Infants and Children With SMA Treated With Nusinersen in Clinical Trials: Experience of Risk for Respiratory or Other Events With Repeat Anesthesia/Sedation for Intrathecal Administration

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Conclusions

- AEs occurring in the context of lumbar puncture procedure were mostly observed in nusinersen-treated patients, and less frequently in sham procedure control–treated patients who did not receive a lumbar puncture procedure.
- There does not appear to be an increased risk for respiratory or other events attributable to repeat anesthesia and/or sedation in infants and children with SMA treated with nusinersen.
- There was no apparent increase in lumbar puncture procedure–related AEs compared with the general population of children who undergo lumbar puncture procedures.[2,3]

Introduction

- Nusinersen is an intrathecally administered antisense oligonucleotide treatment for spinal muscular atrophy (SMA) that modulates *survival motor neuron 2* (*SMN2*) pre–messenger RNA (mRNA) splicing to increase full-length *SMN2* mRNA and SMN protein production.[1]
- In infants and children with SMA, general anesthesia and/or sedation are often used during nusinersen administration to reduce anxiety, pain, and distress associated with the lumbar puncture procedure.[2]
- Typical events associated with the lumbar puncture procedure include back pain, headache, and vomiting.[2,3]
- Ten clinical studies were performed to evaluate the efficacy and safety of nusinersen in presymptomatic, infantile-onset, and later-onset SMA.[4] These analyses evaluated data from 8 of these studies.
- Nusinersen has demonstrated significant and clinically meaningful efficacy on the achievement of motor milestones and measures of motor function across a broad spectrum of SMA and on survival endpoints in infantile-onset SMA (vs. sham procedure control), which is not usually achieved by infants with SMA, as well as a favorable benefit-risk profile.[4]

Objective

- To evaluate the safety of repeated anesthesia and/or intravenous sedation for the lumbar puncture procedure across the nusinersen clinical trial program.

Methods

- These analyses evaluated the safety of repeated anesthesia and/or sedation in infants/children with:
  - Presymptomatic SMA (most likely to develop SMA Type I or II): NURTURE (interim data, study ongoing);
  - Infantile-onset SMA (most likely to develop SMA Type I or II): CS3A and ENDEAR (interim data);
  - Later-onset SMA (has or most likely to develop SMA Type II or III): CS1, CS2, CS10, CS12 (interim data), and CHERISH (interim data; Figure 1).
- Within the evaluated clinical trials, concomitant medications were not designated by the investigators as anesthetics or sedatives. Hence, concomitant medications were reviewed to identify and evaluate any anesthesia or sedation administered on the same day as nusinersen.
  - Events were evaluated up to 7 days following the procedure to capture any latent treatment-emergent adverse events (AEs).

Results

- Older children (later-onset SMA) received inhalational anesthesia or intravenous sedation for a lumbar puncture procedure more commonly than younger infants and children (presymptomatic and infantile-onset SMA; Table 1).
- The majority of AEs in children with later-onset SMA who received anesthesia or sedation for a lumbar puncture procedure were consistent with those expected in the context of lumbar puncture procedures (such as back pain, headache, and vomiting)[2,3] and occurred less frequently in sham procedure control–treated patients who did not receive a lumbar puncture procedure (Table 2).
  - The number of lumbar puncture procedures/sham procedure controls and postprocedure events in children with later-onset SMA are shown in Table 3.
- For infants and children treated with nusinersen who received anesthesia or sedation, respiratory AEs were consistent with events expected to occur in the context of SMA disease[1] (Table 2; Table 4). There was no apparent increase in the incidence of respiratory-related or serious AEs.
- The incidence and nature of the most common lumbar puncture procedure–related AEs were similar in children with and without scoliosis (Figure 2).

