Nusinersen: A Novel Antisense Oligonucleotide for the Treatment of Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) encompasses a group of autosomal recessively inherited degenerative neuromuscular disorders. They range in severity from neonatal onset with rapidly progressive weakness and early mortality (SMA-1), to onset in infancy (SMA-2), to adolescent/adult onset with indolent clinical course (SMA-3/-4). SMA patients share mutations in the survival motor neuron (*SMN*) gene; variations in clinical phenotypes are attributable to copy numbers of the closely related *SMN2* gene. In December 2016, the US Food and Drug Administration (FDA) approved nusinersen (Spinraza, Biogen, Cambridge, MA) to treat SMA. Nusinersen, an antisense oligonucleotide, is administered directly into cerebrospinal fluid. It alters *SMN2* pre-RNA splicing so exon 7 is included, increasing expression of functional SMN protein. Although nusinersen was FDA approved for treatment of all forms of SMA, the initial clinical trials were limited to patients up to age 14 years, diagnosed with SMA-1, -2, -3, not on mechanical ventilation support. Two subsequent phase 3 trials were completed for SMA-1 and SMA-2/-3 and demonstrated improved motor milestones and event-free survival, better than expected based on natural history studies. Efficacy assessments for patients receiving nusinersen are based on serial assessments of performance on age-appropriate standardized motor scales. Treatment requires complex financial and logistics because of the very high drug cost, intrathecal administration, and medical fragility of the patients. Treatment implementation also engenders ethical considerations related to cost, insurance coverage, limited clinical data on groups of patients not in clinical trials, and questions of duration of treatment. Nusinersen has been integrated into the treatment of many SMA patients.

ABBREVIATIONS ASOs, antisense oligonucleotides; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CNS, central nervous system; CSF, cerebrospinal fluid; ENDEAR, Efficacy and Safety of Nusinersen in Infants With Spinal Muscular Atrophy; FDA, US Food and Drug Administration; HFMS, Hammersmith Functional Motor Scale; HFMSE, Hammersmith Functional Motor Scale–Expanded; HINE-2, Hammersmith Infant Neurological Exam–Part 2; SMA, spinal muscular atrophy; SMN, survival motor neuron

KEYWORDS antisense oligonucleotide; intrathecal injections; motor neuron disease; nusinersen; review; spinal muscular atrophy; Werdnig-Hoffmann disease

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SMA Clinical Spectrum

Spinal muscular atrophy (SMA) encompasses a group of autosomal recessively inherited progressive, degenerative neuromuscular disorders. They range in severity from prenatal/neonatal onset (SMA-0), to onset before 6 months of age with rapidly progressive weakness and early mortality (SMA-1), to onset in mid-infancy (SMA-2), and to adolescent or adult onset with indolent clinical course (SMA-3/-4). SMA patients share mutations in the survival motor neuron (*SMN*) gene, and variations in clinical phenotypes are attributed to copy numbers of the closely related *SMN2* gene (more copies result in less severe disease).¹ There is only a single nucleotide that is different in the coding of *SMN1* and *SMN2*. Although the amount of protein produced by *SMN2* is less than that produced by *SMN1*, that lower amount is enough that the severity of SMA is modulated by the

number of copies of *SMN2*.² The pathologic hallmark of SMA is degeneration of large motor neurons (“anterior horn cells”) in the spinal cord and brainstem, and the primary resulting deficits are progressive loss of motor function. SMA-1 typically results in respiratory failure in infancy, and it is the leading genetic cause of death in infants.¹ SMA-1 was previously referred to as Werdnig-Hoffmann disease. There are up to 5% of SMA cases attributable to other rare genetic mutations and these will not be discussed in this review.³

There are multiple subtypes of SMA and within the subtypes there is variability in disease progression, severity, and patient prognosis.^{1,3} SMA-1 has the earliest onset, and most stereotyped clinical course. Patients with SMA-1 may appear normal at birth but become symptomatic within the first 6 months of life. They manifest severe hypotonia, lack age-appropriate head control, lose strength and movement in all but very

Table 1. Clinical SMA Types⁴

SMA Type	Clinical Manifestations	SMN2 Copy Number
0	Reduced prenatal movement, symptoms at birth, death early	Typically 1
1	Symptoms by 6 months of age; lack of sitting; respiratory, feeding, orthopedic complications	Most commonly 2, sometimes 1 or 3
2	Symptoms between 6–18 months, able to sit but not walk, respiratory, feeding and orthopedic complications	Most commonly 3, sometimes 2 or 4
3	Symptoms after 18 months, able to sit, stand, and walk. May have respiratory, feeding, and orthopedic complications	Most commonly 3–4, but variable
4	Symptoms onset in adulthood, typically mild	Typically 4

