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Final Results of the Phase 3 ENDEAR Study Assessing the Efficacy and Safety of Nusinersen in Infants With Spinal Muscular Atrophy (SMA)

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Disclosures

- NK: advisory boards for Biogen; outside of the submitted work, advisory boards and consulting fees for AveXis, Catalyst, Cytokinetics, Marathon, PTC, and Sarepta; advisory capacity to CureSMA and MGFA.
- RSF: grants and personal fees from Ionis Pharmaceuticals during ENDEAR and CHERISH; grants and advisor fees from Biogen, grants from Cytokinetics and advisor to Roche outside the submitted work; advisory capacity to non-profit organizations: the SMA Foundation, Cure SMA, SMA Reach (UK) and SMA Europe; serves on the Data Safety Monitoring Board for the AveXis gene transfer study.
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Introduction

- Spinal muscular atrophy (SMA)
  - SMA is a rare, debilitating, autosomal recessive neuromuscular disorder[1]
  - Caused by insufficient levels of SMN protein[2]
- Nusinersen: an antisense oligonucleotide
  - Modulates splicing of *SMN2* pre-mRNA to promote increased production of full-length SMN protein[3,4,5]
- Phase 2 study (CS3A) interim results[a] in infants with SMA[6]
  - Demonstrated increased SMN protein levels in motor neurons
  - Showed promising safety and efficacy
- ENDEAR interim results[b] in infants with SMA
  - 41% of nusinersen-treated versus 0% of control infants were motor milestone responders ($P<0.0001$)

mRNA = messenger RNA; SMN = survival of motor neuron. [a]Interim analysis data cut conducted 26 January 2016. [b]Interim analysis data cut conducted on 15 June 2016. 1. Lunn MR, Wang CH. *Lancet*. 2008;371(9630):2120-2133. 2. Prior TW. *Curr Opin Pediatr.* 2010;22(6):696-702. 3. Hua Y, *et al. Genes Dev.* 2010;24(15):1634-1644. 4. Passini MA, *et al. Sci Transl Med.* 2011;3(72):72ra18. 5. Darras B, *et al. Neuromusc Disord.* 2014;24(9-10):920. 6. Finkel RS, *et al. Lancet.* 2016; 388(10063):3017-3026.

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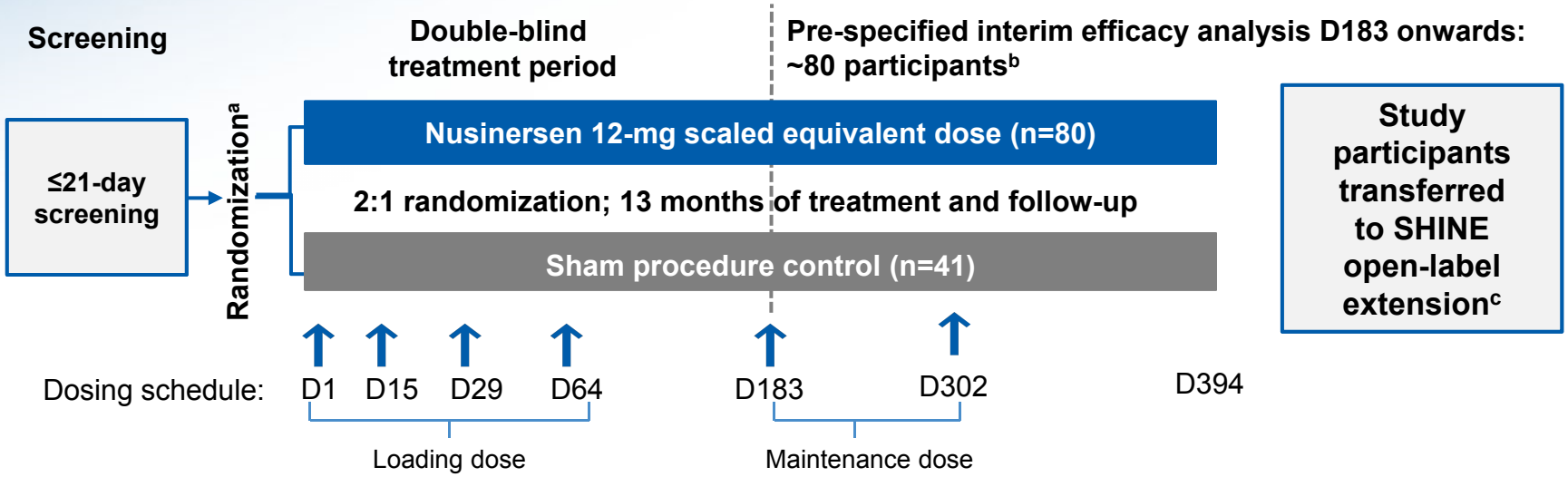
ENDEAR Study Design

- Phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy, safety, and tolerability of intrathecal nusinersen in infants with SMA
  - Key eligibility criteria: genetic diagnosis of SMA, 2 copies of the *SMN2* gene, onset of SMA symptoms at age ≤6 months and age ≤7 months with no hypoxemia at screening



- **ITT and safety population:** randomized and received ≥1 dose of study drug
- **Interim efficacy set (IES):** ITT participants who received nusinersen dose/sham procedure control ≥6 months before cutoff date for interim analysis and/or were assessed at any of the Day 183, 302 or 394 visits
- **Efficacy set:** All infants who received nusinersen dose/sham procedure control ≥6 months before cutoff date for final analysis and/or were assessed at any of the Day 183, 302 or 394 visits

ITT = intention-to-treat. [a]Randomization 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. ClinicalTrials.gov, NCT02193074.

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ENDEAR Hierarchical Endpoints

- Primary endpoints[a]
  - Proportion of motor milestone responders (IES population)
    - Assessed from Day 183 onwards using modified section 2 of the HINE[1]
    - Interim efficacy analysis conducted once ~80 participants had the opportunity to be assessed at the Day 183 visit
      - » Only endpoint with formal statistical testing at interim
  - Event-free survival, i.e., time to death or permanent ventilation (ITT population at end of study)
    - Permanent ventilation: tracheostomy or ≥16 hours ventilatory support per day for >21 days
    - Events adjudicated by a blinded, central, independent EAC
- Secondary endpoints[a]
  - CHOP INTEND responders
    - ≥4-point improvement from Baseline in total score from Day 183 onwards
  - Survival rate
  - Participants (%) not requiring permanent ventilation
  - Proportion of CMAP responders (peroneal nerve)
    - Maintenance or increase by ≥1 mV vs. Baseline from Day 183 onwards
  - Time to death or permanent ventilation in the subgroups of participants below the study median disease duration
  - Time to death or permanent ventilation in the subgroups of participants above the study median disease duration

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; EAC = endpoint adjudication committee; HINE = Hammersmith Infant Neurological Exam; IES = interim efficacy set. [a]Primary analyses must reach statistical significance before inferential conclusions can be drawn from the remaining secondary and tertiary endpoints. 1. Haataja L, *et al*. *J Pediatr.* 1999;135(2 pt 1):153-161.