Table 1. Participants receiving intravenous sedation or anesthesia for lumbar puncture

	Infants/younger children			Older children		
	ENDEAR		NURTURE, CS3A, and ENDEAR	CS1, CS10, CS2, and CS12	CHERISH	
Participants, n (%)	Sham procedure control n=41	Nusinersen n=80	Nusinersen n=117	Nusinersen n=56	Sham procedure control n=42	Nusinersen n=84
Inhalational anesthesia[a]	2 (5)	6 (8)	13 (11)	50 (89)	24 (57)	43 (51)
Intravenous sedation[b]	0	2 (3)	6 (5)	55 (98)	34 (81)	72 (86)

[a]Inhalational anesthetic drugs included isoflurane, nitrous oxide, and sevoflurane
[b]Intravenous sedation drugs included alfentanil, alfentanil hydrochloride, dexmedetomidine, fentanyl, ketamine, ketamine hydrochloride, midazolam, midazolam hydrochloride, morphine, propofol, remifentanil, and thiamylal sodium

Table 2. Treatment-emergent AEs[a] occurring in older children with later-onset SMA (≥5% of nusinersen-treated children and also respiratory AEs) within 7 days following lumbar puncture or sham control procedure where inhalational anesthesia or intravenous sedation was administered

	CHERISH		CS1, CS10, CS2, and CS12[b]
AE, n (%)	Sham procedure control n=42	Nusinersen n=84	Nusinersen n=56
Inhalational anesthesia	n=24 (57)	n=43 (51)	n=50 (89)
Back pain	0	12 (28)	14 (28)
Headache	0	9 (21)	15 (30)
Pyrexia	2 (8)	8 (19)	3 (6)
Vomiting	1 (4)	8 (19)	8 (16)
Tachycardia	1 (4)	4 (9)	0
Upper respiratory tract infection	1 (4)	4 (9)	0
Muscle contractions involuntary	1 (4)	3 (7)	0
Anemia	0	2 (5)	0
Arthropod bite	0	2 (5)	2 (4)
Epistaxis	0	2 (5)	1 (2)
Insomnia	0	2 (5)	0
Nausea	1 (4)	2 (5)	5 (10)
Rhinitis	0	2 (5)	0
Post-lumbar puncture syndrome	0	1 (2)	15 (30)
Other respiratory AEs			
Upper respiratory tract congestion	1 (4)	1 (2)	0
Respiratory tract infection	1 (4)	0	0
Intravenous sedation	n=34 (81)	n=72 (86)	n=55 (98)
Back pain	0	15 (21)	18 (33)
Headache	1 (3)	15 (21)	16 (29)
Vomiting	1 (3)	13 (18)	8 (15)
Pyrexia	4 (12)	12 (17)	3 (5)
Post-lumbar puncture syndrome	0	3 (4)	20 (36)
Nausea	2 (6)	2 (3)	5 (9)
Puncture site pain	0	0	9 (16)
Upper respiratory tract infection	0	5 (7)	1 (2)
Tachycardia	1 (3)	4 (6)	1 (2)
Constipation	0	2 (3)	3 (5)
Joint contracture	2 (6)	1 (1)	3 (5)
Procedural pain	1 (3)	1 (1)	3 (5)
Scoliosis	0	1 (1)	4 (7)
Neck pain	0	0	3 (5)
Oropharyngeal pain	0	0	4 (7)
Other respiratory AEs			
Upper respiratory tract congestion	1 (3)	1 (1)	0
Respiratory tract infection	1 (3)	1 (1)	0

AE = adverse event; SMA = spinal muscular atrophy
[a]Participants could have had >1 AE
[b]There was no field on the medical history case report form specifically for spinal rods. A review of medical history data revealed 2 patients who reported either scoliosis surgery or spinal fusion surgery as medical history before receiving the first dose of nusinersen; 1 additional patient had scoliosis surgery after participation in CS1 (before enrolling in CS2), and 2 patients had spinal surgery while participating in CS12

Table 3. Post-lumbar puncture procedure/sham procedure control events[a] in older children with later-onset SMA

	CHERISH		CS1, CS10, CS2, and CS12
	Sham procedure control n=42	Nusinersen n=84	Nusinersen n=56
No. of procedures	166	328	312
Procedures with ≥1 event, n (%)			
Within 24 h	5 (3)	31 (9)	58 (19)
Within 72 h	5 (3)	47 (14)	84 (27)
Within 120 h	5 (3)	49 (15)	86 (28)
Within 168 h	5 (3)	51 (16)	87 (28)