SMA, spinal muscular atrophy; SMN, survival motor neuron

distal parts of their limbs including fingers and toes, and develop marked diaphragmatic weakness. These infants are unable to sit or roll, they have progressive difficulty in oral feeding, and develop progressive respiratory failure. They generally die by age 2 years, unless they are supported with continuous mechanical ventilation. SMA-2 is less severe and initial symptoms begin between the ages of 6 and 18 months. Children with SMA-2 are able to sit, but typically never walk independently. SMA-2 manifestations include progressive weakness of the shoulder and hip girdle and inability to move arms and legs against resistance. In early childhood, although cognitive maturation is typically normal, self-care including dressing and bathing is limited by weakness.¹³ Most individuals with SMA-2 develop hypoventilation, which is most pronounced during sleep and requires assisted ventilation. Often, they are treated with non-invasive ventilation such as bilevel positive airway pressure. SMA-3 becomes symptomatic after 18 months of age. Typical initial features include delayed age for initiation of walking, sometimes followed by slow progress in learning to run, climbing stairs independently, or increasingly frequent falls. Most individuals with SMA-3 achieve the ability to walk during the course of their life, but may not retain that ability. The need for assisted ventilation is more variable in SMA-3. Individuals with SMA-4 become symptomatic in adulthood; manifestations include slowly progressive decline in strength and rarely, scoliosis. Individuals with SMA-3 and -4 may have normal lifespans and rarely require mechanical ventilation support during adolescence or early adulthood. Table 1 summarizes typical clinical features and SMN2 copy numbers of the major SMA types.⁴

Optimal treatment of individuals requires a multidisciplinary clinical team. The most common areas to address include respiratory, gastrointestinal/nutritional, and orthopedic.¹

Respiratory Management. SMA-1 causes respiratory insufficiency and failure. Initially, non-invasive ventilation may suffice, but typically with progressive respiratory failure, infants require tracheostomy and continuous mechanical ventilation. SMA-2 is associated with sleep-related hypoventilation, commonly during early

childhood; initial treatment is with non-invasive ventilation during sleep. Severity of pulmonary manifestations varies but some affected children require intensive airway clearance and ventilation support. Children with SMA-1 and -2, in particular, are at heightened risk of respiratory infections and often have marked declines in function in association with relatively mild pulmonary infections. All routine immunizations are recommended for all individuals with SMA.

Nutrition. Children with SMA should be routinely evaluated for aspiration, constipation, feeding, and swallowing. These complications are universally experienced by those with SMA-1, increasingly seen with SMA-2 as they near late childhood or adolescence, and are uncommonly part of the course of SMA-3. Caloric intake, nutrition supplementation, and required food consistency should be regularly evaluated. If poor oral intake or aspiration is identified in a patient, management with a nasogastric tube or percutaneous gastric tube is recommended.

Orthopedic Management. Orthopedic surgeons participate in the care of individuals with SMA because contractures and scoliosis are significant comorbidities. Spinal fusion or the placement of spinal growing rods often is recommended for individuals affected by SMA-2 when severe scoliosis results in restrictive lung function. Typically, those with SMA-1 are at lower risk for severe scoliosis because they are unable to sit upright. Durable medical equipment to assist with patient mobility, including power wheelchairs and patient lifts, physical therapy, and spinal surgery to treat scoliosis all may be required. The presence of scoliosis may complicate the administration of nusinersen (Spinraza, Biogen, Cambridge, MA).

Other Modalities. Patient counselling and pharmacotherapy may be required to help the patients and/or families with the management of depression and anxiety associated with SMA, its comorbidities, and its treatments throughout the individual's lifespan.⁵

Nusinersen Background

SMA is caused by mutations in the *SMN1* gene but humans have an extra *SMN* gene called *SMN2*.

There is only a single nucleotide that is different in the coding of *SMN1* and *SMN2*. Although the amount of protein produced by *SMN2* is less than that produced by *SMN1*, that lower amount is enough that the severity of SMA is modulated by the number of copies of *SMN2*.^{2,6} Thus *SMN2* was chosen as a target at which to aim therapeutic treatments, specifically antisense oligonucleotides (ASOs), to increase the amount of SMN protein produced.^{2,6}

In seminal studies, in rodent SMA models, Passini et al⁶ demonstrated that increased *SMN2* expression could augment production of functional SMN protein and thereby overcome the genetic defect in SMA. Additional work focused on using ASOs as the means to increase *SMN2* production.^{2,6} These studies, complemented by robust research in other laboratories, laid the foundation for the development of nusinersen.⁷

