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Nusinersen Demonstrates Efficacy in Infants With and Without Permanent Ventilation: Final Results From the ENDEAR Study

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Overview

- ENDEAR study design
- Motor response to nusinersen
- Survival and ventilation support
- Motor and CMAP responses in ventilation-dependent participants
- Adverse events

Introduction

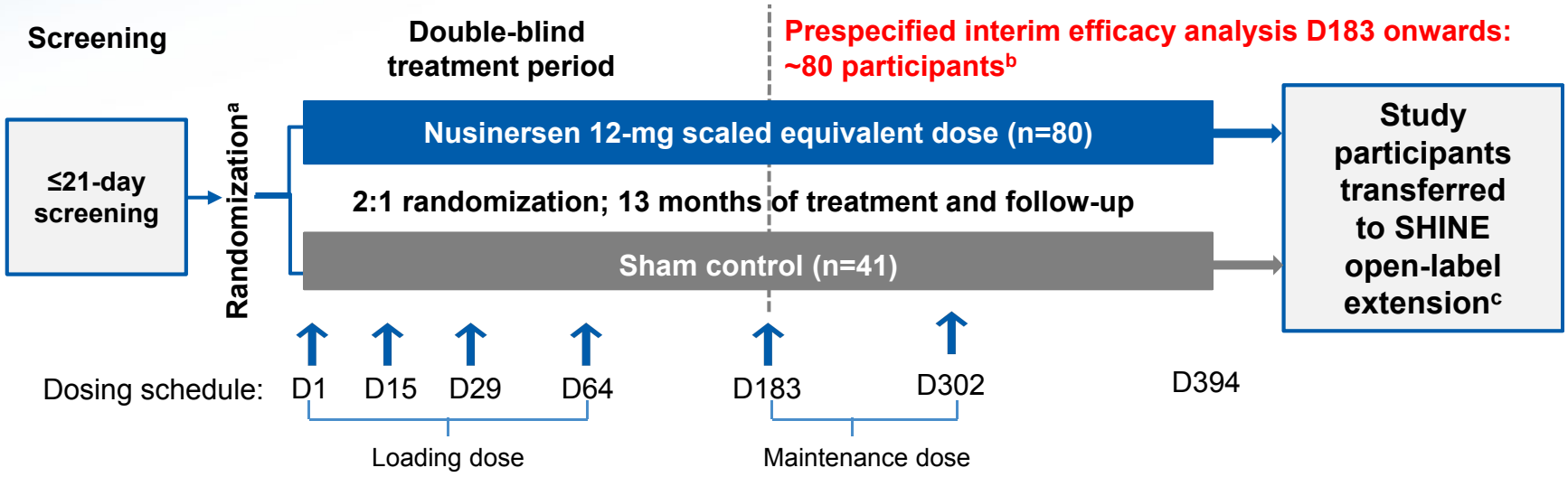
- Spinal muscular atrophy (SMA)
  - SMA is a rare, debilitating, autosomal recessive neuromuscular disorder[1]
  - Caused by insufficient levels of SMN protein[2]
  - Infants with SMA Type I never achieve the ability to sit independently[3,4]
    - Without respiratory support, these infants usually die before the age of 2 years[4,5]
- Nusinersen: an antisense oligonucleotide
  - Modulates splicing of *SMN2* pre-mRNA to promote increased production of full-length SMN protein[6-8]
  - Infants treated with nusinersen had increased SMN protein levels in the spinal cord vs. untreated infants (CS3A[a])[9]
- ENDEAR interim results[b] in infants with SMA
  - 41% of nusinersen-treated vs. 0% of sham control infants were motor milestone responders ($P<0.0001$)

mRNA = messenger RNA; SMN = survival of motor neuron. [a]Interim analysis data cut conducted January 26, 2016. [b]Interim analysis data cut conducted on June 15, 2016.

1. Lunn MR, Wang CH. *Lancet*. 2008;371(9630):2120-2133. 2. Prior TW. *Curr Opin Pediatr*. 2010;22(6):696-702. 3. Oskoui M, Darras BT, De Vivo DC. In: *Spinal Muscular Atrophy*. 2017;1-18. 4. Darras B. *Pediatric Clin North Am*. 2015;62(3):743-766. 5. Wang CH, *et al. J Child Neurol*. 2007;22(8):1027-1049. 6. Hua Y, *et al. Genes Dev*. 2010;24(15):1634-1644. 7. Passini MA, *et al. Sci Transl Med*. 2011;3(72):72ra18. 8. Darras B, *et al. Neuromusc Disord*. 2014;24(9-10):920. 9. Finkel RS, *et al. Lancet*. 2016; 388(10063):3017-3026.

ENDEAR Study Design

- Phase 3, randomized, double-blind, sham-controlled study
- To assess the clinical efficacy, safety, and tolerability of intrathecal nusinersen
- In infants with SMA most likely to develop SMA Type I
- Key eligibility criteria: genetic diagnosis of SMA, 2 copies of *SMN2* gene, onset of SMA symptoms at age ≤6M and age ≤7M, with no hypoxemia



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 June 15, 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.

ENDEAR Primary Endpoint: Definition of HINE Motor Milestone Responders

Modified section 2 of the HINE[1]

