Nusinersen Demonstrates Greater Efficacy in Infants With Shorter Disease Duration: Final Results From the ENDEAR Study in Infants With Spinal Muscular Atrophy (SMA)

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Conclusions

- There were significantly greater proportions of HINE motor milestone responders and CHOP INTEND responders among infants treated with nusinersen compared with sham procedure.
- Nusinersen-treated infants demonstrated increases in event-free survival and overall survival vs. sham procedure infants with significant treatment differences observed in infants with a disease duration ≤12 weeks.
- Overall, nusinersen demonstrated treatment benefits in subgroups of infants with shorter and longer disease duration at treatment initiation in ENDEAR.
- Interim results from NURTURE (NCT02386553) demonstrate the benefits of nusinersen, including achievement of motor milestones over the expected natural history of SMA Types I and II, in infants who initiated nusinersen in the pre-symptomatic stage of SMA.[4]
- Taken together, these results suggest that earlier treatment with nusinersen may improve outcomes for infants with SMA.

Introduction

- Nusinersen is an antisense oligonucleotide approved for the treatment of spinal muscular atrophy (SMA).[1]
- 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 subtypes and on survival endpoints in infantile-onset SMA, as well as a favourable benefit-risk profile.[2-5]

Objectives

- To assess the efficacy and safety of nusinersen in infants with SMA with disease duration ≤12 or >12 weeks.

Methods

- ENDEAR (NCT02193074) was a Phase 3, randomised, double-blind, sham procedure–controlled 13-month study of intrathecal nusinersen in infants with SMA (most likely to develop SMA Type I).
- Primary endpoints:
  - Proportion of Hammersmith Infant Neurological Examination (HINE) motor milestone responders (more categories improving than worsening, excluding voluntary grasp);
  - Event-free survival (i.e., time to death or permanent ventilation).
- Secondary endpoints included:
  - Proportion of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) responders (≥4-point improvement from baseline);
  - Survival rate.
- Pre-specified subgroup analyses based on SMA disease duration (age at screening minus age at SMA symptom onset) ≤12 or >12 weeks at screening were performed.

Results

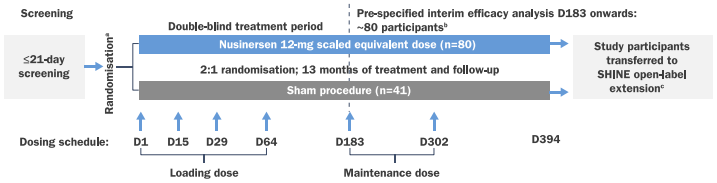
- Of the 121 infants randomised and dosed, 52 (sham procedure, 18; nusinersen, 34) had disease duration ≤12 weeks and 69 (sham procedure, 23; nusinersen, 46) had disease duration >12 weeks. Baseline characteristics are provided in the Table.
- Significant between-group differences (nusinersen vs. sham procedure) in the proportion of HINE responders were observed in infants with disease duration ≤12 weeks (75% vs. 0%; *P*<.0001) and those with disease duration >12 weeks (32% vs. 0%; *P*=.0026; Figure 2A).
- There was a significant treatment benefit of nusinersen in event-free survival in infants with disease duration ≤12 weeks (hazard ratio [HR], 0.158; *P*=.0004; Figure 2B), and a trend favouring nusinersen treatment in those with disease duration >12 weeks (HR, 0.816; *P*=.5325; Figure 2C).
- Similar results were noted for other endpoints with nusinersen, demonstrating benefit in all subgroups and greater efficacy in infants with disease duration ≤12 weeks (Figure 3A–C).

