Safety and Efficacy of Nusinersen in Infants/Children With Spinal Muscular Atrophy (SMA): Part 1 of the Phase 2 EMBRACE Study

Acsadi G,[1] Mueller-Felber W,[2] Shieh PB,[3] Crawford TO,[4] Richardson R,[5] Natarajan N,[6] Castro D,[7] Gheuens S,[8] Bhan I,[8] Gambino G,[9] Sun P,[8] Farwell W,[8] Reyna SP[8]

[1]Division of Pediatric Neurology, Connecticut Children's Medical Center, Hartford, CT, USA; [2]Department of Neuropediatrics, Developmental Neurology and Social Pediatrics, LMU-Campus Innenstadt, University of Munich, Munich, Bayern, Germany; [3]Department of Neurology, UCLA Clinical and Translational Research Center, Los Angeles, CA, USA; [4]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [5]Pediatric Neurology, Gillette Children's Specialty Healthcare, St. Paul, MN, USA; [6]Department of Neurology, Seattle Children's Research Institute, Seattle, WA, USA; [7]Department of Pediatrics, Neurology and Neurotherapeutics, UT Southwestern Medical Center, Dallas, TX, USA; [8]Biogen, Cambridge, MA, USA; [9]Biogen, Maidenhead, Berkshire, UK

Presenting author e-mail: gacsadi@connecticutchildrens.org

Conclusions

- Nusinersen demonstrated a favourable benefit-risk profile profile similar to that observed in other nusinersen clinical trials.[3,4]
- A greater proportion of nusinersen-treated individuals were HINE responders.
- A trend toward smaller mean increases in hours of ventilator use was observed in nusinersen-treated compared with sham procedure–treated individuals between Days 183 and 302.
- Similar increases in weight and body length over time were observed in nusinersen-treated and sham procedure–treated infants and children by Day 183.
- Twenty children have enrolled in the EMBRACE open-label extension Part 2.

Introduction

- Nusinersen is an antisense oligonucleotide currently approved for the treatment of spinal muscular atrophy (SMA) in Europe,[1] the United States,[2] Brazil, Japan and Canada.
- Results of pivotal studies of nusinersen in infantile-onset SMA (most likely to develop SMA Type I; ENDEAR) and later-onset SMA (most likely to develop SMA Type II or III; CHERISH) have shown significant and clinically meaningful improvements in motor function and favourable benefit-risk profiles.[3,4]
- The EMBRACE study targeted enrolment of infants and children ineligible for the 2 pivotal studies.

Objectives

- To assess the safety/tolerability and efficacy of intrathecal administration of nusinersen to a cohort of symptomatic individuals with SMA who were not eligible for the pivotal ENDEAR or CHERISH clinical studies.

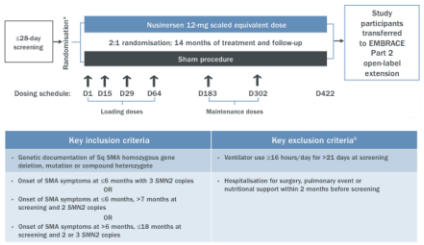
Methods

- EMBRACE (NCT02462759) Part 1 was a Phase 2, randomised, double-blind, sham procedure–controlled 14-month study of intrathecal nusinersen treatment (Figure 1).
- Primary endpoints:
  - Safety and tolerability.
- Exploratory endpoints included:
  - Change from baseline in ventilator use;
  - Attainment of motor milestones as assessed by Section 2 of the Hammersmith Infant Neurological Examination (HINE);
  - Change from baseline in growth parameters;
  - Clinical Global Impression of Change (physician and caregiver assessment).