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

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

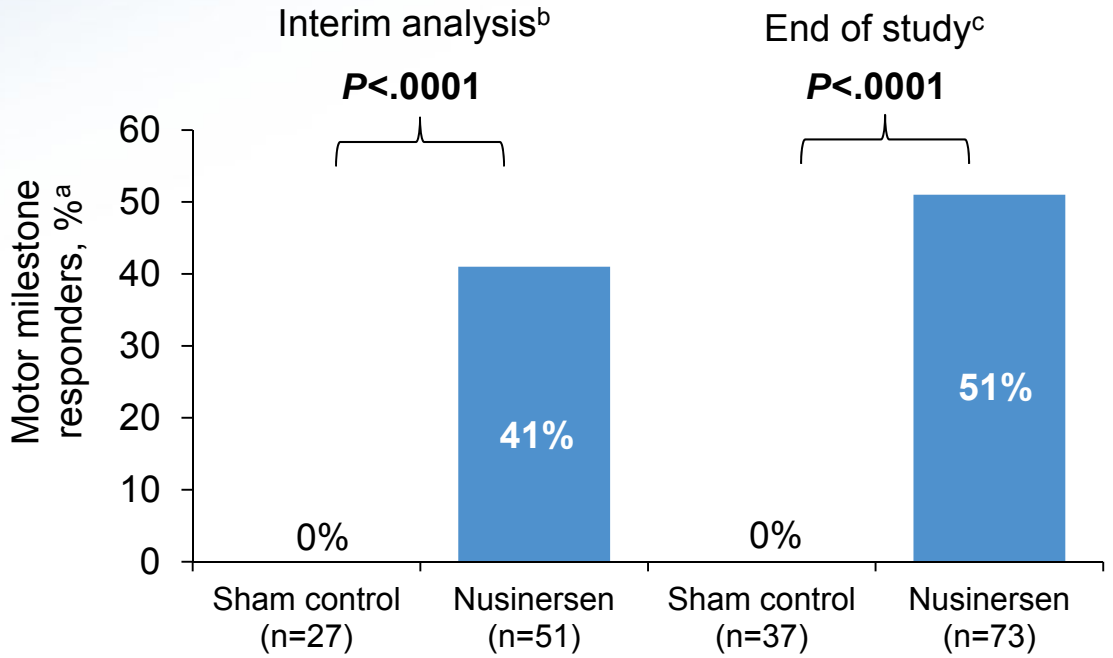
Worsening: ≥2-point worsening in ability to kick (or zero score), or ≥1-point worsening in any other milestone, excluding voluntary grasp

- **Motor milestone responder definition[a]:** more HINE categories with improvement than worsening
  - Participants who died or withdrew were counted as nonresponders

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

Motor Milestone Responders: Interim and End of Study

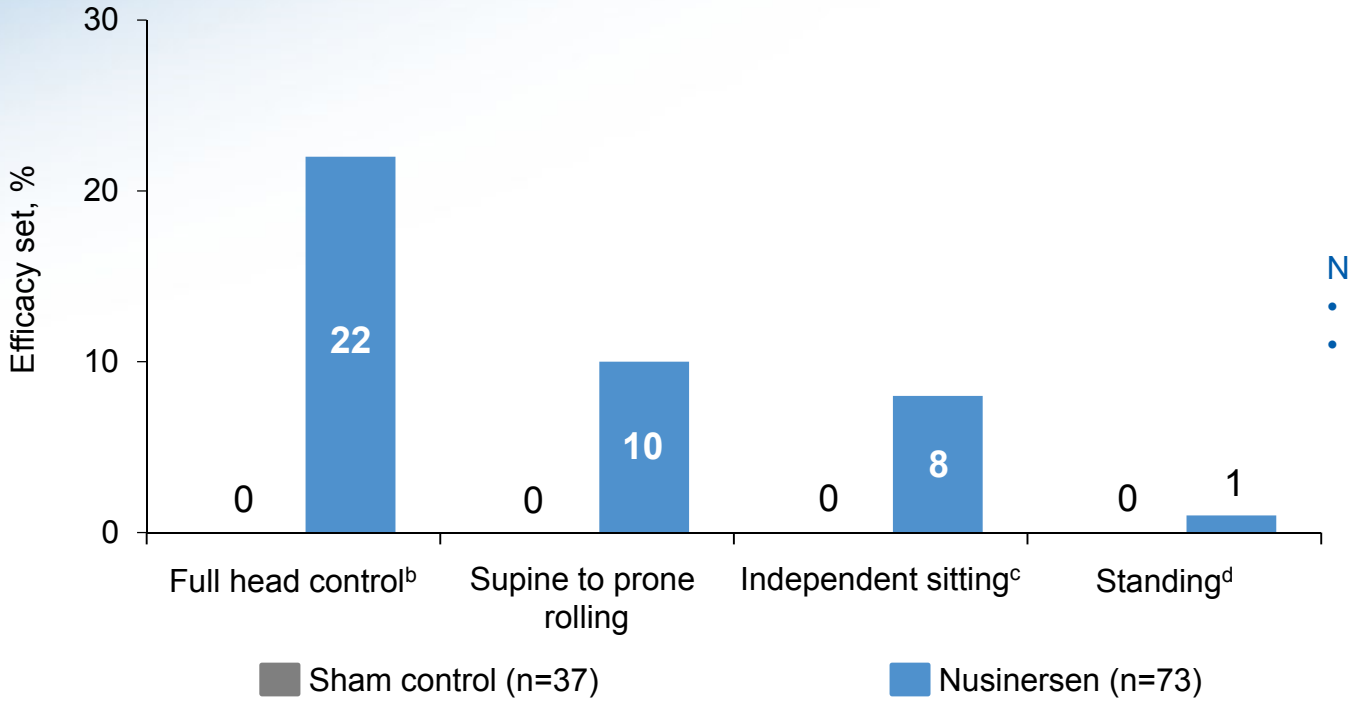
- Nusinersen-treated infants demonstrated continued improvement



[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.

