therapy (six or seven total doses) in 28 patients with later-onset 5q SMA participating in an open-label, multicentre, phase 1b/2a, dose-escalation study (CS2) and its extension (CS12) [25]. In patients with 5q SMA type 2 (symptom onset 7–18 months; $n = 11$), clinically meaningful improvements from baseline in both the total HFMSE score and the Upper Limb Module score (a change of ≥ 3 and

Table 3 Efficacy of nusinersen in patients with later-onset 5q spinal muscular atrophy in CHERISH [22]

Endpoint[a]	Nusinersen ($n = 84$)	Sham control ($n = 42$)
Interim analysis		
LSM change from baseline to month 15 in the total HFMSE score[b]	4.0*	− 1.9
Final analysis		
LSM change from baseline to month 15 in the total HFMSE score[b]	3.9	− 1.0
≥ 3-point increase from baseline to month 15 in the total HFMSE score[c] (% of pts)	57*[d]	26
≥ 1 new WHO motor milestone[e] (% of pts)	20	6
LSM change from baseline in number of WHO motor milestones achieved[f]	0.2	− 0.2
LSM change from baseline in RULM score[g]	4.2	0.5
Ability to stand independently[f] (% of pts)	2	3
Ability to walk with support[f] (% of pts)	2	0

HFMSE Hammersmith Functional Motor Scale Expanded, *LSM* least-squares mean, *pts* patients, *RULM* Revised Upper Limb Module

*$p < 0.001$ vs sham control

[a]Endpoints were evaluated in a hierarchical manner in the intention-to-treat population

[b]Primary endpoint (HFMSE scores range from 0 to 66, with higher scores indicating better motor function)

[c]A change of ≥ 3 points was considered clinically meaningful

[d]Odds ratio 6 (95% CI 2–15)

[e]Out of a total of six WHO motor milestones

[f]$n = 66$ (nusinersen) and 34 (sham control)

[g]RULM scores range from 0 to 37, with higher scores indicating better function

≥ 2 points, respectively, was considered clinically meaningful) were seen at day 1150. In patients with 5q SMA type 3 (symptom onset > 18 months; $n = 17$), total HFMSE scores were stable while the 6-min walk test (6MWT) distance was improved by a clinically meaningful extent (a change of ≥ 30 m) from baseline at day 1150. Such changes were not seen in comparable natural history cohorts [25]. Interim results (data cut-off date of 27 August 2019; median time on study of 6.2 and 6.3 years for patients with 5q SMA type 2 or type 3) from SHINE for these patients further support the maintenance of or improvements in motor function seen with longer-term nusinersen therapy [26]. At day 2010, the total HFMSE score had improved in patients with 5q SMA type 2 ($n = 7$) and were stable in those with 5q SMA type 3 ($n = 9$) compared with baseline. At this timepoint, one patient with 5q SMA type 2 had gained the ability to walk independently, while the mean change from baseline in the 6MWT distance had improved at day 2010 in patients with 5q SMA type 3 ($n = 7$). At day 1770, 83% of 12 patients with 5q SMA type 3 had experienced a clinically meaningful improvement (≥ 30 m) in the 6MWT distance [26].

2.2.2.2 In Real-World Studies Data from the real-world setting support the effectiveness of nusinersen in improving motor function in children with later-onset 5q SMA. For example, in the largest (n = 73–77) of these studies, which enrolled patients with 5q SMA type 2 who were aged > 2.5 to < 18 years, nusinersen significantly ($p < 0.001$) improved mean HFMSE and RULM scores from baseline (mean baseline values of 10.32 and 13.50) by a mean of 1.90 and 1.59 at month 12 [27]. According to a multivariate linear regression analysis, patient age and baseline score, but not *SMN2* copy number, appear to be predictive of changes in HFMSE and RULM scores [27]. These findings are generally supported by those from a cohort of 5q SMA type 3 patients aged < 18 years participating in a recent observational study [28]. Mean HFMSE and RULM scores were significantly ($p < 0.05$) improved, while the mean 6MWT distance was stable after 12 months' nusinersen therapy (respective mean change from baseline of 1.53, 1.26, and 10.32 m; mean baseline values of 43.05, 31.90, and 319.87 m) in these patients (n = 59, 45 and 34) [28].