Results of the clinical trials, summarized in the section Clinical Trials of Nusinersen, provided the evidence that led the US Food and Drug Administration (FDA) to approve nusinersen as the first agent to modify the disease course of SMA, which results from mutations of *SMN1* in chromosome 5q.^{8,9} In December 2016, the FDA approved nusinersen for use in all types of SMA.^{8,10} Nusinersen is an *SMN2*-directed ASO.^{8,10} Antisense oligonucleotides for SMA work by blocking splicing once they are bound to pre-mRNA.¹¹ This allows exon 7, the single exon by which *SMN1* and *SMN2* differ, to be preferentially included and therefore produce more full-length SMN protein.^{9–11}

Pharmacokinetic and Pharmacodynamic — of Nusinersen

Nusinersen is administered into the cerebrospinal fluid (CSF) because ASOs do not penetrate the blood brain barrier and all studies to date have relied on intrathecal drug delivery.¹¹ The pharmacokinetics of nusinersen is best described as a 4-compartment model.¹² The central nervous system (CNS) tissue is the primary site of action for nusinersen.^{10,12} The CNS tissues and CSF are distinct pharmacokinetic compartments when considering the pharmacokinetics of nusinersen. However, at steady-state, the CSF concentration should be proportional to the CNS tissue concentration of the medication.¹² Once nusinersen is in the CNS, it is estimated that there is a redistribution into the CSF before the medication is cleared into the systemic circulation.¹² Although the clinical trials used dosing based on age-to-CSF volume relationships, post hoc CSF half-life values from the pharmacokinetic analysis showed that the CSF half-life of nusinersen was not age or body-weight dependent.^{10,12} Therefore, although the trials used age-based dosing, a fixed dose for all ages and weights was recommended for commercial use because there was no dose-limiting toxicity documented for any trial participants.¹² Dosing for nusinersen was based solely on the pharmacokinetics of the CSF owing to the need

to distribute nusinersen throughout the CNS to all tissues containing the targeted SMN neurons.¹²

Trough plasma concentrations of nusinersen following intrathecal administration remain relatively low when compared with trough concentrations in the CSF.⁸ The pharmacokinetics of nusinersen in the plasma is biphasic.¹² The plasma serves solely as the primary site for CSF clearance of nusinersen. There are no biologically active sites for nusinersen within the tissues or plasma. The kinetic model of nusinersen in the plasma mirrored any medication with a 2-compartment model following systemic administration.¹²

Metabolism and elimination of nusinersen is via exonuclease hydrolysis and urinary excretion.^{8,10} To date, nusinersen has no known interaction with the cytochrome P450 enzymes, indicating limited drug interactions.¹⁰ The manufacturer estimates that the terminal elimination half-life for nusinersen is 135 to 177 days in the CSF and approximately 63 to 87 days in the plasma.⁸ The prolonged half-life of nusinersen is estimated to be due to the distribution of the medication from the CSF to the CNS tissues and a slow elimination phase of clearance back to the CSF and then systemic circulation.¹²

Clinical Trials of Nusinersen

SMA-1. All trials of nusinersen were conducted in children who received the medication via lumbar punctures. Table 2 summarizes the clinical trials of nusinersen by phase, SMA type, dose, and efficacy measurements. The information about the efficacy motor scoring tests is provided in a subsequent section.

Two phase 2/3 trials to evaluate nusinersen efficacy in SMA-1 patients have been published as of April 2018 (PubMed search; April 10, 2018). As of this date, 11 trials have been listed in Clinicaltrials.gov, one of which is the extended access program. The first trial was an open-label, dose-escalation study for 20 type-1 patients. Infants included were between 3 weeks and 7 months of age at start of trial and most had 2 copies of *SMN2*.¹³ Four of the 20 participants were given loading doses of 6 mg each, on days 1, 15, and 85, followed by 12-mg maintenance doses on day 253 and every 4 months after this. The next 16 participants received 12-mg loading and maintenance doses on the same schedule as the smaller-dose group.¹³ This, and all other clinical trials for nusinersen, was sponsored by Ionis Pharmaceuticals/Biogen (Cambridge, MA). The outcome measures used included the Hammersmith Infant Neurological Exam—Part 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). The study was conducted at 4 US sites with enrollment occurring between May 2013 and July 2014. This trial demonstrated safety and tolerability as well as divergence from the Kaplan-Meier survival curve created from a preceding natural history study.¹⁴ In addition, there were improvements in motor function

