Infants and Children With SMA Treated With Nusinersen in Clinical Trials: An Integrated Safety Analysis

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Conclusions

- Across the nusinersen clinical trial program in presymptomatic, infantile-onset, and later-onset SMA, nusinersen demonstrated a favorable safety profile.
- The majority of AEs and SAEs reported in infants and children exposed to nusinersen were consistent with the nature and frequency of events typically occurring in the context of SMA[1] or lumbar puncture procedure.[4]
- All AEs leading to treatment discontinuation were observed in the infantile-onset SMA studies, and were events with fatal outcomes that were consistent with those typically observed for infantile-onset SMA (usually respiratory in nature).
- Comparing the nusinersen- and sham procedure control–treated groups in the 2 randomized controlled trials, ENDEAR and CHERISH, no abnormal patterns or trends in clinical laboratory parameters were observed with nusinersen.

Introduction

- Nusinersen is an antisense oligonucleotide for the treatment of spinal muscular atrophy (SMA) that modulates the splicing of *survival motor neuron 2* (*SMN2*) pre–messenger RNA (mRNA) to increase full-length *SMN2* mRNA and SMN protein production.[1]
- Nusinersen is administered intrathecally (12-mg equivalent dose) with 3 loading doses at 14-day intervals, a fourth loading dose after 30 days, followed by dosing every 4 months.[2]
- Ten clinical studies (Figure 1) were conducted to evaluate the efficacy and safety of nusinersen in presymptomatic SMA (most likely to develop SMA Type I or II), infantile-onset SMA (most likely to develop SMA Type I or II), and later-onset SMA (has or most likely to develop SMA Type II or III).[3]
- 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.[3]

Objective

- To evaluate the safety of nusinersen across the clinical trial program.

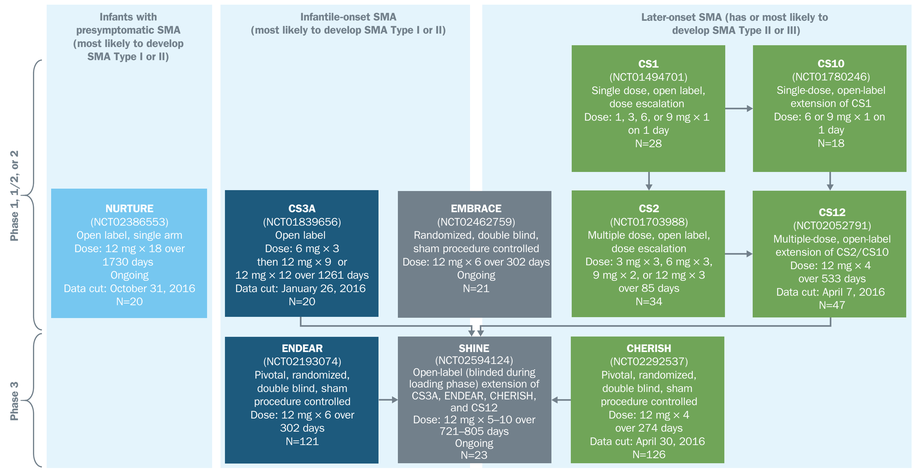
Methods

- In this integrated safety analysis, unblinded data from 8 completed or ongoing studies (NURTURE, CS3A, ENDEAR, CS1, CS2, CS10, CS12, and CHERISH) were evaluated (Figure 1). SHINE and EMBRACE were not included as these trials were blinded and ongoing at the time of the data cut.
- Adverse events (AEs), clinical laboratory assessments, vital signs, and physical and neurological findings were evaluated for possible adverse drug reactions.
  - An AE was defined as any untoward medical occurrence temporally associated with the study or study drug, whether or not it is considered to be related to the treatment.
  - AE and laboratory data were evaluated in detail for toxicities seen with other subcutaneously or intravenously administered antisense oligonucleotide drugs, including thrombocytopenia and hepatic and renal impairment.