Results

- EMBRACE Part 1 (double-blind phase) was terminated early after an interim analysis of a Phase 3 study in infants with SMA (ENDEAR; NCT02193074) demonstrated a positive benefit-risk profile for nusinersen.
  - Eligible participants were transferred to a new open-label EMBRACE Part 2 protocol.
- Nusinersen demonstrated a favourable safety profile (Table 2).
  - No clinically significant findings of thrombocytopenia or elevated urinary protein were observed.
- Before the unblinding transition, a larger proportion of nusinersen-treated (11/14; 79%) vs. sham procedure–treated individuals (2/7; 29%) were HINE motor milestone responders.
  - Though higher proportions of responders were observed in the nusinersen-treated group vs. sham procedure in both subgroups based on age of symptom onset, greater differences between treatment groups were observed in those with symptom onset at ≤6 vs. >6 months; all of the individuals in the sham procedure group with symptom onset at ≤6 months were HINE non-responders (Figure 2A).
- Between the Day 183 and 302 visits, hours of ventilator use changed by a mean (SD) of +1.236 (3.712) hours in nusinersen-treated individuals (n=12) and by +2.123 (3.023) hours in sham procedure–treated individuals (n=7).
- At Day 183, nusinersen-treated (n=14) and sham procedure–treated individuals (n=7) demonstrated similar increases from baseline in weight (mean [SD]: 0.7 [0.5] and 0.6 [0.6] kg) and body length (mean [SD]: 5.6 [2.4] and 4.5 [4.9] cm).

Figure 1. Study design



Key inclusion criteria	Key exclusion criteria[b]
• Genetic documentation of 5q SMA homozygous gene deletion, mutation or compound heterozygote • Onset of SMA symptoms at ≤6 months with 3 *SMN2* copies OR • Onset of SMA symptoms at ≤6 months, >7 months at screening and 2 *SMN2* copies OR • Onset of SMA symptoms at >6 months, ≤18 months at screening and 2 or 3 *SMN2* copies	• Ventilator use ≥16 hours/day for >21 days at screening • Hospitalisation for surgery, pulmonary event or nutritional support within 2 months before screening

SMA = spinal muscular atrophy; SMN = survival of motor neuron
[a]Randomisation was stratified by age at onset of symptoms: >6, ≤6 months
[b]Individuals eligible for ENDEAR (symptom onset ≤6 months, ≤7 months of age at screening; 2 *SMN2* copies) or CHERISH (symptom onset age >6 months, age 2–12 years at screening) were not eligible for EMBRACE

Table 1. Baseline demographic and disease characteristics

	Age of SMA onset				All participants	
	≤6 mo		>6 mo			
	Sham procedure n=4	Nusinersen n=9	Sham procedure n=3	Nusinersen n=5	Sham procedure n=7	Nusinersen n=14
Female, n (%)	3 (75)	4 (44)	2 (67)	1 (20)	5 (71)	5 (36)
Median (range) age at first dose, mo	25.6 (16–53)	15.3 (7–49)	17.0 (15–19)	18.1 (16–19)	18.5 (15–53)	16.7 (7–49)
Median (range) age at symptom onset, mo	3.85 (1.8–5.1)	4.6 (2.0–6.0)	9.0 (7.0–11.0)	9.0 (7.6–11.0)	5.1 (1.8–11.0)	5.5 (2.0–11.0)
Median (range) age at SMA diagnosis, mo	7.7 (5.5–14.0)	8.0 (6.9–11.0)	13.0 (12.0–14.0)	13.0 (9.9–15.0)	12.0 (5.5–14.0)	10.0 (6.9–15.0)
SMN2 copy no., n (%)[a]						
2	3 (75)	3 (33)	1 (33)	0	4 (57)	3 (21)
3[b]	1 (25)	6 (67)	2 (67)	5 (100)	3 (43)	11 (79)
Median (range) weight, kg	11.3 (7.6–15.5)	9.0 (7.1–11.8)	10.6 (9.3–11.5)	9.0 (8.8–12.1)	10.6 (7.6–15.5)	9.0 (7.1–12.1)
Median (range) length, cm	87.8 (74.0–105.5)	78.3 (70.0–90.5)	79.8 (75.5–80.1)	78.8 (72.5–82.5)	80.1 (74.0–105.5)	78.6 (70.0–90.5)