Table 2. Published Clinical Trials* of Nusinersen^{13,15–17}

	SMA-1, Phase 2 ¹³	SMA-2/-3, Phase 1 ¹⁶	SMA-1, Phase 3 ENDEAR ¹⁵	SMA-2/-3, Phase 3 CHERisH ¹⁷
Design	Open label, dose escalation	Open label, dose escalation	Randomized, double blind, sham controlled	Randomized, double blind, sham controlled
No. of patients	20	28	121 (80 nusinersen; 41 control)	126 (84 nusinersen; 42 control)
Patients characteristics	3 wk–7 mo	2–14 yr	<7 mo	Symptom onset after 6 mo Treatment onset at 2–12 years of age
Dose	6 mg, 12 mg	1, 3, 6, 9 mg	12-mg equivalent	12 mg
Efficacy measures [†]	HINE-2, CHOP INTEND	HFMSE, Pediatric QoL	HINE-2	HFMSE

CHERisH, Choosing Healthy Eating for Infant Health; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ENDEAR, Efficacy and Safety of Nusinersen in Infants With Spinal Muscular Atrophy; HFMSE, Hammersmith Functional Motor Scale–Expanded; HINE-2, Hammersmith Infant Neurological Exam–Part 2; QoL, quality of life; SMA, spinal muscular atrophy

* All 4 trials were funded by Ionis Pharmaceuticals and/or Biogen (Cambridge, MA).

[†] See Table 5 for additional information about these tests.

scores (CHOP INTEND and HINE-2) and achievement of motor milestones, compared with the known natural course of SMA-1.¹³

A phase 3, double-blind, sham-controlled, efficacy trial (ENDEAR, Efficacy and Safety of Nusinersen in Infants With Spinal Muscular Atrophy), conducted at 31 international sites, enrolled 120 type-1 infants, 7 months or younger, non-ventilator dependent, with 2 copies of *SMN2*.¹⁵ This study was conducted from August 2014 through November 2016. The infants were randomized in a 2:1 treated:control ratio with those treated receiving active medication via lumbar puncture and controls undergoing sham lumbar punctures with a needle poke and bandage placement. They were dosed with the equivalent of a 12-mg dose, adjusted for CSF volume expected on the basis of age. Doses or sham procedures were administered on days 1, 15, 29, and 64, with maintenance doses given on days 183 and 302. The primary efficacy endpoints were achievement of motor milestones and event-free survival. Treated patients were assessed using the HINE-2 and CHOP INTEND during a planned interim analysis and were found to have more motor-milestone response than non-treated patients. Event-free survival, defined as not using invasive ventilation or >16 hours per day of non-invasive ventilation or death, also was higher in the treated group, especially those treated after shorter disease duration.¹⁵ Based on a planned interim analysis results taken with other trial data, the FDA approved nusinersen for treatment of all types of SMA on December 23, 2016.

Later-Onset SMA. Two studies, one phase 1 and one phase 3, have been published, as of April 2018, studying nusinersen in patients with SMA-2/-3. An open-label, escalating-dose, phase 1 study was performed at 4 US centers in 28 patients aged 2 to 14 years with SMA-2/-3, with 3, 4, or 5 copies of *SMN2*. Respiratory insufficiency;

CSF shunts; brain, spinal cord disease, or meningitis; active infections; or hospitalizations within 2 months of screening were exclusion factors. Clinical assessments during the trial included Hammersmith Functional Motor Scale–Expanded (HFMSE) and Pediatric Quality of Life Inventory. Four dose levels (1, 3, 6, and 9 mg) were tested as a one-time injection, and improvements of at least 3 points on the HFMSE were seen in the 9-mg dose group. There were no significant safety issues during the trial.¹⁶

In a phase 3 study (CHERISH), 126 children with symptom onset after 6 months of age (likely to be SMA-2 or -3), between ages 2 and 12 years, were enrolled in a double-blind, placebo-sham-controlled, multinational, multicenter study using 12 mg of nusinersen.¹⁷ There was a statistically significant greater increase in the HFMSE score for patients in the treated group than in the control after 15 months of evaluation.¹⁷

Presymptomatic SMA. A study of presymptomatic infants enrolled 17 infants (NURTURE) who were identified through newborn screen pilot programs, prenatally diagnosed because of siblings with SMA, or tested because of known carrier status of parents. At the time of treatment onset none demonstrated clinical abnormalities. All patients treated survived and are reported to have had improvements in development.¹⁸ This study is currently unpublished.¹⁹

Standardized, age-appropriate motor efficacy measurements were used in all of the nusinersen clinical trials. Nusinersen-treated patients demonstrated improvements or stabilization in motor scales. Therefore, the same efficacy measurements are being used for assessment when clinic patients are receiving nusinersen. The recent publication of natural history data of SMA-1 infants versus healthy control infants is essential to document the different clinical courses of patients with different *SMN2* copy numbers and also to

demonstrate how unaffected infants progress in time.¹⁴ Additional efficacy measures include survival, lack of use of invasive or extended non-invasive ventilation. Other measurements that are more difficult to standardize include weight gain and growth, ability to feed by mouth, and general well-being.