Table. Baseline characteristics by disease duration

Characteristic	Disease duration ≤12 wk		Disease duration >12 wk	
	Sham procedure n=18	Nusinersen n=34	Sham procedure n=23	Nusinersen n=46
Female, n (%)	7 (39)	18 (53)	17 (74)	25 (54)
Median (range) age at first dose, d	136.0 (30–228)	117.0 (52–235)	213.0 (143–262)	196.0 (127–242)
Median (range) age at symptom onset, wk	8.0 (1–20)	6.0 (3–18)	8.0 (4–16)	8.0 (2–16)
Median (range) disease duration, wk	9.9 (0–12)	8.7 (0–12)	18.0 (13–23)	16.3 (12–26)
Median (range) age at SMA diagnosis, wk	10.5 (2–25)	9.5 (0–22)	20.0 (12–30)	12.0 (2–29)
SMA symptoms, n (%)				
Hypotonia	18 (100)	34 (100)	23 (100)	46 (100)
Developmental motor delay	17 (94)	29 (85)	22 (96)	42 (91)
Paradoxical breathing	16 (89)	29 (85)	11 (48)	42 (91)
Pneumonia or respiratory symptoms	4 (22)	11 (32)	5 (22)	17 (37)
Limb weakness	18 (100)	34 (100)	23 (100)	45 (98)
Swallowing or feeding difficulties	6 (33)	11 (32)	6 (26)	30 (65)
Other	6 (33)	6 (18)	8 (35)	14 (30)
Infants receiving ventilation support, n (%)	2 (11)	4 (12)	4 (17)	17 (37)

SMA = spinal muscular atrophy

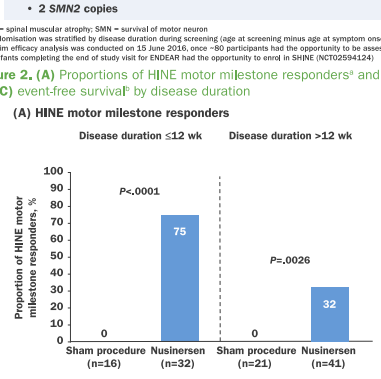
Figure 1. ENDEAR study design

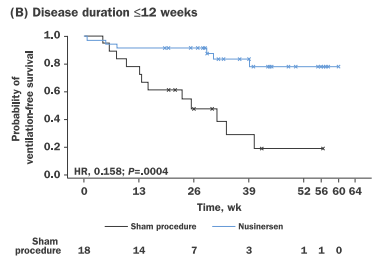


Key inclusion criteria	Key exclusion criteria
• Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age	• Hypoxaemia (oxygen saturation of <96% awake or asleep without ventilation support)
• Genetic diagnosis of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation	• Signs or symptoms of SMA present at birth or within ≤1 week after birth
• ≤7 months of age at screening	• Untreated or treated active infection
• 2 *SMN2* copies	• Previous use of an investigational drug for the treatment of SMA

SMA = spinal muscular atrophy; SMN = survival of motor neuron
[a]Randomisation was stratified by disease duration during screening (age at screening minus age at symptom onset): ≤12 vs. >12 weeks
[b]Interim efficacy analysis was conducted on 15 June 2016, once ~80 participants had the opportunity to be assessed at the Day 183 visit
[c]All infants completing the end of study visit for ENDEAR had the opportunity to enrol in SHINE (NCT02594124)

Figure 2. (A) Proportions of HINE motor milestone responders[a] and **(B, C)** event-free survival[b] by disease duration





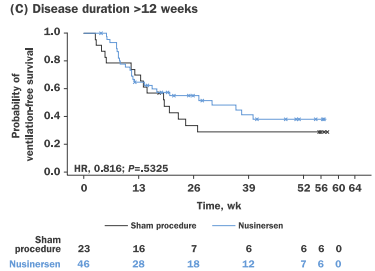
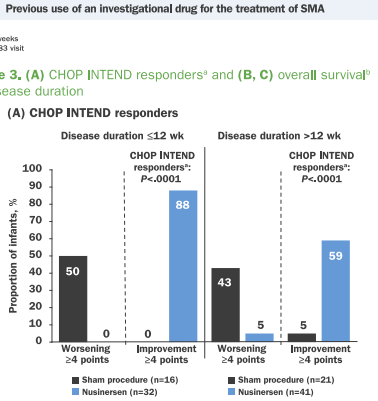
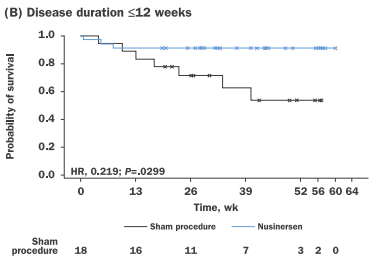
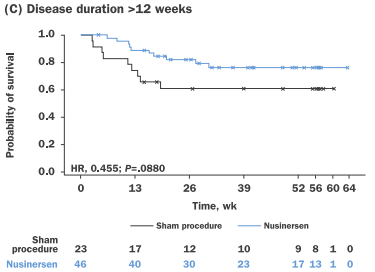