Quality of Motor Responses at End of Study

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

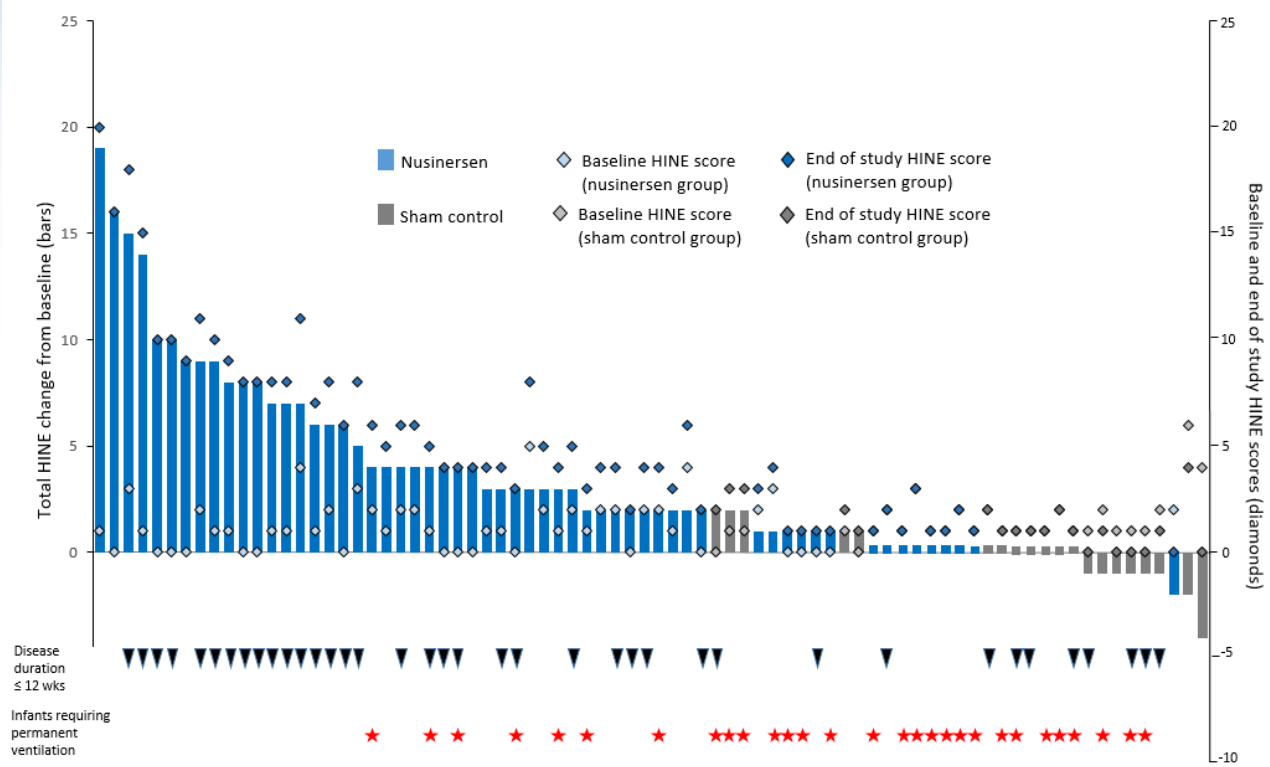


Nusinersen-treated infants achieved:
- Stable sit: 5%
- Pivots (rotate) sit: 3%

[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.

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 control



[a]Total motor milestone change from baseline to later of Day 183, 302, 394. n=78. Shortest bars indicate zero value. Of the 110 infants in the efficacy set, 29 died (nusinersen, n=13; sham control, n=16) and 3 withdrew for a reason other than death (nusinersen, n=2; sham control, n=1) and were not included in this analysis. Light diamonds indicate baseline HINE scores. Dark diamonds indicate end of study HINE scores. Arrowheads indicate infants with disease durations ≤12 weeks at screening. Red stars indicate infants who required permanent ventilation.

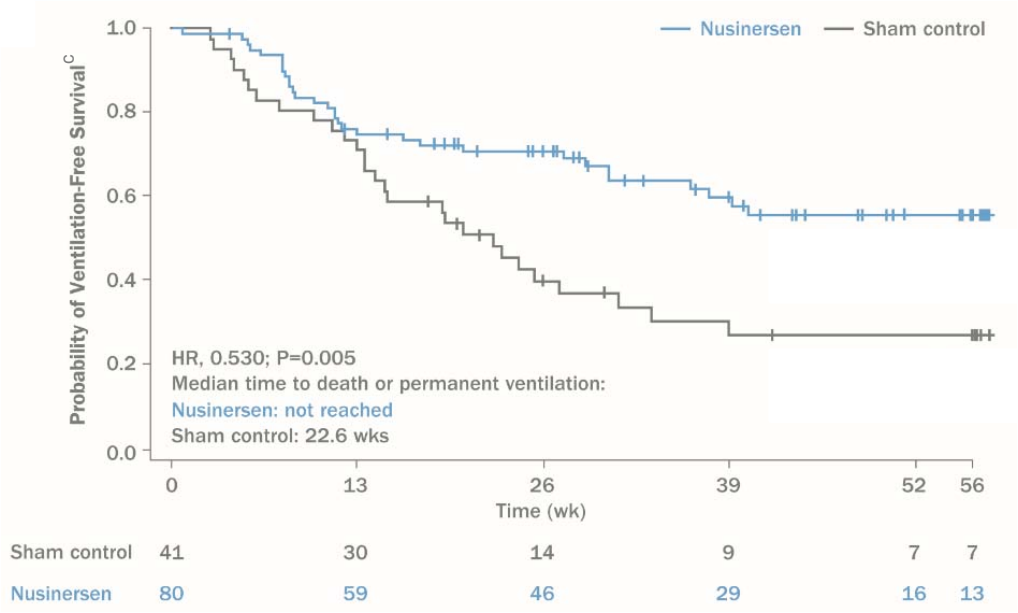
Event-Free Survival and Permanent Ventilation

- Event-free survival
  - Time to death or permanent ventilation
- Permanent ventilation
  - Tracheostomy or ≥16 hours ventilatory support per day for >21 days in the absence of an acute reversible event in the determination of an independent endpoint adjudication committee

Event-Free Survival at End of Study

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

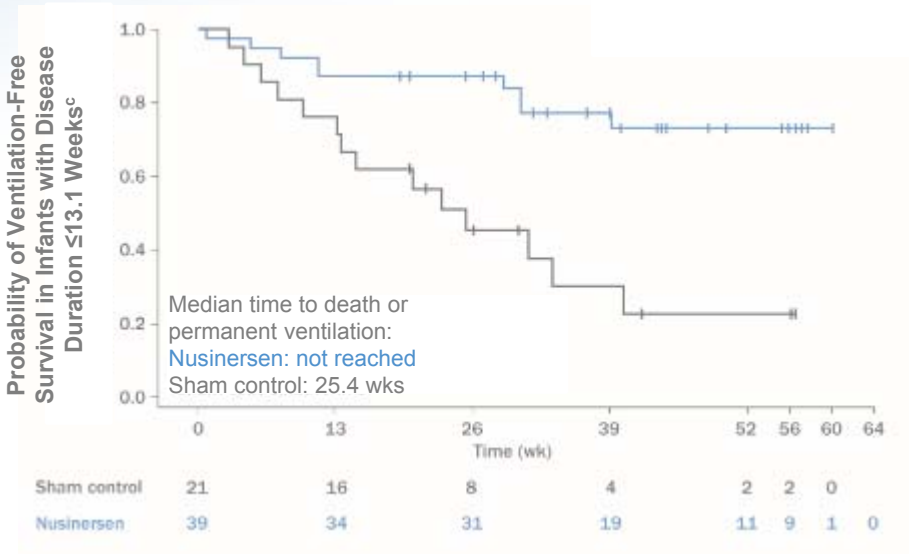
Outcome	Sham control	Nusinersen
Death or permanent ventilation, n (%)	28 (68)	31 (39)
Alive and no permanent ventilation, n (%)	13 (32)	49 (61)