Results from various real-world studies [29–33] also support the effectiveness of nusinersen in improving motor function in adults with later-onset 5q SMA. For example, in the largest of these (a multicentre, observational study [29]), the treatment of patients (aged 16–65 years with a genetic diagnosis of 5q SMA; 98% of 124 evaluable patients had 5q SMA type 2 or 3) with nusinersen for ≥ 6 months was associated with significant ($p \leq 0.0014$) mean changes from baseline in the mean total HFMSE score (primary endpoint) [n = 124, 92 and 57] and the RULM score (n = 120, 90 and 58) at the 6-, 10- and 14-month assessments. Baseline total HFMSE score was significantly ($p = 0.0006$) correlated with an improvement in total HFMSE score at 6 months ($r = 0.3$); there was no correlation between motor function improvement and patient age. Clinically meaningful improvements in the total HFMSE score were seen in 28% of patients at month 6, 35% at month 10 and 40% at month 14. These improvements were seen at the 6-, 10- and 14-month assessments in more patients with 5q SMA type 3 (n = 77, 60 and 37) than type 2 (n = 45, 30 and 20) [month 6: 30% vs 2%; month 10: 32% vs 7%; month 14: 41% vs 5%). There were also significant ($p \leq 0.0022$) mean improvements from baseline in the 6MWT distance (baseline values of 321.76, 353.03 and 371.43 m; n = 124, 92 and 57) of 22.1 m at month 6 (n = 47), 31.1 m at month 10 (n = 37) and 46.0 m at month 14 (n = 25) [29]. Likewise, a retrospective study (nusinersen therapy commenced at > 18 years of age for ≥ 6 months) reported significant ($p \leq 0.012$) median improvements from baseline at months 6, 10 and 14 in the total HFMSE score and at months 10 and 14 in the RULM score in patients with 5q SMA type 3 (n = 103), but not in those with 5q SMA type 2 (n = 13) [30]. In patients with 5q SMA type 3 who were able to take at least a few steps independently or with aids (e.g. a cane), but without the assistance of others, there were significant ($p \leq 0.016$) median improvements from baseline in the 6MWT distance (baseline value of 322 m) of 11 m at month 6 (n = 48), 25 m at month 10 (n = 35) and 20 m at month 14 (n = 24) [30]. Bulbar dysfunction did not appear to deteriorate during nusinersen treatment in a prospective German study in 22 adults with 5q SMA type 2 or 3 who had evidence of bulbar dysfunction prior to commencing therapy [3]. Bulbar function was assessed using the Sydney Swallow Questionnaire (SSQ) and the bulbar subscore of the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) before initiating nusinersen, and after 6 and 14 months of treatment [3].

Patient satisfaction with nusinersen was assessed using the Treatment Satisfaction Questionnaire for Medication Version 1.4 in 91 patients (aged 10–65 years with a genetic diagnosis of 5q SMA; 96% of patients had 5q SMA type 2 or 3) participating in a multicentre observational study [34]. Following a median treatment duration of 10 months, most patients were at least 'somewhat satisfied' with nusinersen (≈ 91%), its ability to prevent or treat the disease (> 90%) and the way it relieves symptoms (≈ 80%). However, over half (≈ 55%; estimated from a figure) confirmed nusinersen was difficult to use, which likely reflects the need for multiple lumbar punctures [34].

2.2.3 Mixed Population

A randomized, double-blind, sham-controlled, phase II study (CS7; EMBRACE) [35] evaluated nusinersen in patients with infantile- or later-onset 5q SMA who did not meet the eligibility criteria for ENDEAR or CHERISH. EMBRACE

enrolled patients with a genetic diagnosis of 5q SMA and one of the following: three copies of *SMN2* who were aged ≤ 6 months at symptom onset; two copies of *SMN2* who were aged ≤ 6 months at symptom onset and > 7 months at screening; or two or three copies of *SMN2* who were aged > 6 months at symptom onset and ≤ 18 months at screening. Randomization to treatment arms [nusinersen (12 mg dose equivalent, administered intrathecally on days 1, 15, 29, 64, 183 and 302) or a sham procedure] was stratified by age at symptom onset (≤ 6 or > 6 months). The 14-month double-blind period of EMBRACE (hereafter referred to as part 1) was halted (data cut-off date of 30 March 2017) following the early termination of ENDEAR, with eligible EMBRACE participants (those who had completed the final part 1 evaluation among other criteria) transferred to a 28-month open-label extension (part 2; consisting of a 24-month treatment period and an ≈ 4-month follow-up period). In part 2, patients originally treated with nusinersen in part 1 continued to receive nusinersen every 4 months while those originally treated with sham control in part 1 commenced nusinersen therapy, receiving doses on days 1, 15, 29, 64, and then every 4 months thereafter. Overall, a median of 10 (range 8–12) nusinersen doses were administered. Part 2 of EMBRACE was terminated early to permit participants to transition to the SHINE study [35].