Figure 3. (A) CHOP INTEND responders[a] and **(B, C)** overall survival[b] by disease duration







HINE = Hammersmith Infant Neurological Exam; HR = hazard ratio
[a]Infants were considered HINE motor milestone responders if they demonstrated: (1) ≥1-point increase in head control, rolling, sitting, crawling, standing or walking or a ≥2-point increase or achievement of maximal score in kicking ability; and (2) improvement in more HINE categories than worsening. Infants with 6-month, 10-month or 13-month data were included. The last available assessment was used for this analysis. Infants who died or who withdrew from the study were considered non-responders
[b]Event-free survival was defined as the time to death or permanent ventilation (tracheostomy or ≥16 hours of ventilator support per day continuously for >21 days in the absence of an acute reversible event). A HR <1 indicates lower risk of event for the nusinersen treatment group. The HR was calculated based on Cox regression adjusted for each infant's disease duration at screening

CHOP = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HR = hazard ratio
[a]CHOP INTEND responders were defined as infants with ≥4-point score increase from baseline. Infants with 6-month, 10-month or 13-month data were included. The last available assessment was used for this analysis
[b]A HR <1 indicates lower risk of event for the nusinersen treatment group. The HR was calculated based on Cox regression adjusted for each infant's disease duration at screening

References 1. Hoy SM. *Drugs*. 2017;77(4):473-479. 2. Finkel RS, *et al*. Primary efficacy and safety results from the phase 3 ENDEAR study of nusinersen in infants diagnosed with spinal muscular atrophy (SMA). Presented at: 43rd Annual Congress of the British Paediatric Neurology Association; January 11–13, 2017; Cambridge, UK. 3. Finkel RS, *et al*. *Lancet*. 2016:388(10063):3017-3026. 4. De Vivo DC, *et al*.; NURTURE study group. Neurology. 2017;88(16)(suppl):S46.003. 5. Chiriboga C, *et al*. Nusinersen in treatment-naïve patients with late-onset spinal muscular atrophy (SMA): efficacy results from a phase 1b/2a multicenter study (CS2) and its open-label extension (CS12). Presented at: Annual Spinal Muscular Atrophy Conference; June 29–July 2, 2017; Orlando, FL, USA.
Disclosures LS: SMA study advisory boards for AveXis, Biogen and Roche; principal investigator for Ionis Pharmaceuticals, Inc. and Roche trials; MF: advisory board for Biogen; RSF: grants and personal fees from Ionis Pharmaceuticals, Inc. during ENDEAR and CHERISH; grants and advisor fees from Biogen; outside the submitted work: grants from Cytokinetics and advisor to Roche; advisory capacity to non-profit organisations: Cure SMA, SMA Europe, SMA Reach (UK) and the Spinal Muscular Atrophy Foundation; data safety monitoring board for the AveXis gene transfer study and Roche Moonfish studies; JK: advisory boards for AveXis, Biogen, Ionis Pharmaceuticals, Inc. and Roche; funding for clinical research projects from Biogen, BioMarin, Ionis Pharmaceuticals, Inc., Novartis, PTC and Roche; FM: principal investigator for Ionis Pharmaceuticals, Inc. nusinersen trials and Roche olesoxime trial in SMA; advisory board for Biogen; member of the Pfizer rare disease advisory board; PS, SG and WF: employees of and hold stock/stock options in Biogen; ES: employee of and holds stock/stock options in Ionis Pharmaceuticals, Inc. **Acknowledgments** This study was 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 (Southport, CT, USA); funding was provided by Biogen.