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ENDEAR Primary Endpoint: Definition of HINE Motor Milestone Responders

Modified section 2 of the HINE[1]

Improvement

Motor function	Milestone progression score				
	0	1	2	3	4
Voluntary grasp	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick (supine)	No kicking	Kick horizontal, legs do not lift	Upward (vertical)	Touches leg	Touches toes
Head control	Unable to maintain upright	Wobbles	All the time upright		
Rolling	No rolling	Rolling to side	Prone to supine	Supine to prone	
Sitting	Cannot sit	Sit with support at hips	Props	Stable sit	Pivots (rotates)
Crawling	Does not lift head	On elbow	On outstretched hand	Crawling flat on abdomen	On hands and knees
Standing	Does not support weight	Supports weight	Stands with support	Stands unaided	
Walking	No walking	Bouncing	Cruising (walks holding on)	Walking independently	

Improvement

Improvement: ≥2-point improvement in ability to kick (or maximal score), or ≥1-point improvement in any other milestone, excluding voluntary grasp

Worsening: ≥2-point worsening in ability to kick (or zero score), or ≥1-point worsening in any other milestone, excluding voluntary grasp

- **Motor milestone responder definition[a]:** more HINE categories with improvement than worsening
  - Participants who die or withdraw are counted as non-responders

[a]Study participants on permanent ventilation will be assessed. 1. Haataja L, *et al*. *J Pediatr.* 1999;135(2 pt 1):153-161.

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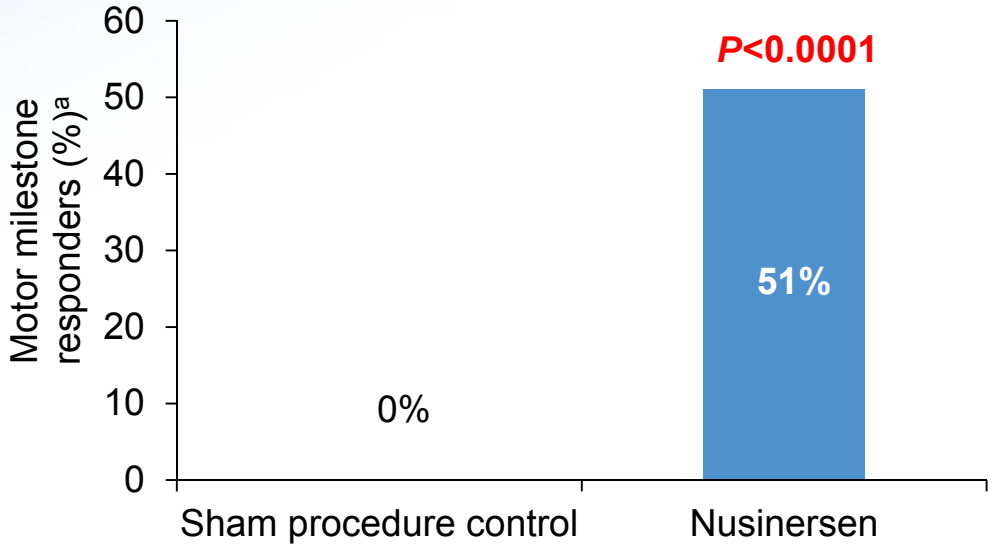
Baseline Disease Characteristics: ITT Population

Characteristic	Sham procedure control n=41	Nusinersen n=80
Female, n (%)	24 **(59)**	43 **(54)**
Median (range) age at first dose, d	205 (30, 262)	165 (52, 242)
Median (range) age at symptom onset, wk	8.0 (1, 20)	6.5 (2, 18)
Median (range) age at SMA diagnosis, wk	20.0 (2, 30)	11.0 (0, 29)
Median (range) disease duration, wk	12.7 (0, 23)	13.1 (0, 26)
SMA symptoms, n (%)		
Hypotonia	41 **(100)**	80 **(100)**
Developmental motor delay	39 **(95)**	71 **(89)**
Paradoxical breathing	27 **(66)**	71 **(89)**
Pneumonia or respiratory symptoms	9 **(22)**	28 **(35)**
Limb weakness	41 **(100)**	79 **(99)**
Swallowing or feeding difficulties	12 **(29)**	41 **(51)**
Other	14 **(34)**	20 **(25)**
Participants requiring ventilation support, n (%)	6 **(15)**	21 **(26)**

Motor Milestone Responders at End of Study

- Highly clinically and statistically significant percentage of motor milestone responders

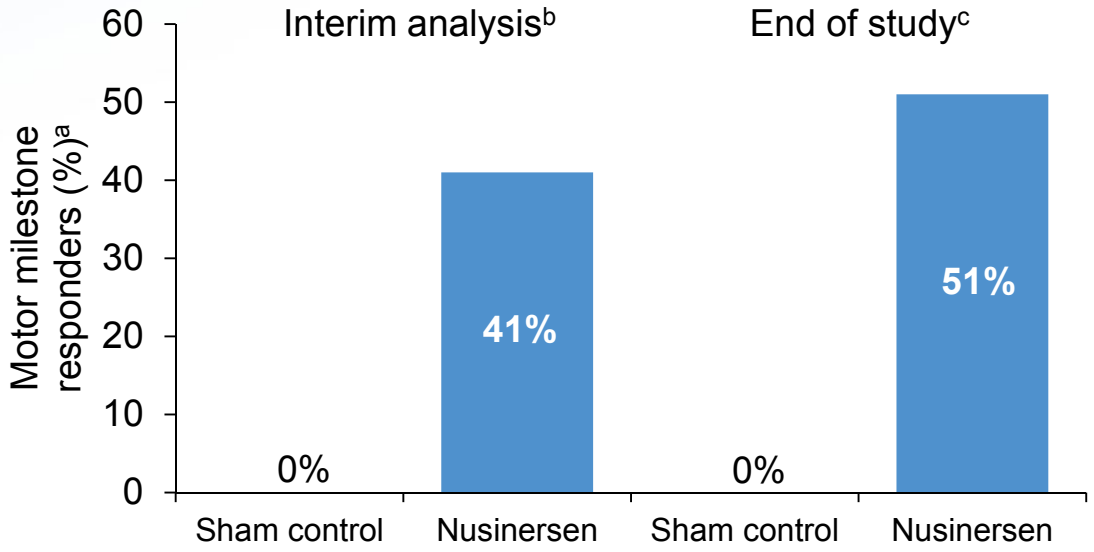


Motor milestone responders, %	Sham procedure control	Nusinersen	*P* value
6-month visit (n=110)	5	41	<0.0001
10-month visit (n=77)	0	45	<0.0001
13-month visit (n=58)	0	54	<0.0001

[a]Interim endpoint re-evaluated with final study data with no alpha spending. Infants with opportunity for at least a 6-month (Day 183) assessment were included in the analysis; last available assessment of 6-month (Day 183), 10-month (Day 302), or 13-month (Day 394) was used. n=110.