SMA = spinal muscular atrophy; SMN = survival of motor neuron
[a]Based on central laboratory results
[b]For 1 individual in the nusinersen group (age of onset ≤6 months), central laboratory results were not clearly categorised and the individual's records indicated that the individual had 3 *SMN2* copies. For all analyses, this individual was considered to have 3 *SMN2* copies

Table 2. AE summary

AE, n (%)	Sham procedure n=7	Nusinersen n=14
No. who died	**1 (14)**	**0**
No. who withdrew	**0**	**0**
Any AE[a]	**6 (86)**	**14 (100)**
Moderate or severe AE	**5 (71)**	**10 (71)**
Severe AE	**3 (43)**	**5 (36)**
AE possibly related or related to study treatment	**0**	**0**
Serious AE	**3 (43)**	**5 (36)**
AE leading to treatment discontinuation	**0**	**0**
AE leading to study withdrawal	**1 (14)**	**0**
Common AEs (≥20% in either treatment group)[b]		
Cough	1 (14)	7 (50)
Pyrexia	1 (14)	6 (43)
Pneumonia	0	6 (43)
Upper respiratory tract infection	2 (29)	5 (36)
Respiratory tract infection	1 (14)	4 (29)
Vomiting	1 (14)	4 (29)
Nasal congestion	0	3 (21)
Pain in extremity	0	3 (21)
Procedural pain	0	3 (21)
Tachycardia	2 (29)	2 (14)
Erythema	2 (29)	1 (7)
Hypoxia	2 (29)	1 (7)
Teething	2 (29)	1 (7)
Shift in ECG results[c]		
Shift to abnormal, not clinically significant[d]	3 (43)	1 (8)
Shift to abnormal, clinically significant[e]	0	0

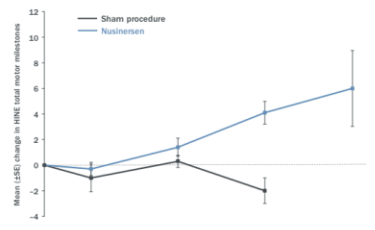
AE = adverse event; ECG = electrocardiogram
[a]Number of individuals with an event
[b]Individuals were counted only once in each Medical Dictionary for Regulatory Activities Preferred Term
[c]Presented as number with a shift/number at risk. Number at risk is the number of individuals whose baseline value was not abnormal and who had ≥1 post-baseline value
[d]Shifts to abnormal, not clinically significant included unknown or normal to abnormal, not clinically significant (sham procedure, n=7; nusinersen, n=12)
[e]Shifts to abnormal, clinically significant included unknown or normal to abnormal, clinically significant

Figure 2. (A) HINE motor milestone responders[a] stratified by age of SMA onset[b] and **(B, C)** mean change from baseline in HINE total milestones by visit by age of SMA onset

(A)

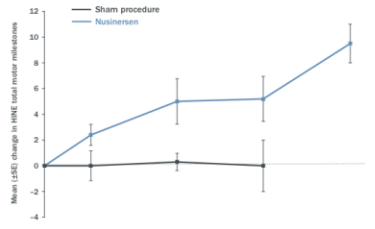
	Age of SMA onset				All participants	
	≤6 mo		>6 mo			
	Sham procedure n=4	Nusinersen n=9	Sham procedure n=3	Nusinersen n=5	Sham procedure n=7	Nusinersen n=14
No. of individuals achieving the following motor milestone improvements from baseline[c]						
Ability to kick						
≥2-point increase	0	1 (11)	0	1 (20)	0	2 (14)
Achievement of touching toes[d]	0	1 (11)	0	1 (20)	0	2 (14)
Head control (≥1-point increase)	0	4 (44)	0	1 (20)	0	5 (36)
Rolling (≥1-point increase)	0	6 (67)	0	3 (60)	0	9 (64)
Sitting (≥1-point increase)	0	5 (56)	1 (33)	4 (80)	1 (14)	9 (64)
Crawling (≥1-point increase)	0	0	1 (33)	3 (60)	1 (14)	3 (21)
Standing (≥1-point increase)	0	0	2 (67)	2 (40)	2 (29)	2 (14)
Walking (≥1-point increase)	0	0	0	1 (20)	0	1 (7)
Individuals demonstrating improvement in more motor milestone categories than worsening	**0**	**7 (78)**	**2 (67)**	**4 (80)**	**2 (29)**	**11 (79)**
HINE motor milestone responder[e]	0	7	2	4	2	11
Proportion (95% CI)[e]	0 (0.00–0.60)	0.78 (0.45–0.94)	0.67 (0.21–0.94)	0.80 (0.38–0.96)	0.29 (0.08–0.64)	0.79 (0.52–0.92)