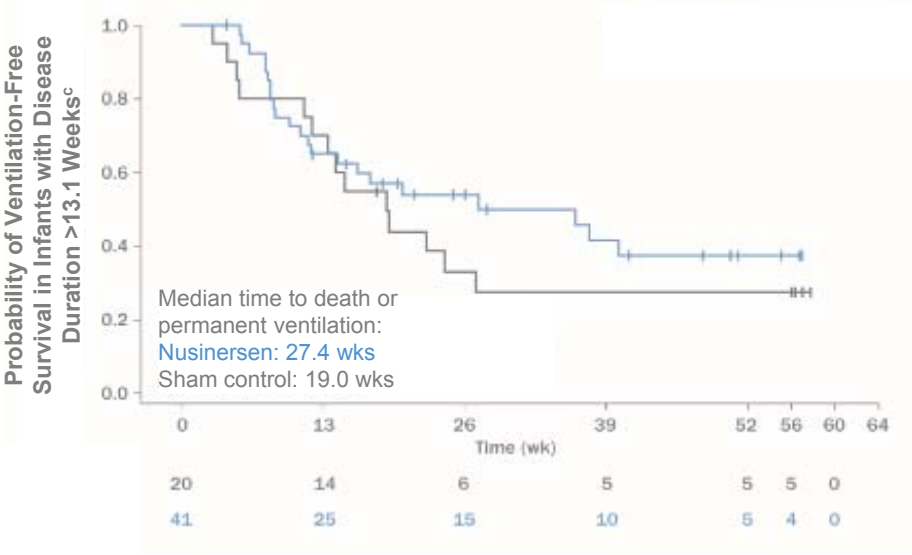
HR = hazard ratio. All infants randomized who received ≥1 dose of nusinersen or sham control were included in the analysis. [a]Event-free survival = time to death or permanent ventilation (permanent ventilation was defined as tracheostomy or ≥16 hours ventilatory support per day for >21 days in the absence 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.

Event-Free Survival in Infants With Disease Duration Below and Above the Study Median

- In infants with a median disease duration ≤13.1 weeks, 23% of nusinersen-treated vs. 67% of sham control infants died or required permanent ventilation
- HR = 0.24[a]; nominal *P*<0.001[b]



- In infants with a median disease duration >13.1 weeks, 54% of nusinersen-treated vs. 70% of sham control infants died or required permanent ventilation
- HR = 0.84[a]; nominal *P*=0.40[b]

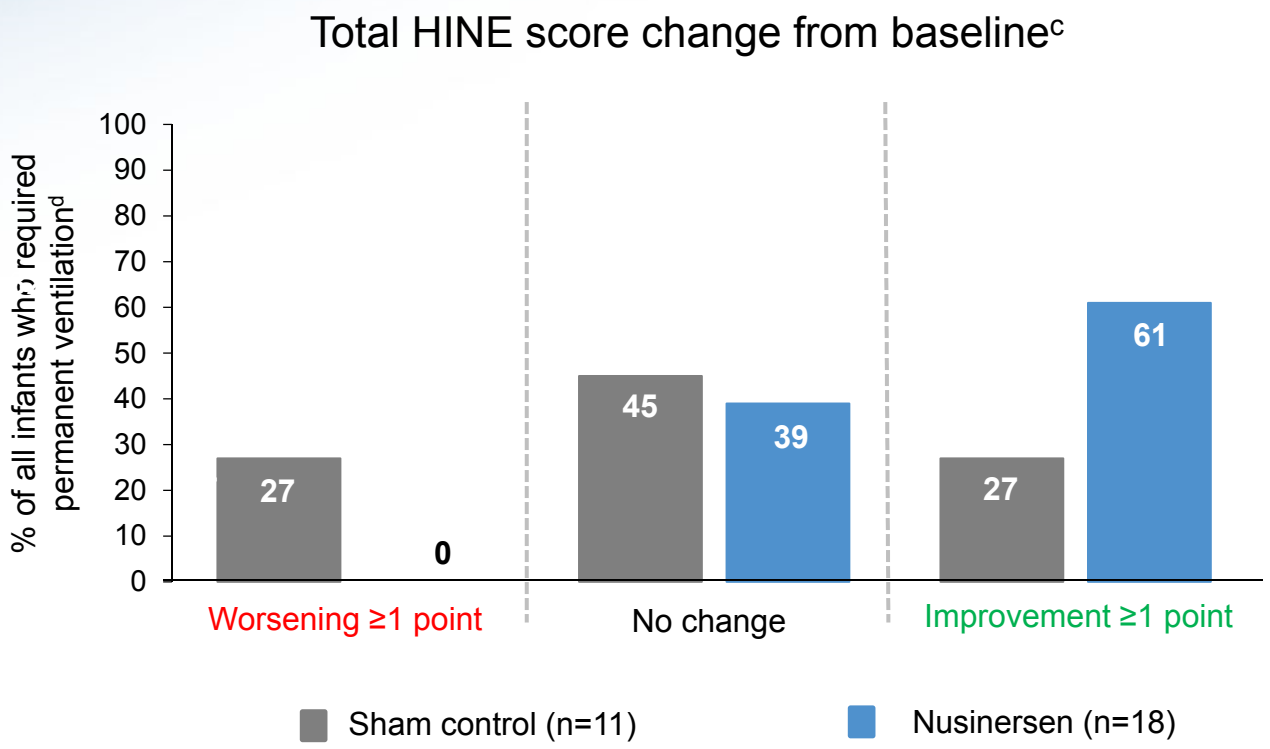


Nusinersen Sham control

A hazard ratio (HR) <1 indicates lower risk of event for the nusinersen group. The HR is calculated based on Cox regression adjusted for each infant's disease duration at screening.
[a]Based on Cox proportional hazards model adjusted for each infant's disease duration at screening. [b]Based on log-rank test. [c]Estimated from the Kaplan-Meier method.