Findings from EMBRACE are consistent with those from ENDEAR and CHERISH, and support the use of nusinersen among a broad population of infants and children with 5q SMA (i.e. not just those fulfilling ENDEAR and CHERISH enrolment criteria) [35]. Despite the small sample size [$n = 14$ (nusinersen) and 7 (sham control)] and the shortened duration of part 1, 79% of nusinersen recipients and 29% of sham control recipients were motor milestone responders at the time of the part 1 final assessment. At the time of the final assessment in part 2, 93% of 14 patients originally randomized to nusinersen and 83% of 6 patients originally randomized to sham control were responders. Outcomes were independent of age at the onset of SMA [35].

These findings are generally supported by data from 12 ± 2 months of nusinersen therapy in a multicentre retrospective study ($n = 123$; 34 and 89 patients had 5q SMA type 1 or 2), which reported significant ($p < 0.001$) improvements from baseline in motor function (HINE-2 scores in patients aged < 2 years and Motor Function Measure scores in patients aged > 2 years), but not in the number of patients requiring ventilatory or nutritional support [36].

3 Safety and Tolerability of Nusinersen

Nusinersen demonstrated a favourable safety profile in clinical studies in presymptomatic [8] and symptomatic [24, 35, 37, 38] patients with 5q SMA, and in real-world studies in symptomatic patients with later-onset 5q SMA [29, 30]. Most adverse events (AEs) associated with nusinersen administration via lumbar puncture (e.g. back pain, headache, vomiting) occur within 72 h of the procedure [23]. Serious lumbar puncture complications (e.g. serious infection) have been reported in the post-marketing setting [23, 39].

Results from an integrated analysis [37] of the CS1, CS2, CS3A, CS10, CS12, ENDEAR and CHERISH studies in symptomatic patients with infantile- ($n = 141$) or later-onset ($n = 182$) 5q SMA found that most AEs and serious AEs (SAEs) were consistent with the nature and frequency of events commonly seen with the disease itself or the lumbar puncture procedure. At least one AE occurred in 96% of 240 nusinersen recipients (total nusinersen exposure of 375.9 patient–years) and 99% of 83 sham control recipients, with the most common (occurring with a higher incidence in the nusinersen group) being pyrexia (48% vs 47%), upper respiratory tract infection (URTI; 38% vs 34%), nasopharyngitis (25% vs 23%), vomiting (24% vs 16%), headache (22% vs 4%) and constipation (20% vs 17%) [37].

One AE (procedural nausea) in a nusinersen recipient was considered by the study investigators to be treatment related [37]. Possibly treatment-related AEs were reported in 17% of nusinersen recipients (vs 12% of sham control recipients), with headache ($n = 9$), pyrexia ($n = 8$), back pain ($n = 7$), post-lumbar puncture syndrome ($n = 4$), vomiting ($n = 3$) and tachycardia ($n = 2$) occurring in more than one patient. SAEs were reported in 41% of nusinersen recipients and 61% of sham control recipients [37].

Several toxicities associated with ASOs, including increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, proteinuria and thrombocytopenia, have been seen in clinical studies [37]. They appear to result from the chemical structure of the ASO and the individual nucleic acid sequence, are related to the dose (i.e. systemic exposure) and are usually self-limiting following treatment cessation. In the integrated analysis, there was no systemic evidence of such toxicities. In nusinersen recipients, there were no cases of severe, sustained thrombocytopenia, no reports of glomerulonephritis, nephrotic syndrome or renal failure, and median alkaline phosphatase, ALT, AST, and direct and indirect bilirubin levels were stable over time [37]. According to a recent retrospective analysis of laboratory parameter data from 50 adults with 5q SMA type 2 or 3 receiving nusinersen, there was no evidence of clinically relevant thrombocytopenia, coagulopathies, or renal or hepatic toxicities [40].

The nature and frequency of AEs with nusinersen in presymptomatic patients in NURTURE was consistent with those reported in the integrated analysis [8].