Results

- Across the 8 unblinded studies, 260 infants and children were treated with nusinersen for a total of 355 patient-years (Table 1).
- Common AEs were respiratory events, headache, vomiting, and back pain (Table 2). Such events are consistent with those observed in the context of SMA disease[1] and lumbar puncture.[4]
  - Presymptomatic infants had a lower incidence of AEs and serious AEs (SAEs) than those infants who were symptomatic at diagnosis (Table 2).
- In ENDEAR, 13 (16%) patients in the nusinersen group died compared with 16 (39%) of the control group; the main causes of death were respiratory disorders (9% vs. 29%, respectively).
- Across the 8 unblinded studies, no abnormal patterns or trends in clinical laboratory parameters, including renal and liver function, were observed with nusinersen. Changes in hematology, blood chemistry, or urinalysis in the sham procedure–controlled studies (ENDEAR and CHERISH) are shown in Table 3 and Figure 2.
  - There were no cases of sustained or severe thrombocytopenia in patients treated with nusinersen, nor were there any bleeding-related AEs associated with decreased platelet counts reported in the nusinersen-treated population.
  - Proteinuria (%) was similar between nusinersen- and sham procedure control–treated patients when the presence of potentially confounding bacteria, nitrites, or leukocyte esterase were excluded (Table 3).

Figure 1. Clinical trial program and studies used for the integrated safety analyses



SMA = spinal muscular atrophy

Table 1. Exposure to nusinersen[a]

	Presymptomatic SMA	Infantile-onset SMA	Later-onset SMA	All nusinersen-treated patients
Study	NURTURE	ENDEAR and CS3A	CS1, CS2, CS10, CS12, and CHERISH	NURTURE, ENDEAR, CS3A, CS1, CS2, CS10, CS12, and CHERISH
No. of patients dosed with nusinersen	20	100	140	260
Median (range) exposure, d	329 (6–531)	308 (6–994)	453 (31–1536)	397 (6–1536)
Total no. of patient-years	16.5	91.2	247.6	355.3
Median (range) no. of doses received	6 (1–7)	5 (1–9)	4 (1–8)	4 (1–9)

SMA = spinal muscular atrophy
[a]Patients were considered to be exposed to study treatment from the time the very first dose was administered to the last day of follow-up

Table 2. AE summary

	Nusinersen-treated patients				Sham procedure control–treated patients
	Presymptomatic SMA	Infantile-onset SMA	Later-onset SMA	All nusinersen-treated patients	
n (%)	NURTURE n=20	ENDEAR and CS3A n=100	CS1, CS2, CS10, CS12, and CHERISH n=140	NURTURE, ENDEAR, CS3A, CS1, CS2, CS10, CS12, and CHERISH n=260	ENDEAR and CHERISH n=83
Patient death[a]	**0**	**17 (17)**	**0**	**17 (7)**	**16 (19)**
AEs leading to discontinuation[b]	**0**	**16 (16)**	**0**	**16 (6)**	**16 (19)**
Treatment-related AE[c]	**0**	**0 (0)**	**1 (<1)**	**1 (<1)**	**0**
Common AEs					
No. of events	141	1627	1187	2955	909
No. of patients	16 (80)	97 (97)	134 (96)	247 (95)	82 (99)
Incidence of AEs by System Organ Class[d]					
Respiratory, thoracic, and mediastinal disorders	6 (30)	79 (79)	60 (43)	145 (56)	53 (64)
Infections and infestations	13 (65)	84 (84)	106 (76)	203 (78)	64 (77)
Gastrointestinal disorders	8 (40)	71 (71)	58 (41)	137 (53)	42 (51)
Skin and subcutaneous tissue disorders	9 (45)	37 (37)	29 (21)	75 (29)	21 (25)
General disorders and administration site conditions	6 (30)	65 (65)	67 (48)	138 (53)	45 (54)
Musculoskeletal and connective tissue disorders	3 (15)	25 (25)	71 (51)	99 (38)	17 (20)
Injury, poisoning, and procedural complications[e]	3 (15)	30 (30)	66 (47)	99 (38)	15 (18)
Nervous system disorders	3 (15)	18 (18)	58 (41)	79 (30)	9 (11)
Investigations[f]	3 (15)	28 (28)	13 (9)	44 (17)	18 (22)
Cardiac disorders[g]	2 (10)	24 (24)	7 (5)	33 (13)	16 (19)
Metabolism and nutrition disorders[h]	4 (20)	19 (19)	9 (6)	32 (12)	17 (20)
Immune system disorders	2 (10)	13 (13)	13 (9)	28 (11)	7 (8)
Adverse events by Preferred Term with an incidence of >10% in nusinersen-treated patients[i]					
Pyrexia	5 (25)	59 (59)	49 (35)	113 (43)	39 (47)
Upper respiratory tract infection	8 (40)	36 (36)	50 (36)	94 (36)	25 (30)
Nasopharyngitis	4 (20)	21 (21)	33 (24)	58 (22)	15 (18)
Vomiting	0	22 (22)	33 (24)	55 (21)	8 (10)
Headache	0	0	51 (36)	52 (20)	0
Constipation	2 (10)	37 (37)	0	50 (19)	14 (17)
Back pain	0	0	44 (31)	45 (17)	0
Cough	3 (15)	15 (15)	26 (19)	44 (17)	17 (20)
Pneumonia	2 (10)	30 (30)	0	41 (16)	14 (17)
Respiratory distress	0	28 (28)	0	31 (12)	12 (14)
Scoliosis	0	11 (11)	18 (13)	29 (11)	0
Diarrhea	0	16 (16)	0	27 (10)	7 (8)
Respiratory failure	0	26 (26)	0	27 (10)	16 (19)
Post-lumbar puncture syndrome	0	0	26 (19)	26 (10)	0
Incidence of SAEs[j]	**6 (30)**	**77 (77)**	**19 (14)**	**102 (39)**	**50 (60)**
SAEs					
Respiratory, thoracic, and mediastinal disorders	2 (10)	63 (63)	4 (3)	69 (27)	33 (40)
Infections and infestations	4 (20)	60 (60)	13 (9)	77 (30)	29 (35)
Cardiac disorders[g]	0	12 (12)	0	12 (5)	7 (8)
Metabolism and nutrition disorders[h]	2 (10)	10 (10)	0	12 (5)	7 (8)
Gastrointestinal disorders	1 (5)	7 (7)	1 (<1)	9 (3)	7 (8)
General disorders and administration site conditions	1 (5)	7 (7)	1 (<1)	9 (3)	1 (1)
Injury, poisoning, and procedural complications[e]	0	3 (3)	3 (2)	6 (2)	3 (4)
Investigations[f]	0	3 (3)	0	3 (1)	3 (4)
Nervous system disorders	0	3 (3)	0	3 (1)	0
Vascular disorders	0	2 (2)	0	2 (<1)	0
Immune system disorders	0	0	1 (<1)	1 (<1)	–
Musculoskeletal and connective tissue disorders	0	1 (1)	0	1 (<1)	–
Skin and subcutaneous tissue disorders	0	1 (1)	0	1 (<1)	0