Significantly, none of the patients included in the trials were on invasive ventilation or non-invasive ventilation for more than 6 hours in a 24-hour period, which likely excluded older patients. Antisense oligonucleotide treatment in adolescents and adults with SMA has not been evaluated during clinical trials although nusinersen carries an FDA label for all types of SMA.²⁰ Therefore, questions have been raised about efficacy assessments for individuals with characteristics that were not included during the trials.

Dosage and Administration

The recommended dose for nusinersen is 12 mg (5 mL) of colorless solution administered intrathecally regardless of patient size.⁸ Although intrathecal administration is typically achieved via lumbar puncture, in individuals for whom this is not feasible (e.g., because of severe scoliosis), high cervical or intraventricular administration has been suggested as an alternative. Nusinersen is administered intrathecally in order to optimize delivery of the medication to the site of activity.^{11,12} Antisense oligonucleotides do not adequately cross the blood brain barrier. If the medication were to be administered systemically, doses approximately 100-fold higher would be required to achieve therapeutic concentrations in the CNS.

Population simulations investigated if age-adjusted dosing was needed with nusinersen or if fixed dosing of the medication would be feasible.¹² The results indicated that fixed dosing resulted in greater exposure for smaller patients. In contrast, the age-based dosing algorithm resulted in equivalent medication exposure across all age groups when evaluated for $C_{p_{max}}$ and area under the curve. Despite the discrepancies in exposure noted with the fixed-dose regimen, there are no dose-limiting toxicities associated with the medication. The simplified fixed-dose regimen was adopted.

Initiation of treatment requires a loading dose period.⁸ Four total loading doses are required to completely load the patient. The first 3 loading doses are administered over intervals of 14 days. The final loading dose should be administered 30 days following the third dose. This dosing schedule is based on manufacturer recommendations, but no other schedules were tested or have been published. Maintenance therapy can begin once the loading doses have been completed. In maintenance, patients receive a dose of nusinersen every 4 months. Table 3 summarizes the dosing schedule and routine monitoring for nusinersen. If therapy is interrupted or a dose is missed, the missed dose should be administered as soon as possible and

then dosing continued as prescribed.⁸ The infrequent dosing interval of the medication is supported by the long terminal half-life of the medication.¹²

Each vial of nusinersen is intended for a single administration.⁸ Nusinersen vials should be stored in their cartons and in the refrigerator until the time of use. The medication should be protected from light until the time of use. Before administration, nusinersen should be warmed to room temperature. External heating sources cannot be used to warm the product.⁸

Clinicians are advised to consider a number of benefits and risks associated with the administration of nusinersen.⁸ Sedation may be indicated for the successful administration of the intrathecal medication, but the patients' clinical status should be carefully considered. Each patient should have 5 mL of CSF removed before medication administration.

Adverse Effects

The most common adverse events associated with nusinersen were lower respiratory tract infection, upper respiratory tract infection, and constipation.^{8,10} Patients treated with nusinersen were also found to have a higher incidence of paradoxical breathing, pneumonia, respiratory symptoms, and increased requirements for respiratory support than patients who underwent sham procedures in clinical studies.¹⁰ Table 4 summarizes adverse effects as cited in the phase 3, SMA-1 study.¹⁵ These adverse effects were not attributed to nusinersen. These are all common in infants and children diagnosed with SMA, and therefore it is challenging to determine and differentiate when adverse effects are related to the disease or to the intervention.

In open-label studies of patients aged 2 to 15 years, the reported side effects could be considered common for patients undergoing a lumbar puncture.¹⁰ These side effects included headache, back pain, and post lumbar puncture syndrome.

Antisense oligonucleotides have been associated with coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia.^{8,11} Patients may be at an increased risk of bleeding complications associated with nusinersen therapy. The manufacturer recommends that all patients have platelet counts and routine coagulation assays checked before each dose of nusinersen and as needed based on clinical status.⁸ In clinical trials, no participant developed a platelet count of fewer than 50,000 cells/mL or developed a sustained low platelet count with continued medication exposure.¹⁰ However, among patients with normal platelet levels at baseline, 11% of nusinersen recipients developed a platelet level below the lower limit of normal during the course of treatment.⁸

Antisense oligonucleotides have also been associated with renal toxicities, including fatal glomerulonephritis.⁸ The manufacturer recommends quantitative urine protein checks at baseline and before each dose