(B) Mean change from baseline in HINE total milestones by visit in infants with age of onset ≤6 months[f]



Study visit	Baseline	Day 64	Day 183	Day 302	Day 422
Sham procedure	4	4	4	2	0
Nusinersen	9	9	9	7	4

(C) Mean change from baseline in HINE total milestones by visit in infants with age of onset >6 months[f]



Study visit	Baseline	Day 64	Day 183	Day 302	Day 422
Sham procedure	3	3	3	2	0
Nusinersen	5	5	5	5	2

HINE = Hammersmith Infant Neurological Exam; SMA = spinal muscular atrophy
[a]HINE motor milestone responders were defined as individuals with more HINE categories improving (≥2-point increase or maximal score in kicking ability, or ≥1-point increase in head control, rolling, sitting, crawling, standing or walking) than worsening (≥2-point decrease or maximal score in kicking ability, or ≥1-point decrease in head control, rolling, sitting, crawling, standing or walking). Individuals who died or who withdrew from the study were considered non-responders
[b]Individuals with opportunity for at least a 6-month (Day 183) assessment were included
[c]Individuals with a 6-month (Day 183), 10-month (Day 302) or 14-month (Day 422) assessment. The last available assessment was used for this analysis
[d]Toe touching is the highest milestone in the ability to kick category
[e]Wilson score CI with continuity correction
[f]If ≥1 milestone was assessed at a visit, any missing milestones were imputed to allow the total score to be evaluated

References 1. European Medicines Agency. Spinraza 12 mg solution for injection [summary of product characteristics]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004312/WC500229704.pdf. Accessed August 30, 2017. 2. Spinraza [prescribing information]. Cambridge, MA: Biogen; 2017. 3. 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. 4. Mercuri E, *et al.* Efficacy and safety of nusinersen in children with later-onset spinal muscular atrophy (SMA): end of study results from the phase 3 CHERISH study. Presented at: 69th Annual Meeting of the American Academy of Neurology; April 22–28, 2017; Boston, MA.

Disclosures GA: advisory boards for AveXis, Biogen, Genentech and Sarepta; consultation and speaker engagements for Biogen; WM-F: advisory boards for AveXis and Biogen; clinical trial research contracts with Biogen, Santhera and Sarepta; PBS: advisory boards for Biogen; outside of current submitted work: advisory boards for AveXis, Marathon, PTC and Sarepta; clinical trial research contracts with Biogen, Bristol-Myers Squibb, Catalyst, Ionis, Marathon, Pfizer, PTC, Sarepta and Ultragenyx; TOC: advisor/consultant for AveXis, Biogen, Catalyst, Cure SMA, Cytokinetics, Marathon, Novartis, Roche, Sarepta and the Spinal Muscular Atrophy Foundation; RR: advisory boards for and clinical trial research contracts with Biogen; NN: research funding from Biogen for execution of clinical trial projects; DC: advisory boards for Marathon and Sarepta; SG, IB, GG, PS, WF and SPR: employees of and hold stock/stock options in Biogen. **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.