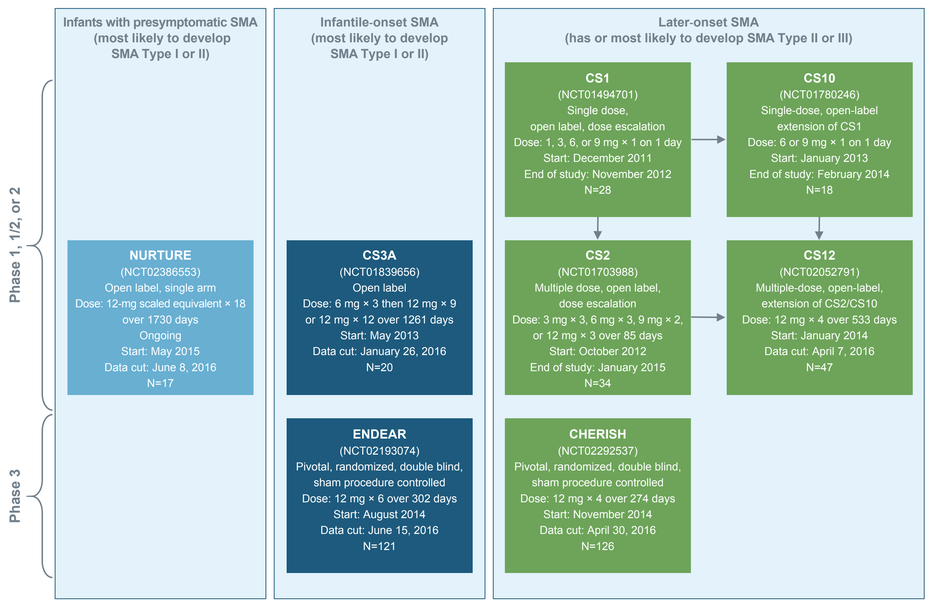
SMA = spinal muscular atrophy
[a]Including back pain, cerebrospinal fluid leakage, headache, nausea, post-lumbar puncture syndrome, procedural pain, procedural nausea, procedural headache, and vomiting (Preferred Terms)

Table 4. Treatment-emergent AEs occurring in infants/younger children with presymptomatic or infantile-onset SMA within 7 days following lumbar puncture or sham control procedure where inhalational anesthesia or intravenous sedation was administered

	ENDEAR		NURTURE, CS3A, and ENDEAR
AE, n (%)	Sham procedure control n=41	Nusinersen n=80	Nusinersen n=117
Inhalational anesthesia	n=2 (5)	n=6 (8)	n=13 (11)
Weight decreased	0	2 (33)	2 (15)
Feeding disorder of infancy/early childhood	0	1 (17)	1 (8)
Gastritis	0	1 (17)	1 (8)
Gastroesophageal reflux disease	0	1 (17)	1 (8)
Impetigo	0	1 (17)	1 (8)
Medical observation	0	1 (17)	1 (8)
Oral candidiasis	0	1 (17)	1 (8)
Pyrexia	0	1 (17)	1 (8)
Respiratory distress	0	1 (17)	2 (15)
Respiratory failure	0	1 (17)	1 (8)
Rhinitis	1 (50)	1 (17)	1 (8)
Rhinorrhea	0	1 (17)	1 (8)
Vomiting	0	1 (17)	1 (8)
Weight gain poor	0	1 (17)	1 (8)
Heart rate increased	0	0	1 (8)
Hypophagia	0	0	1 (8)
Lower respiratory tract infection	1 (50)	0	0
Nasopharyngitis	0	0	1 (8)
Rash	1 (50)	0	0
Intravenous sedation	n=0	n=2 (3)	n=6 (5)
Bradycardia	–	1 (50)	1 (17)
Pyrexia	–	1 (50)	1 (17)
Respiratory distress	–	1 (50)	1 (17)
Restlessness	–	1 (50)	1 (17)
Tachycardia	–	1 (50)	1 (17)
Nasopharyngitis	–	0	1 (17)