Table 3. Overview of Protocol for Nusinersen Administration*						
Eligibility Determination	Additional Clinical Decisions	Orders, Notification	Dose Schedule	Evaluation Before Each Dose	Testing Before Each Dose	Roles of Pharmacy Team Members
Genetic testing to confirm <i>SMN1</i> mutations and ≥1 <i>SMN2</i> copy	Routine LP vs. interventional radiology for severe scoliosis/difficult positioning	Coordinated scheduling of physical therapy, clinic visits, pulmonary function testing	Loading: every 14 days x 3	Pulmonary function tests, with results reviewed by pulmonologist	Complete blood count including platelets. Coagulation assays	Verify drug order, procedure timing, and oversee transport of nusinersen vial to procedure suite
Multidisciplinary medical evaluation	Topical lidocaine or need for sedation or anesthesia	Coordinate availability of procedure suite	Last loading: 30 days after third dose	Neurology evaluation, re-consent	Urine protein	Two pharmacy staff members double-check nusinersen vial and prepare solution for LP administration
Explanation of protocol, timing, required visits	Identify need for specialized personnel to monitor patient during and after LP		Maintenance doses: every 4 mo	Physical therapy assessment and standardized efficacy measures before first dose and selected subsequent doses	Physician verifies normal results before LP	
Obtain consent						
Initiate insurance prior authorization						

LP, lumbar puncture; SMN, survival motor neuron

* Based on Clinical Practice Guideline at CS Mott Hospital, Michigan Medicine, Ann Arbor, MI.

with recommendations to consider repeated testing and further evaluation for patients in whom the urinary protein concentration is greater than 0.2 g/L.⁸ In clinical trials, of 51 patients treated with nusinersen, 33% developed an elevated urine protein level.¹⁰ This is compared with 25 patients receiving placebo therapy, of whom 20% developed elevated urine protein. Renal toxicity from nusinersen was not associated with any increases in serum creatinine or cystatin C.

The immunologic response to nusinersen has been evaluated.¹⁰ In 126 patients, baseline and post exposure antidrug antibody assessments were made. Five patients (4%) developed antidrug antibodies; in 3, antibodies were transient, and in 2 cases, these antibodies persisted. Currently, there is insufficient data to evaluate the impact of antidrug antibodies on the pharmacokinetics, efficacy, or tolerability of nusinersen.

One open-label study of infants with symptomatic SMA reported severe hyponatremia in a patient receiving nusinersen therapy.¹⁰ The patient required salt supplementation for 14 months to correct the electrolyte abnormality.

Efficacy Assessments

Age-appropriate standardized motor efficacy assessments have been included in clinical trials that evaluated response to nusinersen in SMA patients. Three assessments were used most frequently: HINE-2 and CHOP INTEND mostly for SMA-1, and the HFMSE for SMA-2 and -3 (Table 5). The HINE was developed to assess normal neurological development in typically developing infants and an additional standardized tool was added for the HINE-2.²¹ Changes in abilities including head control, sitting, voluntary grasp, rolling, kick, crawling, standing, and walking are measured.²¹ A natural history study that used the HINE showed that infants with SMA-1 do not improve their motor development over time.²² The HINE-2 measures 8 motor milestones and awards points from 0 to 4 in a graded fashion ranging from no effort, to initial attempts, to complete mastery of a skill, with a maximum score of 26, with higher scores indicating better motor abilities.²² The phase 2, open-label study for SMA-1 reported the number of infants who demonstrated an improvement of 2 or more levels on at least 1 of the 8 milestones on the HINE-2, for example, from no grasp to grasping using index finger and thumb or from grasp using whole hand to a pincer grasp or from no kicking to kicking upward (vertically).¹³ The

Table 4. Nusinersen Adverse Reactions, SMA-1, Phase 3 Trial¹⁵

Adverse Reaction*	Nusinersen (N = 80)	Sham/Control (N = 41)
Any adverse event	77 (96)	40 (98)
Pyrexia	45 (56)	24 (59)
Constipation	28 (35)	9 (22)
Upper respiratory tract infection	24 (30)	9 (22)
Pneumonia	23 (29)	7 (17)
Respiratory distress	21 (26)	12 (29)
Respiratory failure	20 (25)	16 (39)
Atelectasis	18 (22)	12 (29)
Vomiting	14 (18)	8 (20)
Acute respiratory failure	11 (14)	10 (24)
Gastro reflux disease	10 (12)	8 (20)
Decreased O ₂ saturation	10 (12)	10 (24)
Cough	9 (11)	8 (20)
Dysphagia	9 (11)	9 (22)

SMA, spinal muscular atrophy

* All data presented as n (%)

phase 3 SMA-1 study reported 28% of treated infants exhibited a HINE-2 increase of 5 points or more.¹⁵ There are no well-defined standards on which to base what is a clinically significant change on the HINE-2 score in SMA-1. It is known that in typically developing children, as age and developmental milestones are reached, the score on the HINE-2 increases. However, in SMA-1, functional deterioration is invariable, and treatment interventions that halt declines in performance could be considered clinically meaningful.