Infants Who Required Permanent Ventilation[a]: Total HINE Scores

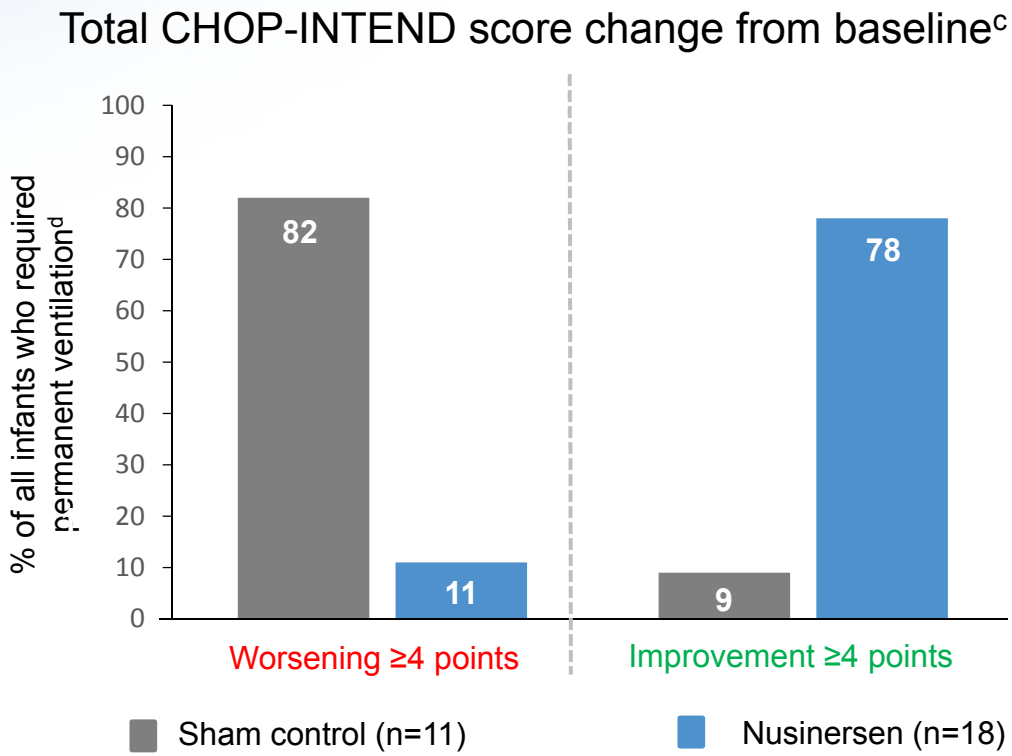
- Nusinersen-treated infants demonstrated more improvement and less worsening in total HINE scores[b]



HINE = Hammersmith Infant Neurological Examination. [a]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]Versus sham control–treated patients. [c]Change from baseline to last assessment after permanent ventilation. [d]One sham control infant died on Day 122 and was not included in the analysis.

Infants Who Required Permanent Ventilation[a]: CHOP INTEND Scores

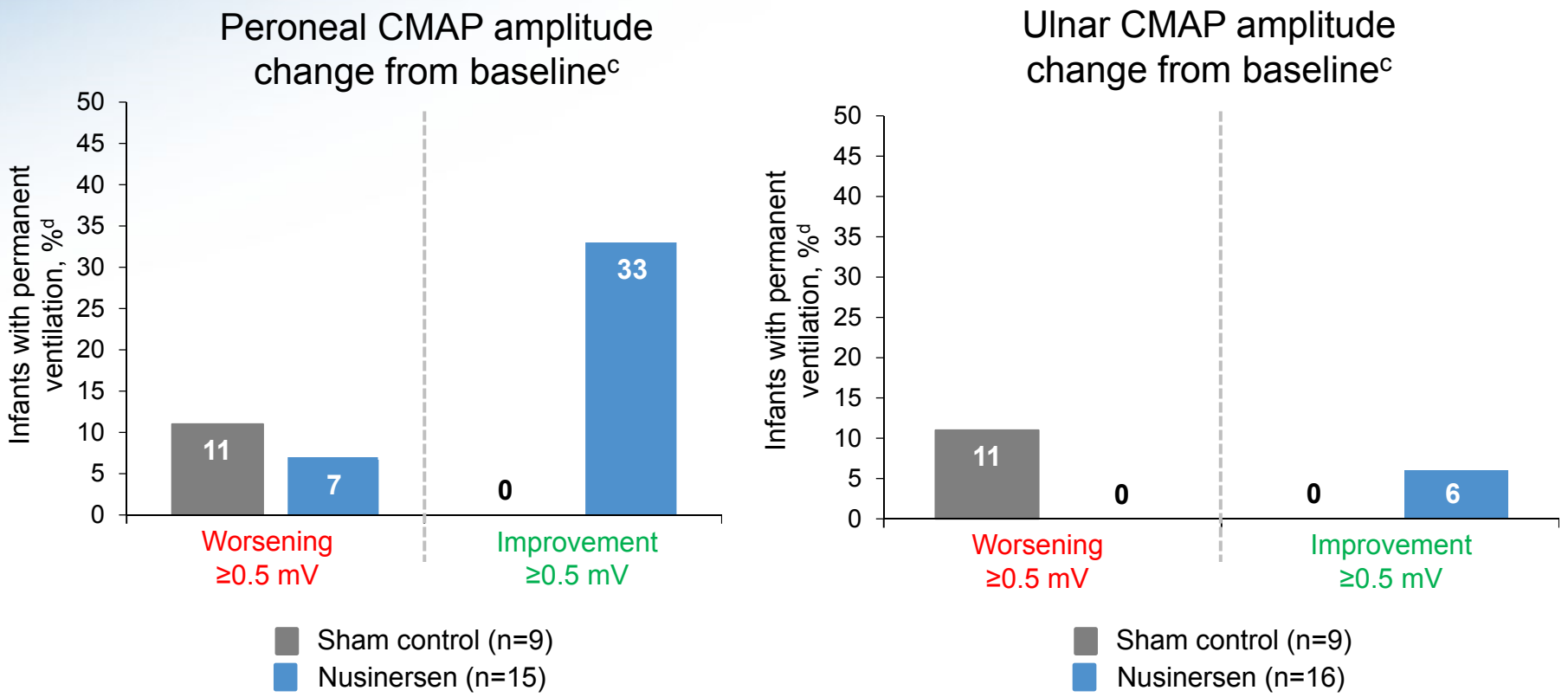
- Nusinersen-treated infants demonstrated more improvement and less worsening in CHOP INTEND scores[b]



CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. An increase of ≥4 points in CHOP INTEND score from baseline is generally considered to be outside the range of test variability. [a]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]Versus sham control–treated patients. [c]Change from baseline to last assessment after permanent ventilation. [d]One sham control infant died on Day 122 and was not included in the analysis.