AE = adverse event; SAE = serious adverse event; SMA = spinal muscular atrophy
[a]The causes of death in the infantile-onset studies were all consistent with those typically observed for infantile-onset SMA (usually respiratory in nature) and considered to be unrelated to nusinersen by the study investigator
[b]All AEs leading to study discontinuation were events with fatal outcomes
[c]Investigators assessed whether an AE was related to study drug
[d]AEs included are those occurring in >10% of all patients treated with nusinersen
[e]Covers cases where an injury, poisoning, procedural, or device complication factor is significant in the medical event being reported, and includes: post-lumbar puncture syndrome; procedural pain, nausea, complication, headache, or site reaction; post-procedural swelling, complication, or discomfort
[f]Includes clinical laboratory tests, radiologic tests, physical examination parameters, and physiologic tests
[g]This class is partly based on anatomy (endocardial, myocardial and pericardial disorders, coronary artery disorders, and valve disorders) and partly on pathophysiology (neoplasms, arrhythmias, cardiac failure, congenital cardiac disorders, and cardiac signs and symptoms)
[h]Includes disorders in the handling of specific substances by the body (e.g., purine and pyrimidine metabolism disorders, inborn errors of metabolism, and lipid metabolism disorders), conditions associated with nutritional disorders in general (e.g., appetite and general nutritional disorders, vitamin-related disorders), and medical conditions that may not be associated with a specific metabolic or nutritional pathogenesis (e.g., acid-base disorders, electrolyte and fluid balance conditions)
[i]AEs included are those with an event for all patients
[j]An SAE was any untoward medical occurrence that resulted in death/risk of death, hospitalization/prolonged hospitalization, persistent or significant disability/incapacity, or that resulted in a congenital anomaly/birth defect