Preliminary data from SHINE suggest that the safety findings of nusinersen over the longer term are consistent with

previously reported results [24, 38, 41]. Among patients with infantile-onset 5q SMA participating in SHINE [data cut-off date of 27 August 2019; median time on study of 3.7 years for patients aged ≤ 7 months at screening ($n = 100$) and 3.0 years for patients aged > 7 months at screening ($n = 37$)], SAEs occurred in 91% of patients in the ≤ 7-months' screening group and 84% of those in the > 7-months' screening group [41]. Most SAEs were related to the disease; none were considered to be related to nusinersen therapy [41]. Among patients with later-term onset 5q SMA who started nusinersen therapy in the CS1, CS2, EMBRACE, CHERISH and/or SHINE studies (data cut-off date of 27 August 2019; median time of observation of 4.0 years), the incidence of AEs typically associated with the lumbar puncture procedure appeared to decrease/stabilize over time [38]. Post-lumbar puncture syndrome was reported in 13% of 190 patients in year 1 and in 6–23% of 35–182 patients in years 2–7. Most events were mild to moderate in severity, with serious post-lumbar puncture syndrome seen in 2% of patients in year 1 and in 3% in each subsequent year. In general, the incidence of headache (26% in year 1 and 10–17% in years 2–7) and vomiting (20% in year 1 and 7–14% in years 2–7) decreased over time; most cases were mild in severity. No cases of meningitis or hydrocephalus were reported [38].

3.1 Immunogenicity

As with all oligonucleotides, there is a potential for immunogenicity with nusinersen [39]. In 346 patients with baseline and post-baseline anti-drug antibody (ADA) assessments, 15 (4%) patients developed ADAs [23]. In four patients the ADAs were transient and in five they were persistent; the ADA response in six patients had not been classified by the data cut-off date. Although the immunogenicity impact on safety has not been formally analysed (as the number of patients with ADAs is low), no AEs of interest were identified among treatment-emergent ADA-positive cases [23].

4 Dosage and Administration of Nusinersen

Nusinersen is approved for the treatment of 5q SMA in numerous countries worldwide, including those of the EU [23], as well as the USA [39]. The recommended dose is 12 mg, administered intrathecally [23, 39]. Therapy should be initiated with four loading doses (with the first three administered at 14-day intervals and the fourth administered 30 days [39] or 35 days [23] after the third), with maintenance doses administered once every 4 months thereafter. A clinically meaningful benefit may not be experienced by patients with profound hypotonia and respiratory failure at birth (where nusinersen has not been studied) due to severe SMN protein deficiency, and the need for continued therapy should be regularly reviewed based on the patient's clinical presentation and therapeutic response [23].

Local prescribing information should be consulted for detailed information regarding administration procedures, missed or delayed doses, contraindications, use in special patient populations, and warnings and precautions.

5 Place of Nusinersen in the Management of 5q SMA

While symptomatic and supportive care continue to be important components of the ongoing management of patients with 5q SMA, the approval of disease modifying agents has significantly changed the treatment landscape. Nusinersen was the first to be approved for the treatment of 5q SMA [7, 23, 39], followed by onasemnogene abeparvovec (an adeno-associated viral vector-based gene therapy that delivers a functional copy of *SMN1* to the motor neuron cells of patients with 5q SMA) [42–44] and the small molecule risdiplam (which is available as a once-daily oral solution) [45–47]. Like nusinersen (Table 1), risdiplam [45, 46] acts by modifying *SMN2* pre-mRNA splicing, resulting in an increase in the production of full-length SMN protein, although nusinersen binds to one site (in intron 7) while risdiplam binds to two sites (one in intron 7 and one in exon 7) on *SMN2* pre-mRNA [48]. Both intrathecal nusinersen [23, 39] and oral risdiplam [45, 46] require repeated administrations (with nusinersen maintenance doses administered once every 4 months and risdiplam once daily), while onasemnogene abeparvovec requires only a single intravenous infusion [42, 43].

In presymptomatic infants with 5q SMA and two or three copies of *SMN2*, substantial clinical benefits were associated with the early (i.e. immediately after establishing a genetic diagnosis) initiation of nusinersen (Sect. 2.1). At a data cut-off date of 19 February 2020, all NURTURE participants ($n = 25$; median age at last visit of 3.8 years) were alive without permanent ventilation, and most were able to walk independently and swallow. Such milestones are incongruent with the natural history of this patient population and highlight the value of an early diagnosis and treatment [8]. Further data from studies in presymptomatic patients are awaited with interest.

In clinical studies in symptomatic patients with infantile- or later-onset 5q SMA (Sect. 2.2), nusinersen improved motor function relative to sham control, with the likelihood of EFS (i.e. survival without the use of permanent assisted ventilation) and overall survival also improved in the former patient population. Interim longer-term data showed that motor function outcomes were maintained or improved in patients with infantile- and later-onset 5q SMA regardless of their initial treatment regimen, although the greatest benefits

were seen in infantile-onset 5q SMA patients in whom therapy was initiated early. Eligibility criteria for these studies (ENDEAR and CHERISH) were strictly prescribed; however, findings consistent with these were seen in a study in a symptomatic patient population who did not meet ENDEAR and CHERISH eligibility criteria (Sect. 2.2.3), supporting the use of nusinersen in a broad population of infants and children with 5q SMA.