Infants Who Required Permanent Ventilation[a]: CMAP Amplitude

- Nusinersen-treated infants demonstrated more improvement and less worsening in measures of motor function[b]



CMAP = compound muscle action potential. [a]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]Versus sham control–treated patients. [c]Change from baseline to last assessment after permanent ventilation. [d]Percentages do not total 100 because infants with changes <0.5 mV were not counted. One sham control infant died on Day 122 and was not included in the analysis.

AE Summary: End of Study Analysis

AE, n (%)	Sham 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)
Treatment-related serious AE[a]	0	0
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, medical or surgical intervention to prevent one of the other outcomes listed in this definition, 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.

Conclusions

- Nusinersen-treated infants with SMA, most likely to develop SMA Type I, demonstrated clinically and statistically significant increases in multiple measures of motor function and in event-free and overall survival vs. sham control
- Fewer nusinersen-treated vs. sham control infants required permanent ventilation
- Among infants with disease durations below the study median, those treated with nusinersen demonstrated significantly prolonged event-free survival vs. those treated with sham control
- Among infants who required permanent ventilation, those treated with nusinersen achieved more motor milestones and exhibited higher CHOP INTEND scores vs. those treated with sham control
- Nusinersen demonstrated a favorable benefit-risk profile

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

Acknowledgments

- The authors thank the patients who are participating in this study and their parents/guardians and family members, without whom this effort cannot succeed
- The authors thank the ENDEAR study investigators
- The authors also thank all the contributors to the ENDEAR study, including the clinical monitors, study coordinators, physical therapists, pharmacists, and laboratory technicians
- Patient advocacy groups assisted in promoting awareness of this study

Backup

Participant Eligibility Criteria

Key inclusion criteria

- Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age
- Genetic diagnosis of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation
- ≤7 months of age at screening[a]
- 2 *SMN2* copies

Key exclusion criteria

- Hypoxaemia (oxygen saturation of <96% awake or asleep without ventilation support)
- Signs or symptoms of SMA present at birth or within ≤1 week after birth
- Untreated or treated active infection
- Previous use of an investigational drug for the treatment of SMA

[a]Additionally, a gestational age of 37–42 weeks was required.

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; ITT = intent to treat. [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.

Permanent Ventilation Requirement at End of Study

- The risk of permanent ventilation was 34% lower in nusinersen-treated vs. sham control infants
  - Estimated percentage of nusinersen vs. sham control infants who required permanent ventilation[a]: HR=0.66; *P*=0.1329[b]

A hazard ratio (HR) <1 indicates lower risk of event for the nusinersen group. All infants randomized who received ≥1 dose of nusinersen or sham control were included in the analysis. Death was not counted as an event and data were censored at the time of death. Only surviving infants were considered at each time point. [a]Based on the Kaplan-Meier product limit method. [b]Based on log-rank test stratified by disease duration.

ENDEAR Primary Endpoint: Definition of HINE Motor Milestone Responders

Modified section 2 of the HINE[1]

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

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 died or withdrew were counted as nonresponders

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

Baseline Disease Characteristics: ITT Population

Characteristic	Sham 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 receiving ventilation support, n (%)	6 (15)	21 (26)

ITT = intention-to-treat.

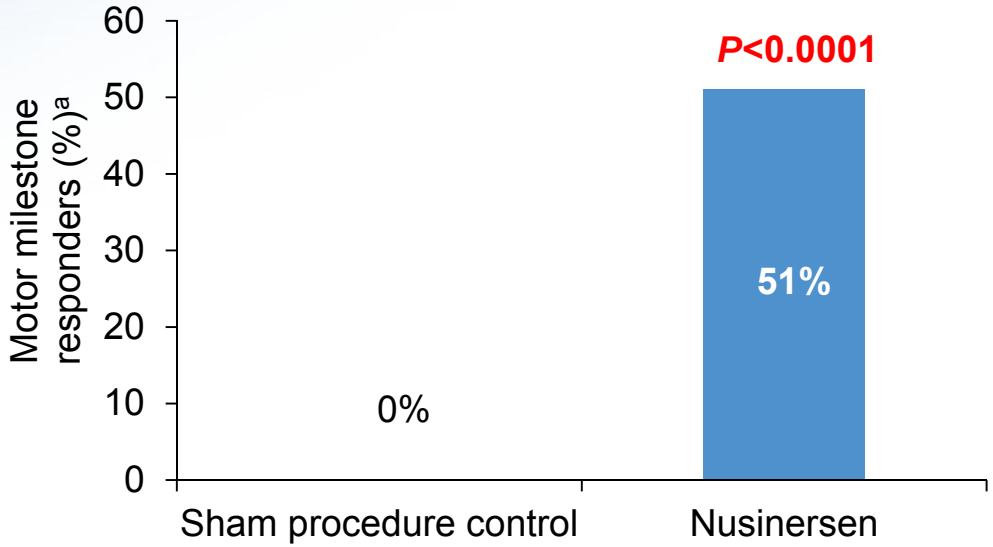
Baseline Disease Characteristics: ITT Population

Characteristic	Sham procedure control n=41	Nusinersen n=80
Median (range) gestational age, wk	40 (37, 42)	39 (36, 41)
Geographic region, n (%)		
North America	22 **(54)**	38 **(48)**
Europe	17 **(41)**	30 **(38)**
Asia-Pacific	2 **(5)**	12 **(15)**
Ethnicity, n (%)		
Hispanic or Latin American	4 **(10)**	12 **(15)**
Not Hispanic or Latin American	37 **(90)**	68 **(85)**
Median (range) age at screening, d	190 (20, 211)	152 (32, 210)
Age at symptom onset, wk, n (%)		
≤12	32 **(78)**	72 **(90)**
>12	9 **(22)**	8 **(10)**
Disease duration, wk, n (%)		
≤12	18 **(44)**	34 **(43)**
>12	23 **(56)**	46 **(58)**
Mean (SD) time on ventilation support at baseline,[a] h	6.8 **(4.2)**	8.4 **(4.3)**

ITT = intent to treat. [a]Based on those infants requiring ventilator support at baseline.