Motor Milestone Responders: Interim vs. End of Study

- Nusinersen-treated infants demonstrated continued improvement over the previous interim analysis



[a]Interim endpoint re-evaluated with final study data with no alpha spending. [b]The interim efficacy analysis was conducted on June 15, 2016, once ~80 participants had the opportunity to be assessed at the Day 183 visit; n=78. [c]The end of study analysis was conducted on November 21, 2016. Infants with opportunity for at least a Day 183 assessment were included; n=110.

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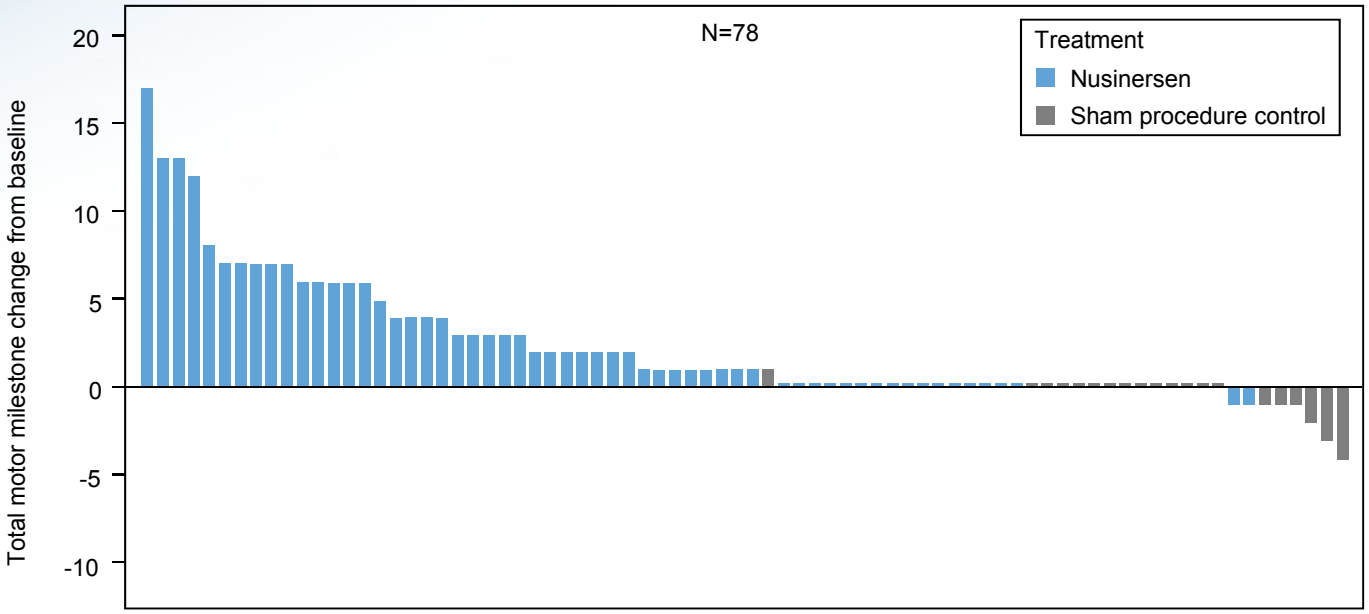
Improvement in Total Motor Milestone Score (HINE Section 2) at End of Study

- Infants treated with nusinersen had greater improvement in total motor milestone score[a] vs. sham procedure control



[a]Total motor milestone change from baseline to later of Day 183, 302, 394. Shortest bars indicate zero value. Of the 110 infants in the efficacy set, 29 died (nusinersen, n=13; sham procedure control, n=16) and 3 withdrew for a reason other than death (nusinersen, n=2; sham procedure control, n=1) and were not included in this analysis.

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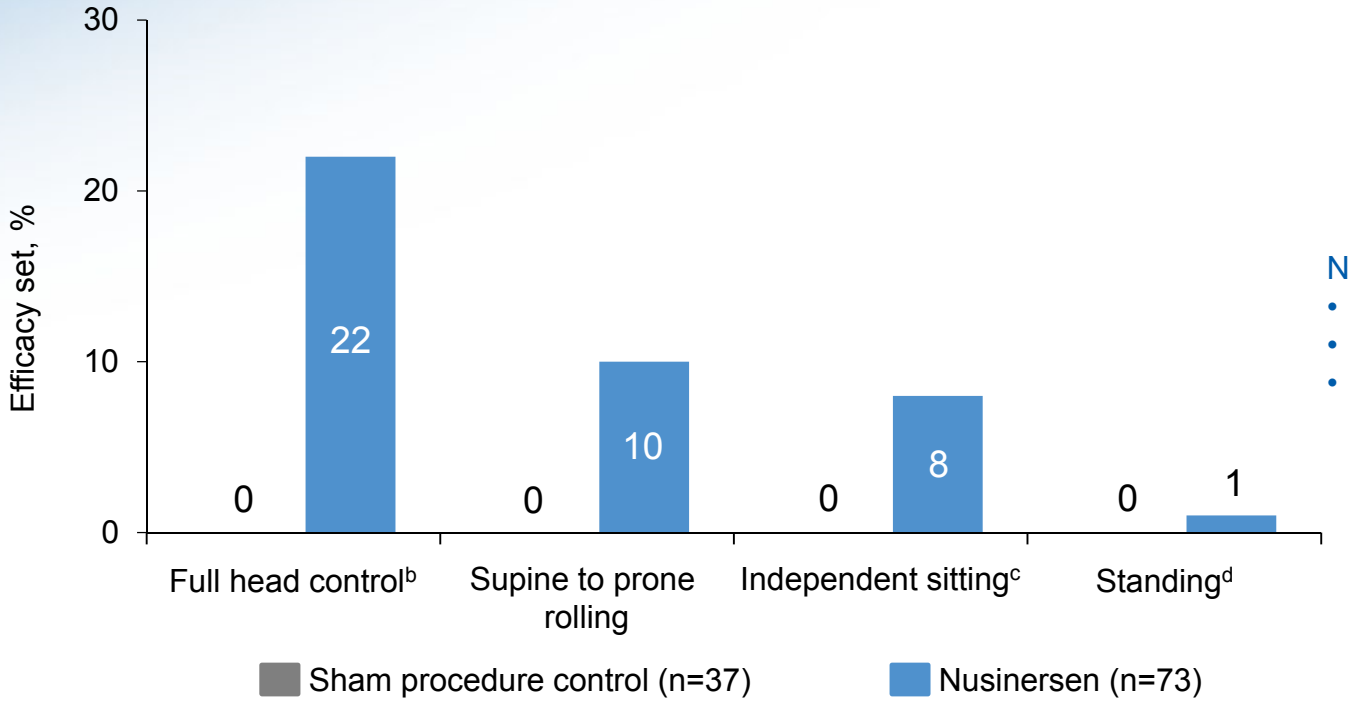
Quality of Motor Responses at End of Study