Limitations (e.g. natural disease course of 5q SMA, observational or retrospective design, lack of a comparator, missing data, and/or floor and ceiling effects on evaluating scales) notwithstanding, real-world studies in symptomatic patients with infantile- and later-onset 5q SMA (Sect. 2.2) support the effectiveness of nusinersen on motor function outcomes, including in adults with later-onset 5q SMA. With evidence still emerging on the efficacy of nusinersen in adults with 5q SMA [31–33], caution is advised when counselling these patients and tailoring their expectations in relation to their 5q SMA phenotype (type 2 or 3) and ambulatory level [49]. Further natural history data in this patient population would be of interest [49]. Also of interest is the effect of disease modifying agents on impaired bulbar function. Recent data from a small retrospective analysis suggest that bulbar dysfunction (assessed using the Paediatric Functional Oral Intake Scale) persists in children with 5q SMA type 1 [50], and did not deteriorate in adults with 5q SMA types 2 and 3 (Sect. 2.2.2.2) treated with nusinersen. Further studies, particularly those of a longer duration, evaluating bulbar function would be of value [3].

In patients with 5q SMA, respiratory problems are the major cause of hospitalization, morbidity and mortality [51]. Although the strict eligibility criteria of CHERISH excluded patients with respiratory insufficiency [22], the effects of nusinersen on lung function (Table 1) may improve survival and reduce the need for respiratory support [52]. Further studies assessing the effect of nusinersen on respiratory function would be of interest.

Nusinersen demonstrated a favourable safety profile in clinical studies in presymptomatic and symptomatic patients and in real-world studies in symptomatic patients with later-onset 5q SMA (Sect. 3). Most AEs were consistent with the disease itself or the lumbar puncture procedure, with AEs associated with the administration of nusinersen mostly occurring within 72 h. Preliminary longer-term data suggest that the safety findings of nusinersen in patients with infantile and later-onset 5q SMA are consistent with previously reported results (Sect. 3). In the post-marketing setting, hydrocephalus has been reported in patients receiving nusinersen [23, 39]. According to a recent retrospective analysis of US electronic health record data from patients with 5q SMA ($n = 5354$) and matched non-5q SMA controls prior to the approval of nusinersen, patients with 5q SMA had an approximately fourfold increased risk of hydrocephalus compared with controls, regardless of sex and age [53]. This suggests that hydrocephalus may be part of the natural history of 5q SMA in some patients, although whether there is a causal relationship between 5q SMA and hydrocephalus is not yet known [53]. Further studies are awaited with interest.

5q SMA is associated with a substantial economic burden, and pharmacoeconomic considerations play an important role in determining pricing and reimbursement in a contemporary healthcare system [54]. Pharmacoeconomic analyses using standard willingness-to-pay thresholds indicate that none of the currently available treatments for 5q SMA are cost effective [55–57]. Interpreting such estimates is difficult because of the limited evidence supporting longer-term benefits, the difficulty in clearly distinguishing between the SMA subtypes and the difference in what can be achieved for these various patients without treatment [58]. Economic modelling in a rare disease is often challenging and frequently does not portray the full picture of the unmet medical needs of the community or adequately address how to objectively assign monetary value to quality of life [59]. The UK's National Institute for Health and Care Excellence (NICE) also acknowledged that cost-effectiveness estimates for nusinersen were above the range normally considered cost effective by NICE, initially recommending it for a prescribed 5q SMA patient population as part of a Managed Access Agreement [58]. Following a review of data collected as part of this Managed Access Agreement, NICE has extended the clinical eligibility criteria for nusinersen [60].

In conclusion, nusinersen improved motor function in presymptomatic and symptomatic patients with 5q SMA, has maintained this benefit in those who have received treatment longer term and showed a favourable safety profile in these patient populations. Thus, nusinersen continues to represent an important treatment option among a broad range of 5q SMA patients, with its early initiation associated with clinically meaningful benefits.

Data Selection Nusinersen: 647 records identified	
Duplicates removed	134
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	243
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	203
Cited efficacy/tolerability articles	29
Cited articles not efficacy/tolerability	38

Search Strategy: EMBASE, MEDLINE and PubMed from 2018 to present. Previous Adis Drug Evaluation published in 2018 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were nusinersen, Spinraza, spinal muscular atrophy. Records were limited to those in English language. Searches last updated 19 October 2021

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