Motor Milestone Responders at End of Study

- Highly clinically and statistically significant percentage of motor milestone responders



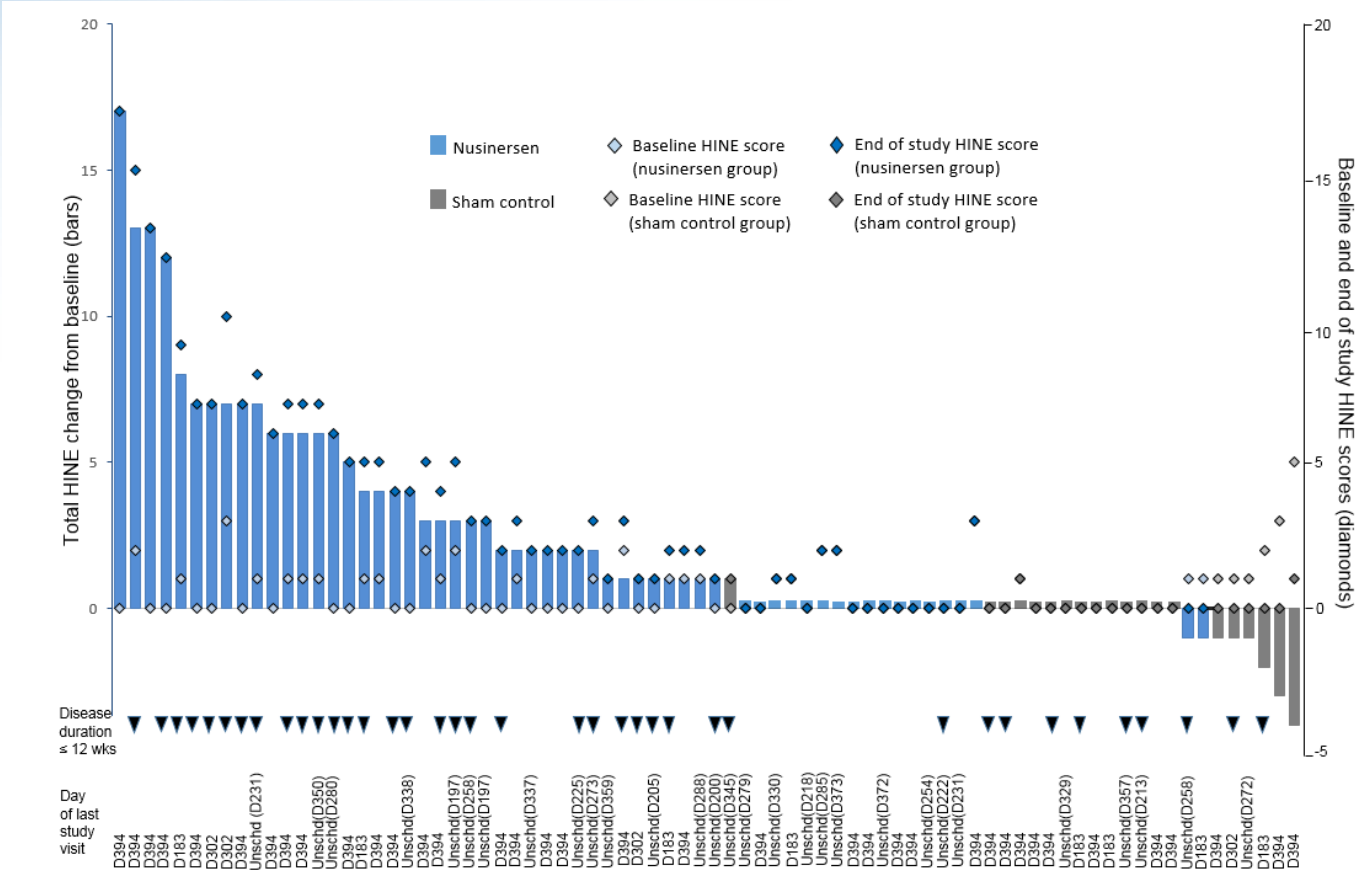
Motor milestone responders, %	Sham procedure control	Nusinersen	*P* value
6-month visit (n=110)	5	41	<0.0001
10-month visit (n=77)	0	45	<0.0001
13-month visit (n=58)	0	54	<0.0001

[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.