- Infants treated with nusinersen achieved motor milestones unexpected for infants with SMA Type I[a]



Nusinersen-treated infants achieved:
- Supine to prone rolling: 10%
- Stable sit: 5%
- Pivots (rotate) sit: 3%

[a]HINE motor milestone achievement in infants at the later of Days 183, 302 and 394.[b]Full head control was defined as all the time upright (HINE score = 2). [c]Independent sitting includes HINE score categories: stable sit and pivots (rotates). [d]Standing includes HINE score categories: stands with support and stands unaided.

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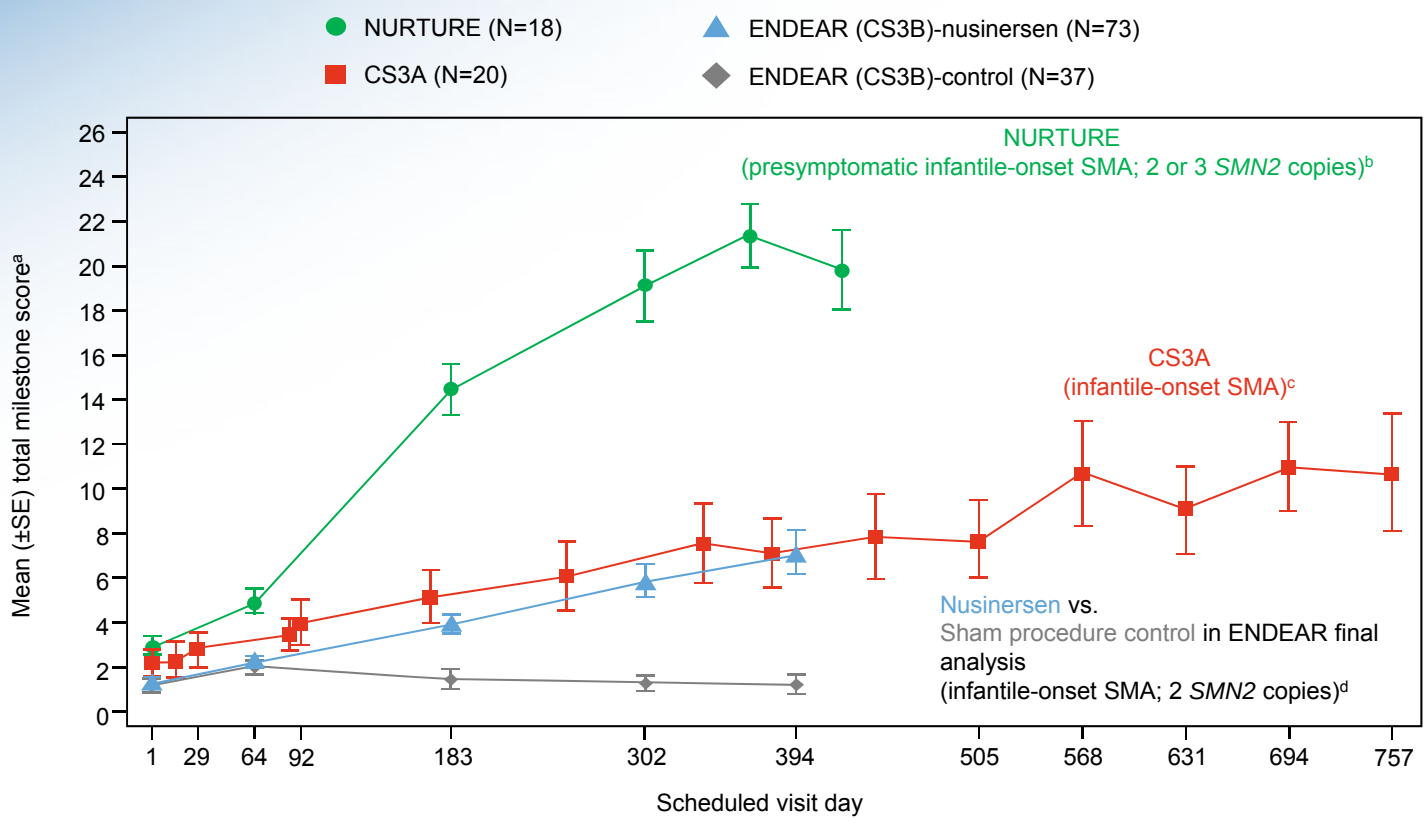
Change in HINE Motor Milestone Scores Across Studies



Populations: NURTURE (232SM201) = interim efficacy set, CS3A = all dosed infants; ENDEAR (CS3B) = interim efficacy set. For each study, visits with n<5 are not plotted. [a]Maximum total milestone score = 26. [b]Median (range) age at first dose: 19.0 (3–42) days. [c]Median (range) age at enrolment: = 155 (36–210) days. [d]Median (range) age at first dose: 175.0 (30–262) days.