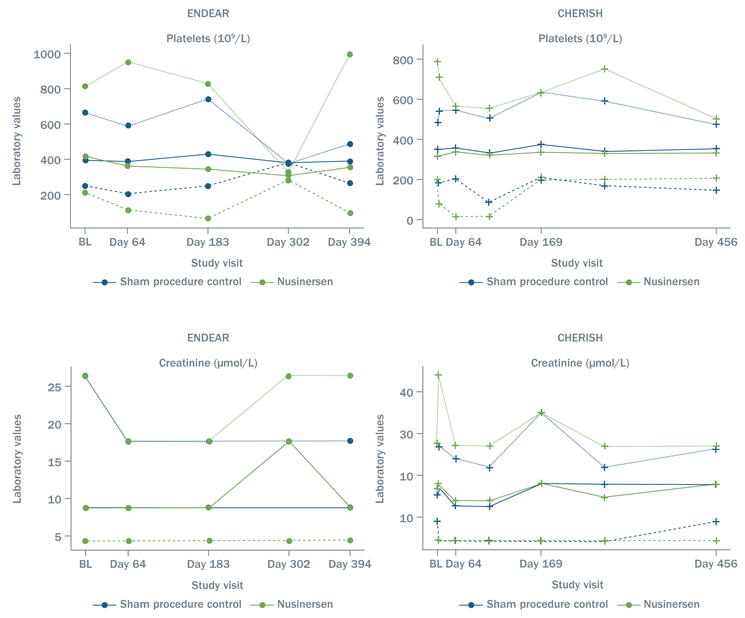
Table 3. Assessment of hematology, blood chemistry, or urinalysis in the sham procedure–controlled studies (ENDEAR and CHERISH)

	Nusinersen-treated patients n=164	Sham procedure control–treated patients n=83
Shift in hematology, blood chemistry, or urinalysis[a]		
Low platelets	24/146 (16)	10/72 (14)
Median (range) at Day 394/456, 10^9/L	341 (95 to 992)	377 (147 to 741)
High alanine aminotransferase	12/151 (8)	7/73 (10)
Median (range) at Day 394/456, U/L	17 (7 to 214)	18 (9 to 60)
High aspartate aminotransferase	7/153 (5)	2/73 (3)
Median (range) at Day 394/456, U/L	32.0 (19 to 155)	31.5 (21 to 48)
High creatinine	1/157 (<1)	0
Median (range) at Day 394/456, μmol/L	17.68 (4.4 to 27.0)	17.68 (4.4 to 27.0)
High cystatin C	2/156 (1)	1/75 (1)
Median (range) at Day 394/456, mg/L	0.62 (0.4 to 1.1)	0.62 (0.4 to 0.8)
High urine protein	70/123 (57)	22/65 (34)

	ENDEAR		CHERISH	
	Nusinersen-treated patients n=80	Sham procedure control–treated patients n=41	Nusinersen-treated patients n=84	Sham procedure control–treated patients n=42
Summary of urinary protein results[b]				
Positive protein at baseline	4/76 (5)	1/38 (3)	1/84 (1)	1/42 (2)
≥1 positive protein result	7/66 (11)	6/32 (19)	13/83 (16)	4/41 (10)
≥2 positive protein results	1/55 (2)	0	0	1/41 (2)
≥1 positive protein results in the absence of other urinalysis abnormality at same visit	4/66 (6)	3/32 (9)	9/83 (11)	4/41 (10)
≥2 positive protein results in the absence of other urinalysis abnormality at same visit	1/55 (2)	0	0	1/41 (2)

High = above the upper limit of normal; low = below the lower limit of normal (local or central laboratory normative ranges were used to determine change from baseline)
The values are number of patients with low (or high)/number at risk (percentage). Number at risk for shift to low (or high) is the number of patients whose baseline value was not low (or high) and who had ≥1 postbaseline value. Numbers in parentheses are percentages based on the number at risk. Shift to low includes normal to low, high to low, and unknown to low. Shift to high includes normal to high, low to high, and unknown to high
[a]Any shift from a normal value at baseline to out of range at 1 time point post baseline
[b]1+ or greater on urine dipstick considered positive

Figure 2. Median (minimum, maximum) platelet counts and serum creatinine levels over time in nusinersen- and sham procedure control–treated patients in ENDEAR and CHERISH[a]



BL = baseline
Dashed lines represent the minimum, solid lines the median, and dotted lines the maximum
[a]Symbols often overlap, in which case only the nusinersen symbol is shown

References 1. Finkel RS, *et al. Lancet*. 2016;388(10063):3017-3026. 2. Spinraza [prescribing information]. Cambridge, MA: Biogen; 2016. 3. Hoy SM. *Drugs*. 2017;77(4):473-479. 4. Haché M, *et al. J Child Neurol*. 2016;31(7):899-906. **Disclosures** EM: SMA study advisory boards for AveXis, Biogen, Ionis Pharmaceuticals, Inc., Novartis, and Roche; funding from Famiglie SMA Italy, Italian Telethon, and SMA Europe; 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; MF: scientific advisory board honoraria from Biogen; SR: former employee of and holds stock/stock options in Biogen; 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. **Acknowledgments** These studies were sponsored by Ionis Pharmaceuticals, Inc. (Carlsbad, CA, USA) and Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Excel Scientific Solutions (Horsham, UK): funding was provided by Biogen.