Another prospective, longitudinal natural history study of infants, beginning when they were younger than 7 months of age, diagnosed with SMA-1, as well as healthy, typically developing age-matched infants used the CHOP INTEND for assessments.²³ The CHOP INTEND was designed specifically to assess motor skills that are clinically significant and relevant for the SMA-1 population.^{24,25} The range of difficulty of test items is broader and augments ability to distinguish performance levels. The CHOP INTEND assesses spontaneous movements of the upper and lower extremities, hand grip, movement of head and head control, hip adductors, rolling movements initiated by legs and by arms, shoulder and elbow movements, knee extension, hip flexion, foot dorsiflexion, elbow flexion, neck flexion, head and neck extension, and Galant reflex.²⁴ The test is scored for both the left and right sides with graded responses, giving 0 to 4 points for each item and each side with a maximum score of 64 points, with a higher score indicating better motor abilities.²⁴ In the phase 3

trial for SMA-1, 73% of treated infants had an increase of at least 1 point from baseline CHOP INTEND score, compared with only 3% of control infants, a statistically significant difference.¹⁵ Similar to the HINE-2, there are no established standards for what change in score on the CHOP INTEND is clinically significant in an individual with SMA-1.

The Hammersmith Functional Motor Scale (HFMS) and the Expanded test (HFMSE) were developed to assess SMA patients who are stronger and able to perform more motor activities.²⁶ The HFMSE includes the HFMS plus 13 additional items.²⁷ The HFMSE was specifically designed for SMA and has been validated and reliability tested on SMA-2 and -3.²⁷ This test evaluates sitting on floor and chair with and without arm/hand support, raising hands/arms to eye level, rolling, getting to lying position, crawling and being in crawling position, standing with and without support, half kneeling, walking, etc.^{26,27} The HFMSE consists of 33 items scored from 0 to 2 for a maximum score of 66 points, with higher score indicating improved motor abilities. Specific instructions are provided for what counts, including pictures as examples.²⁸ The phase 1 SMA-2/-3 trial found a 5.8-point mean increase in the 9-mg dosing cohort after 9 to 14 months in the trial, while a previous trial presumed that a 3-point increase in 6 months would be clinically significant.^{16,29} In the phase 3 SMA-2/-3 trial, 57% of treated children had at least a 3-point increase in the HFMSE, compared with 26% of control participants.¹⁷ SMA-2 and SMA-3 are expected to have a slower decline compared with SMA-1. However, it remains uncertain over what time interval treatment-related stabilization and/or improvement would be expected.

At this point, criteria to determine whether treatment with nusinersen should be stopped (based on worsening of clinical condition and reduction in the efficacy measurement scores) have not been established. Although insurance companies generally require that one of these standardized performance measurements be completed before starting nusinersen and at subsequent intervals, no uniformly accepted stopping criteria have been established.

Formulary Considerations

The first challenge when considering the addition of nusinersen to a hospital formulary is the cost of therapy. During the first year of treatment, the medication is estimated to cost \$750,000. The medication will then cost \$375,000 annually thereafter. A single dose costs \$125,000.³⁰ These amounts do not include the substantial medical costs associated with the administration of the medication. Administration considerations are variable and need to be tailored to the individual patients on the basis of their care needs.³¹

The logistics of administering nusinersen to patients with SMA are complex and should be considered within

Table 5. Established Tests of Motor Performance to Evaluate Children With SMA

Efficacy Measurements	Scoring*	Patient Population	Test Developed for:
Hammersmith Infant Neurological Exam–Part 2 (HINE-2) ²²	0–26	SMA-1	Typically developing infants
Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) ²⁴	0–64	SMA-1	Specifically for SMA-1
Hammersmith Functional Motor Scale–Expanded (HFMSE) ^{27,28}	0–66	SMA-2 and -3	Patients with SMA; typically SMA-2 and -3

SMA, spinal muscular atrophy

* Higher score = better motor skills.

the context of the overall medical system and resources available, and include strategies and plans for keeping the patients as safe as possible. The fragile nature of their pulmonary status requires that pulmonary function be optimized before beginning treatment. A visit before the procedure allows for the development of contingency plans for what non-invasive ventilation settings would be preferred if any respiratory complications were to occur. The overarching goal is to avoid intubation of any non-ventilator-dependent SMA patient during the nusinersen administration procedure because it is often medically complex to subsequently extubate those with compromised respiratory function. Therefore, gathering a team of medical providers aware of the possible medical complications who will be participating in administration of the drug is essential. Using the smallest amount of anesthesia or anxiolytic drugs that still allow the lumbar puncture to be done safely and quickly is the goal.