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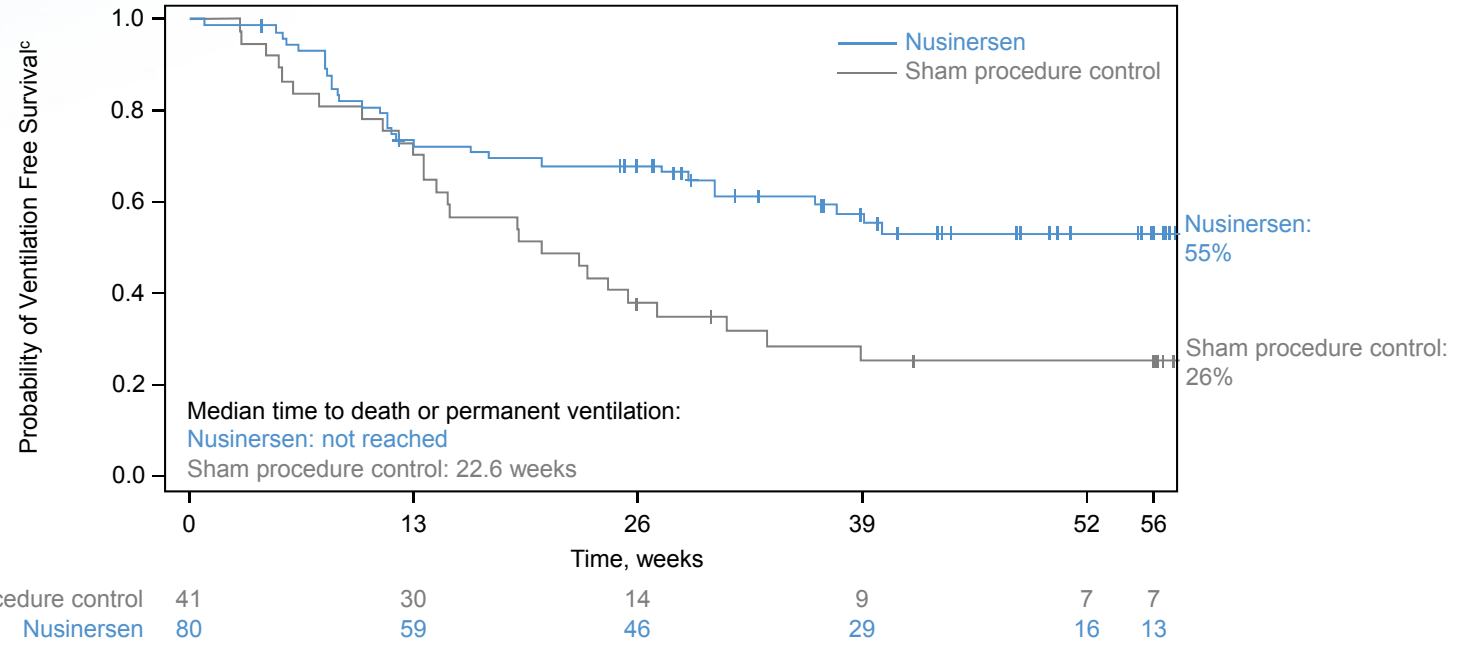
Event-Free Survival at End of Study

- Significantly prolonged event-free survival[a] in nusinersen-treated infants (HR, 0.53; *P*=0.0046[b])

Outcome	Sham procedure control	Nusinersen
Death or permanent ventilation, n (%)	28 (68%)	31 (39%)
Alive and no permanent ventilation, n (%)	13 (32%)	49 (61%)



All infants randomized who received at least one dose of nusinersen or sham procedure were included in the analysis. [a]Event-free survival = time to death or permanent ventilation (permanent ventilation was defined as tracheostomy or ≥16 hours ventilatory support per day for >21 days in the absence of acute reversible event in the determination of an independent endpoint adjudication committee). [b]Log-rank statistical test stratified by disease duration. [c]Estimated from the Kaplan-Meier method. HR = hazard ratio.

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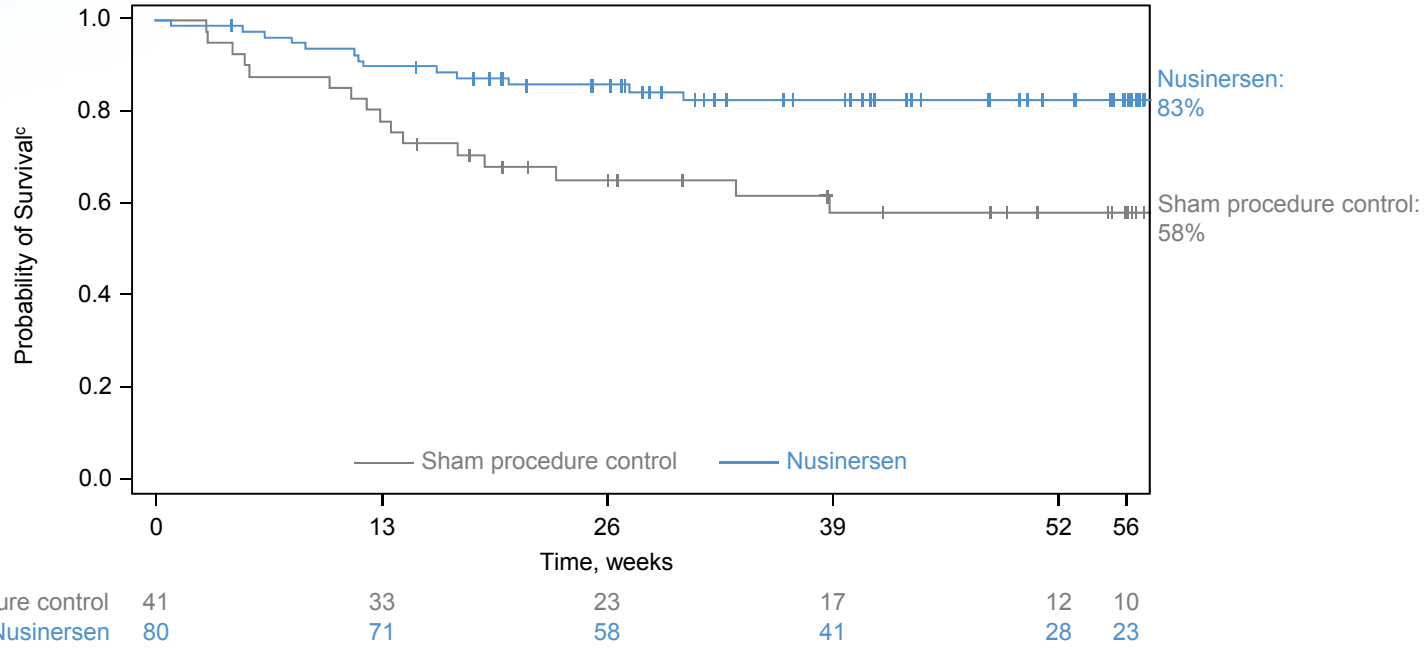
Overall Survival at End of Study

- Significantly prolonged overall survival in nusinersen-treated infants[a] (HR, 0.372; *P*=0.0041[b])

Outcome	Sham procedure control	Nusinersen
Death, n (%)	16 (39%)	13 (16%)
Alive, n (%)	25 (61%)	67 (84%)



All infants randomized who received at least one dose of nusinersen or sham procedure were included in the analysis [a]Versus sham control-treated patients. HR = hazard ratio. [b]Log-rank statistical test stratified by disease duration. [c]Estimated from the Kaplan-Meier method.