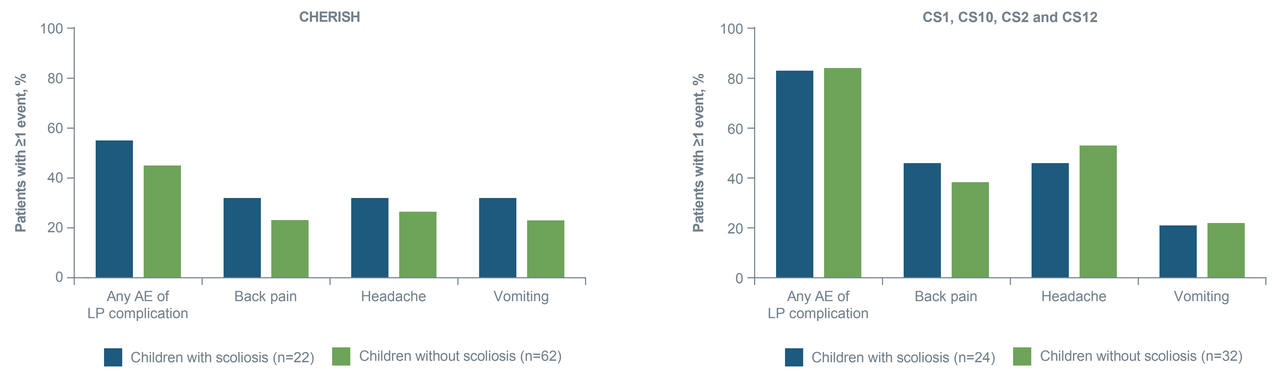
AE = adverse event; SMA = spinal muscular atrophy

Figure 1. Studies used to assess the safety of repeat anesthesia and/or sedation for intrathecal administration of nusinersen



SMA = spinal muscular atrophy

Figure 2. Incidence of lumbar puncture procedure–related AEs in children with and without scoliosis



AE = adverse event; LP = lumbar puncture
Children with scoliosis had a medical history of scoliosis, scoliosis surgery, spinal fusion surgery, or kyphoscoliosis before the first nusinersen dose

References 1. Finkel RS, *et al. Lancet*. 2016;388(10063):3017-3026. 2. Haché M, *et al. J Child Neurol*. 2016;31(7):899-906. 3. Ebinger F, *et al. Pediatrics*. 2004;113(6):1588-1592. 4. Hoy SM. *Drugs*. 2017;77(4):473-479. **Disclosures** RSF: grants and personal fees from Ionis Pharmaceuticals, Inc. during ENDEAR and CHERISH; grants and advisory fees from Biogen; outside the submitted work, grants from Cytokinetics, and advisor to Roche; advisory capacity to nonprofit organizations: Cure SMA, SMA Europe, SMA Reach (UK), and the Spinal Muscular Atrophy Foundation; data safety monitoring board for the AveXis gene transfer study; EM: SMA study advisory boards for AveXis, Biogen, Ionis Pharmaceuticals, Inc., Novartis, and Roche; funding from Famiglie SMA Italy, Italian Telethon, and SMA Europe; CAC: advisory boards for AveXis, Biogen, Ionis Pharmaceuticals, Inc., and Roche; grants from Biogen, Ionis Pharmaceuticals, Inc., and the Spinal Muscular Atrophy Foundation; NK: advisory boards for Biogen; outside the submitted work, advisory boards and consulting fees for AveXis, Catalyst, Cytokinetics, Marathon, PTC, and Sarepta; advisory capacity to Cure SMA and the Myasthenia Gravis Foundation of America; SR: former employee of and holds stock/stock options in Biogen; IB, RF, WF, and SG: employees of and hold stock/stock options in Biogen; SH: employee of and holds stock/stock options in Ionis Pharmaceuticals, Inc.

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