A comprehensive program with established practice guidelines and team members who coordinate the administration of the medication are essential. At our institution (CS Mott Hospital, Michigan Medicine, Ann Arbor, MI), establishment of this program has involved the Pharmacy and Therapeutics Committee, hospital administration, interventional radiology, schedulers, a team to obtain insurance authorization, procedure room staff, scheduling for clinic rooms, neurology and pulmonary/ventilator team clinic appointments, physical therapy, etc. Establishing the protocol and communication among the many involved parties took more than 5 months to implement. A detailed comprehensive Clinical Practice Guideline was developed and approved by hospital leadership; the authors are able to share this protocol, which may be useful for hospitals who are developing a nusinersen administration plan (contact: eneil@med.umich.edu).

Our clinical program has already encountered several situations that diverge from the standard protocol. Some SMA patients cannot receive nusinersen via routine lumbar puncture because of scoliosis or other positioning difficulties, and for these individuals, Interventional Radiology has provided support. Another unusual situation that has arisen has been transitioning children who have participated in clinical trials at sites distant from their homes whose families

request to receive continuing treatment at our site; this change would require insurance coverage for the medication. Information about dosing schedule, efficacy measurements, and other logistical considerations are prerequisites to support such transitions.

Treatment Challenges

Many complex ethical and medical considerations influence decisions to treat individual SMA patients with nusinersen. In addition to the cost of therapy, there are significant limitations in the currently published data outlining the benefits and risks of nusinersen therapy. The currently published data may not be generalizable to all individuals with SMA. The clinical trials also had a very short duration and provide minimal insight on the long-term effects of nusinersen therapy.^{20,31}

Nusinersen therapy is currently the only alternative to supportive therapy management of SMA. Patients and families may be willing to assume the risks of therapy given the available treatment options. Current information about the risks and benefits of treatment should be routinely assessed for each patient and regularly discussed with patients and families. One challenge that may emerge is when the risks of continuing therapy for a particular patient outweigh the possible ongoing benefits. The discussion surrounding the discontinuation of nusinersen therapy can pose a major challenge for clinical care teams, and divergent perspectives among team members may further complicate treatment decisions.^{31,32,33}

With the high cost of nusinersen therapy, reimbursement and insurance company coverage of medication costs is another item that requires careful consideration. Insurers may be willing to support costs for initiation of treatment, but continued reimbursement may be dependent upon demonstrated efficacy. As discussed above, no uniform criteria have been implemented across insurers to determine the duration of coverage for this treatment before ascertainment of quantifiable benefit.³¹ The criteria used in the clinical trials to detect patient improvement may not be readily generalizable to a broader patient population. There is no consensus (among clinicians, insurers, families) regarding standard measures to define therapeutic benefit of nusinersen treatment.

Additional Treatments and Newborn Screening for SMA

Numerous other small molecules, compounds, neuroprotectant agents, and gene therapy are in development or already undergoing evaluation in clinical trials. Positive results from at least some of these trials will undoubtedly add to treatment options for SMA, augment clinical complexity and financial considerations, and influence outcome measurements and decisions regarding the role of nusinersen in SMA treatment.^{33–35} Hoffmann-LaRoche (Basel, Switzerland) has an oral small molecule, RO7034067/RG7916, which is in phase 2/3 studies for both SMA-1 and SMA-2/-3.³³ Gene therapy using intravenous adeno-associated virus serotype 9 to deliver DNA encoding the missing SMN protein to SMA-1 patients has been studied in 15 patients and demonstrated improvements in survival, motor milestones, and motor outcomes.³⁵

Newborn screening for SMA is moving forward with recent recommendation by the Advisory Committee on Heritable Disorders in Newborns and Children for inclusion of SMA on the Recommended Uniform Screening Panel. Earlier diagnosis of SMA will allow for presymptomatic initiation of therapy, and preliminary studies have demonstrated that nusinersen is less effective when treatment is started after longer disease duration.⁹ Yet, additional medications and the possibility of newborn screening and presymptomatic diagnosis for SMA create questions about appropriate timing of treatment initiation particularly for individuals likely to have milder forms of SMA, whether treatment with more than 1 medication is indicated, and insurance coverage for medications in presymptomatic infants who are identified by newborn screening.

Conclusions

The availability of nusinersen has dramatically altered clinical care of infants and children with SMA. Although the results of the clinical trials continue to be published, many questions remain unanswered. Much remains to be learned about identification of the range of patients who will benefit from nusinersen, optimal timing for initiation of treatment, rigorously defining sustained efficacy criteria, combining nusinersen with other SMA therapies that become available, and the impact of treatment on long-term outcomes of children with the most severe forms of SMA.

ARTICLE INFORMATION

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