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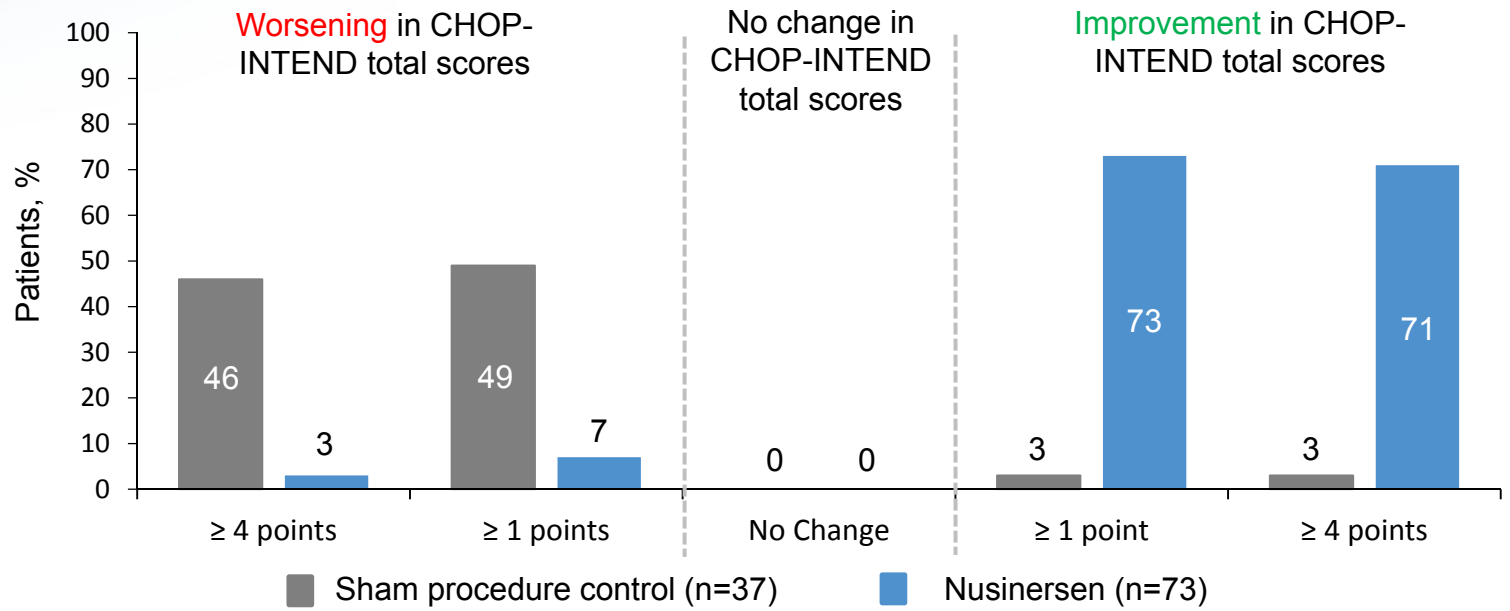
CHOP INTEND Motor Function Scores at End of Study

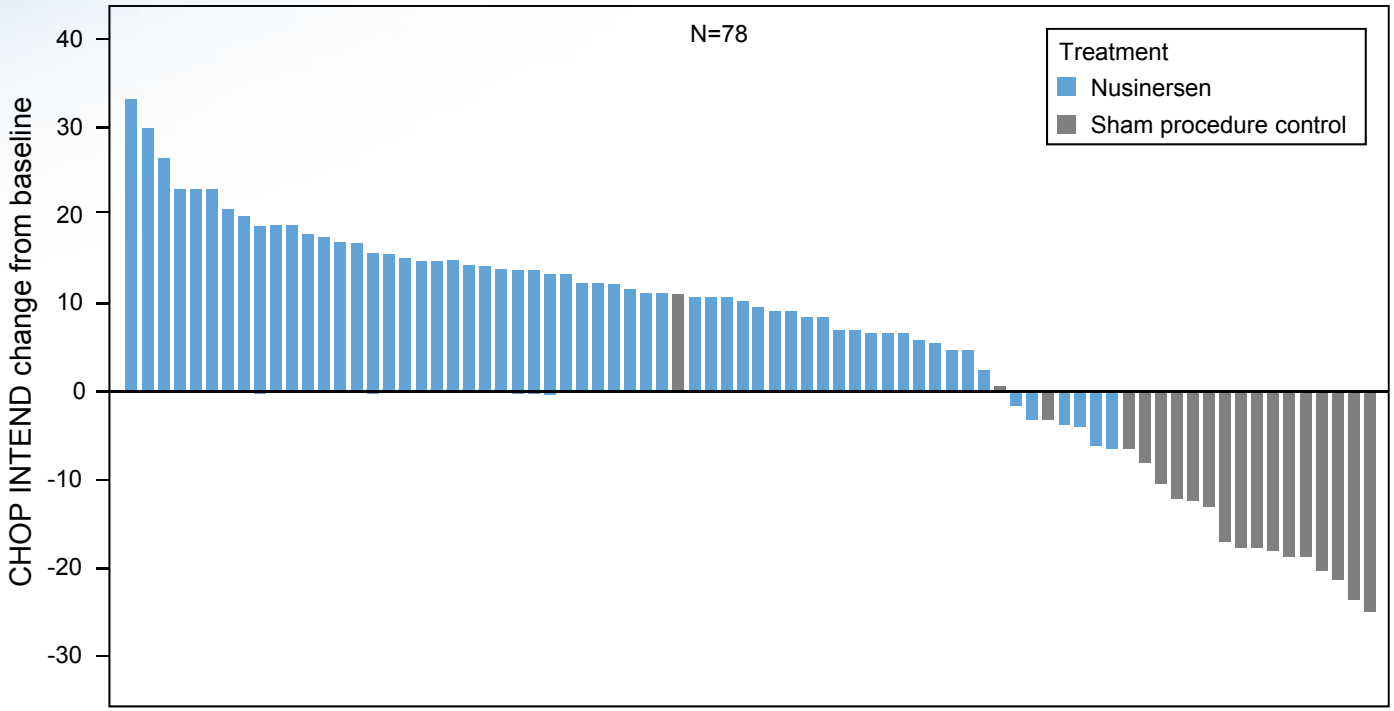
- More improvement and less worsening in nusinersen-treated patients[a]
- A significantly greater proportion of nusinersen-treated patients[a] were CHOP INTEND responders (≥4-point improvement;[b] 71% vs. 3%; *P*<0.0001)



[a]Versus sham control-treated patients. Infants with opportunity for at least a 6-month (Day 183) assessment were included in the analysis; last available assessment of 6-month (Day 183), 10-month (Day 302), or 13-month (Day 394) was used. [b]The proportion of infants with ≥4 point increase from Baseline in CHOP INTEND score at the later of the Day 183, 302, or 394 study visit assessment.

CHOP INTEND Motor Function Scores at End of Study

- More improvement and less worsening in motor function assessment (CHOP INTEND) in nusinersen-treated patients[a]



Infants with opportunity for at least a 6-month (Day 183) assessment were included in the analysis; last available assessment of 6-month (Day 183), 10-month (Day 302), or 13-month (Day 394) was used. Shortest bars indicate zero value. Of the 110 infants in the efficacy set, 29 died (nusinersen, n=13; sham procedure control, n=16) and 3 withdrew for a reason other than death (nusinersen, n=2; sham procedure control, n=1) and were not included in this analysis. [a]Versus sham-control treated infants.

Permanent Ventilation Requirement at End of Study

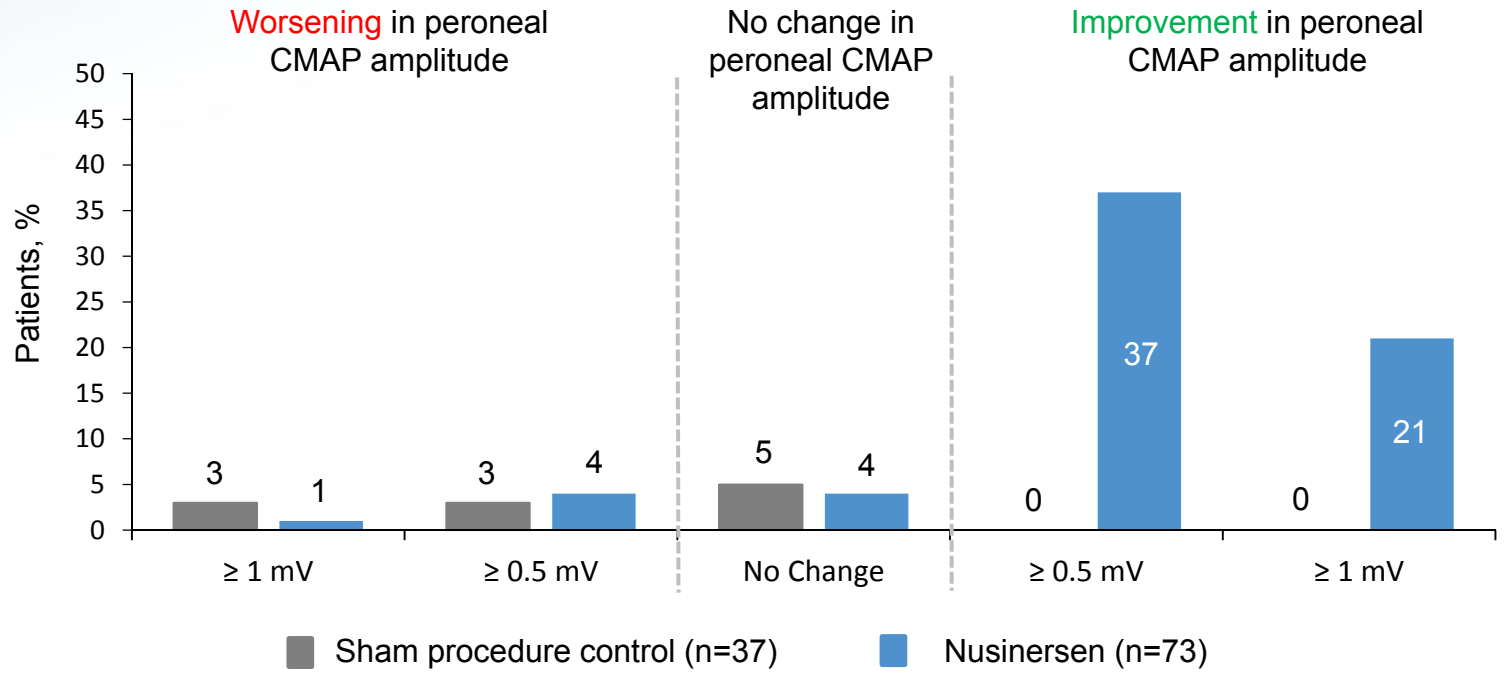
- The risk of permanent ventilation was 34% lower in nusinersen-treated infants vs. sham procedure control

Estimated % of patients who required permanent ventilation[b]	Sham procedure control	Nusinersen
Day 91	8.1	14.7
Day 182	38.6	16.2
Day 273	48.5	25.5
Day 364	48.5	30.9
Day 394	48.5	30.9
HR for nusinersen vs. sham procedure control		0.66[c]

All infants randomized who received at least one dose of nusinersen or sham procedure were included in the analysis [a] Versus sham control-treated patients. [b]Based on the Kaplan-Meier product limit method. [c]*P*=0.1329 based on log-rank test stratified by disease duration. HR=hazard ratio.

Peroneal CMAP Amplitude at End of Study

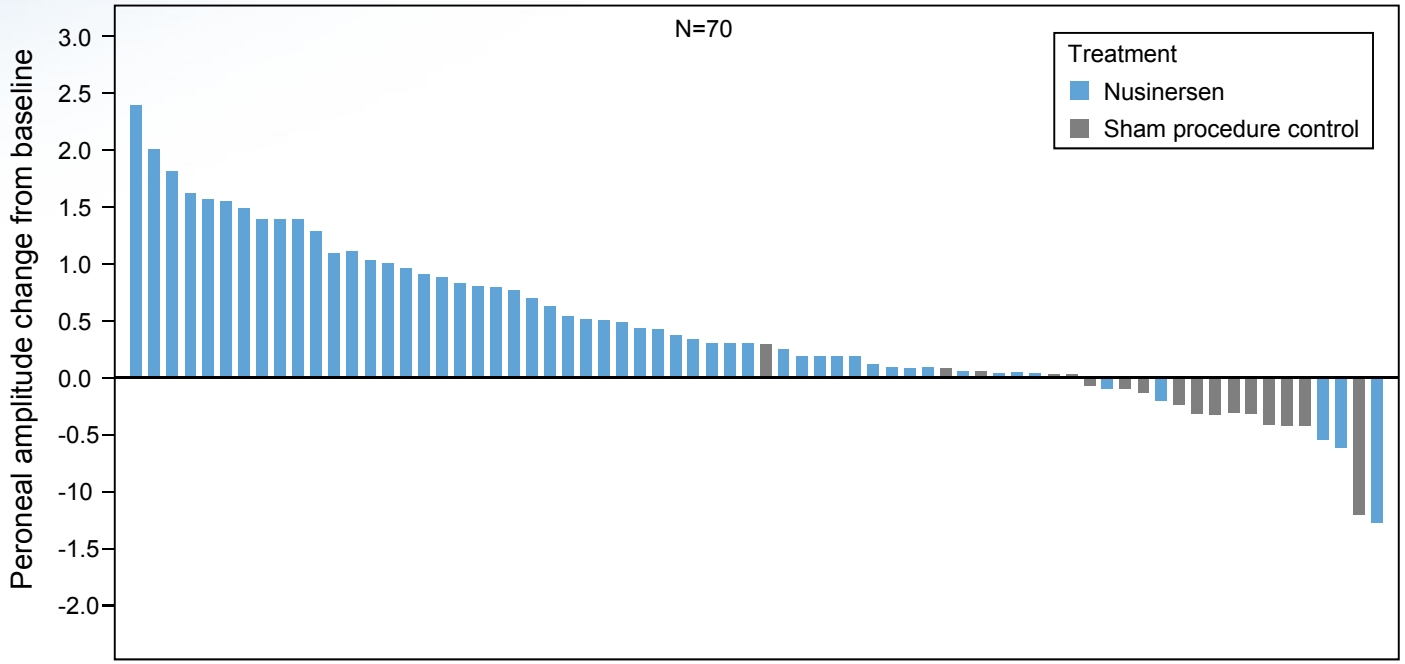
- More improvement was observed in nusinersen-treated patients[a]
- A significantly greater proportion of nusinersen-treated patients[a] were peroneal CMAP responders[b] (36% vs. 5%; nominal *P*=0.0004)



[a]Versus sham control-treated patients. Infants with opportunity for at least a 6-month (Day 183) assessment were included in the analysis; last available assessment of 6-month (Day 183), 10-month (Day 302), or 13-month (Day 394) was used. [b]CMAP responder was defined as an infant with peroneal CMAP amplitude increasing to or maintained at ≥1mV compared to Baseline at the later of the Day 183, 302, or 394 study assessments.

Peroneal CMAP Amplitude at End of Study

- More improvement and less worsening in nusinersen-treated patients[a]
- Similar improvements in ulnar CMAP amplitude were observed



Infants with opportunity for at least a 6-month (Day 183) assessment were included in the analysis; last available assessment of 6-month (Day 183), 10-month (Day 302), or 13-month (Day 394) was used. Shortest bars indicate zero value. Of the 110 infants in the efficacy set, 29 died (nusinersen, n=13; sham procedure control, n=16), 3 withdrew for a reason other than death (nusinersen, n=2; sham procedure control, n=1), and 8 had missing data and were not included in this analysis. [a]Versus sham-control treated infants.

AE Summary: End of Study Analysis

- No AEs were considered related to treatment by the investigator
- All AEs that led to discontinuation were AEs with fatal outcomes

AE, n (%)	Sham procedure control n=41	Nusinersen n=80
Any AE	40 **(98)**	77 **(96)**
AEs leading to discontinuation	16 **(39)**	13 **(16)**
Treatment-related AE[a]	0	0
Possibly treatment-related AE[a]	6 **(15)**	9 **(11)**
Severe AE	33 **(80)**	45 **(56)**
Serious AE	39 **(95)**	61 **(76)**
Serious AE with fatal outcome	16 **(39)**	13 **(16)**
Respiratory, thoracic and mediastinal disorders	12 **(29)**	7 **(9)**
Cardiac disorders	3 **(7)**	2 **(3)**
General disorders	1 **(2)**	2 **(3)**
Nervous system disorders	0	2 **(3)**

AE = adverse event. [a]Investigators assessed whether the AE was related to study drug. A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalisation/prolonged hospitalisation, persistent or significant disability/incapacity or that resulted in a congenital anomaly/birth defect. Severe AEs were defined as symptoms causing severe discomfort, incapacitation or significant impact on daily life; participants reporting >1 AE were counted once for total incidence, using the highest severity.

AE Summary: End of Study Analysis (cont)

AE, n (%)	Sham procedure control n=41	Nusinersen n=80
Common AEs (≥20% in either treatment group)		
Pyrexia	24 **(59)**	45 **(56)**
Constipation	9 **(22)**	28 **(35)**
Upper respiratory tract infection	9 **(22)**	24 **(30)**
Pneumonia	7 **(17)**	23 **(29)**
Respiratory distress	12 **(29)**	21 **(26)**
Respiratory failure	16 **(39)**	20 **(25)**
Atelectasis	12 **(29)**	18 **(23)**
Vomiting	8 **(20)**	14 **(18)**
Acute respiratory failure	10 **(24)**	11 **(14)**
Gastroesophageal reflux disease	8 **(20)**	10 **(13)**
Oxygen saturation decreased	10 **(24)**	10 **(13)**
Cough	8 **(20)**	9 **(11)**
Dysphagia	9 **(22)**	9 **(11)**
Most frequent serious AEs (≥10% in either treatment group)		
Respiratory distress	8 **(20)**	21 **(26)**
Respiratory failure	16 **(39)**	20 **(25)**
Pneumonia	5 **(12)**	19 **(24)**
Atelectasis	4 **(10)**	14 **(18)**
Acute respiratory failure	9 **(22)**	11 **(14)**
Pneumonia aspiration	5 **(12)**	8 **(10)**
Cardiorespiratory arrest	5 **(12)**	5 **(6)**
Respiratory arrest	4 **(10)**	5 **(6)**
Viral upper respiratory tract infection	6 **(15)**	3 **(4)**
Bronchial secretion retention	5 **(12)**	1 **(1)**

Conclusions

- Nusinersen-treated infants demonstrated a clinically and statistically significantly greater percentage of motor milestone responders vs. sham procedure control
  - Greater improvements in CHOP INTEND scores and CMAP amplitude were displayed by nusinersen-treated infants vs. sham procedure control
- Nusinersen-treated infants demonstrated statistically significant increases in event-free survival and overall survival vs. sham procedure control
- Nusinersen was well tolerated and no safety concerns were identified
  - Commonly reported AEs were consistent with those expected in the general population of infants with SMA
- Participants from ENDEAR have been transitioned to the SHINE open-label extension[1]
  - SHINE is enrolling all participants with SMA who were previously entered into and completed nusinersen investigational studies
  - Safety, efficacy and tolerability will be assessed

1. ClinicalTrials.gov, NCT02594124.

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