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

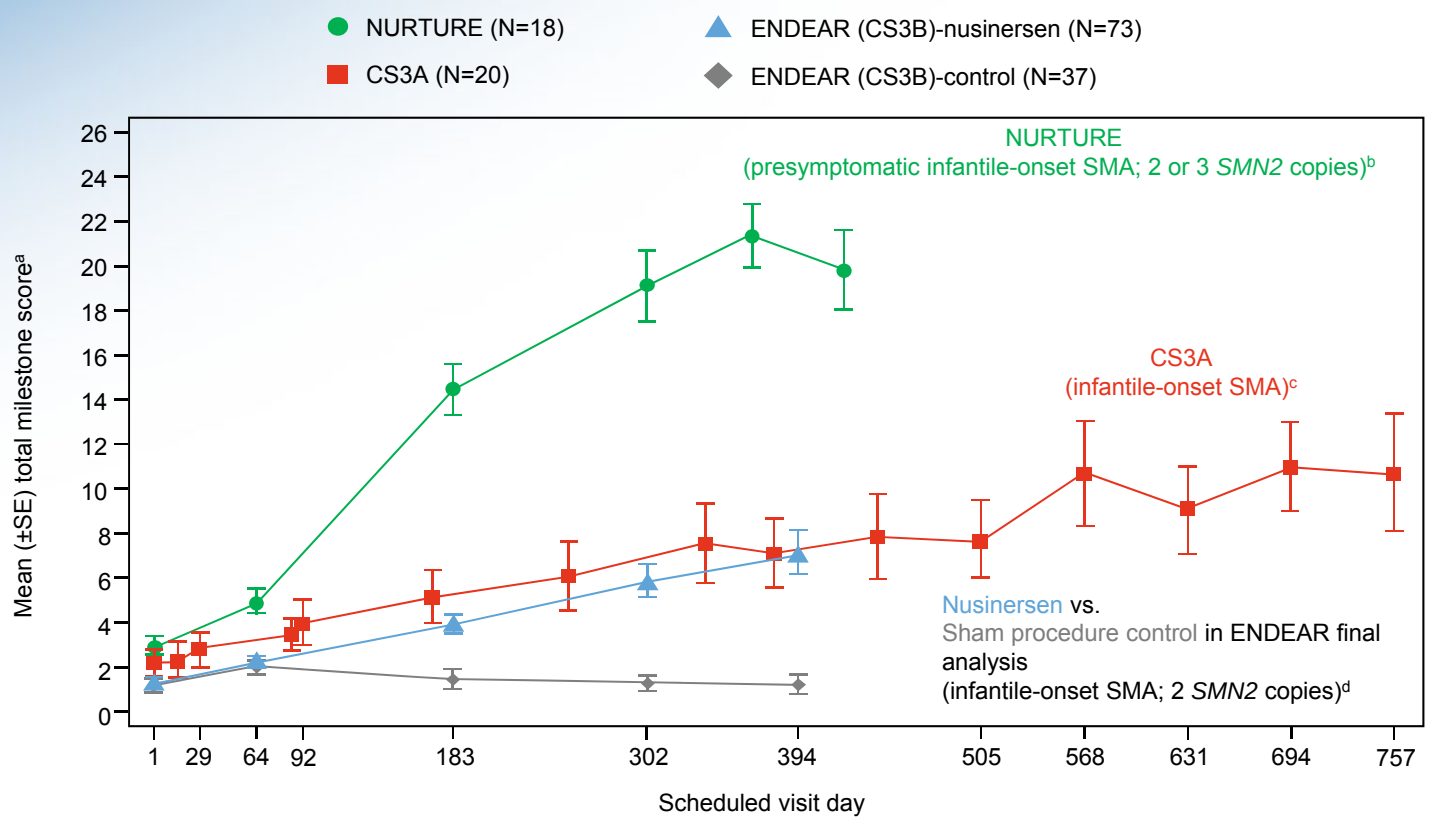
Please note, this slide has builds

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



[a]Total motor milestone change from baseline to later of Day 183, 302, 394. n=78. Shortest bars indicate zero value. Of the 110 infants in the efficacy set, 29 died (nusinersen, n=13; sham control, n=16) and 3 withdrew for a reason other than death (nusinersen, n=2; sham control, n=1) and were not included in this analysis. Light diamonds indicate baseline HINE scores. Dark diamonds indicate end of study HINE scores. Unschd = unscheduled. Arrowheads indicate infants with disease durations ≤12 weeks at screening.

Change in HINE Motor Milestone Scores Across Studies



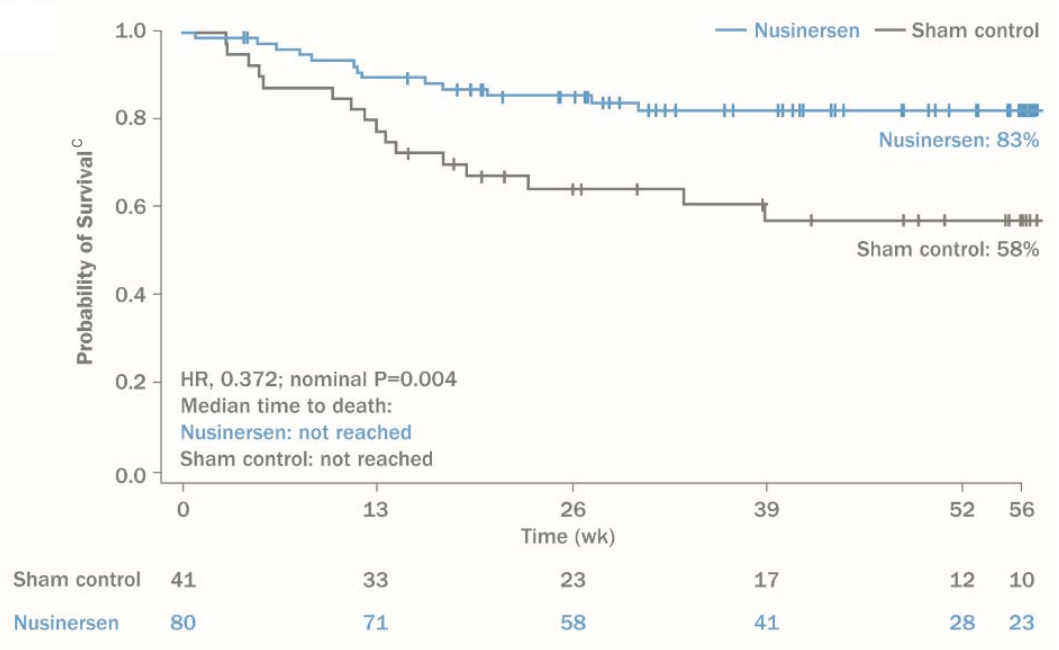
NURTURE	18		18				16				11		9	5									
CS3A	20	20	19		19	18		17			17			14	15		13		14		11	11		10		7
CS3B-nusinersen	73			66				59				36			26								
CS3B-control	37			30				23				16			11								

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.

Overall Survival at End of Study

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

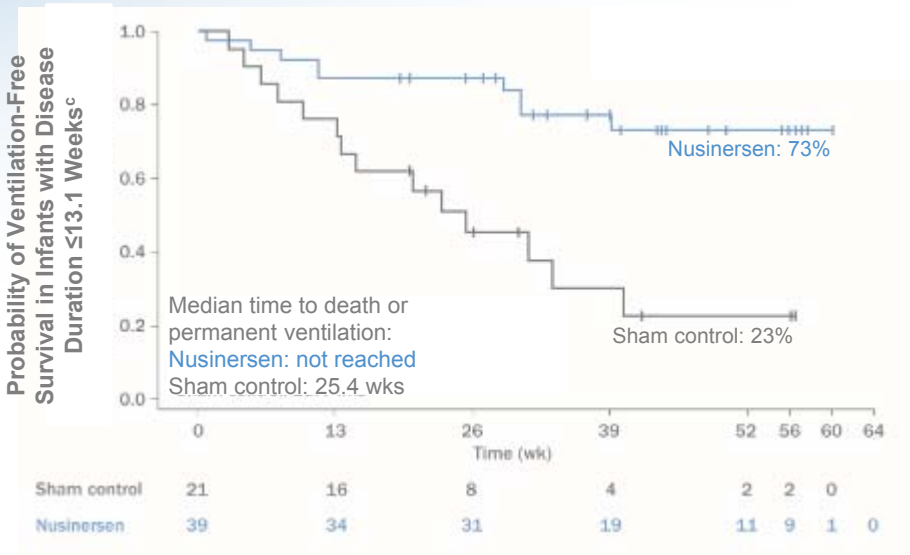
Outcome	Sham procedure control	Nusinersen
Death, n (%)	16 (39%)	13 (16%)
Alive, n (%)	25 (61%)	67 (84%)

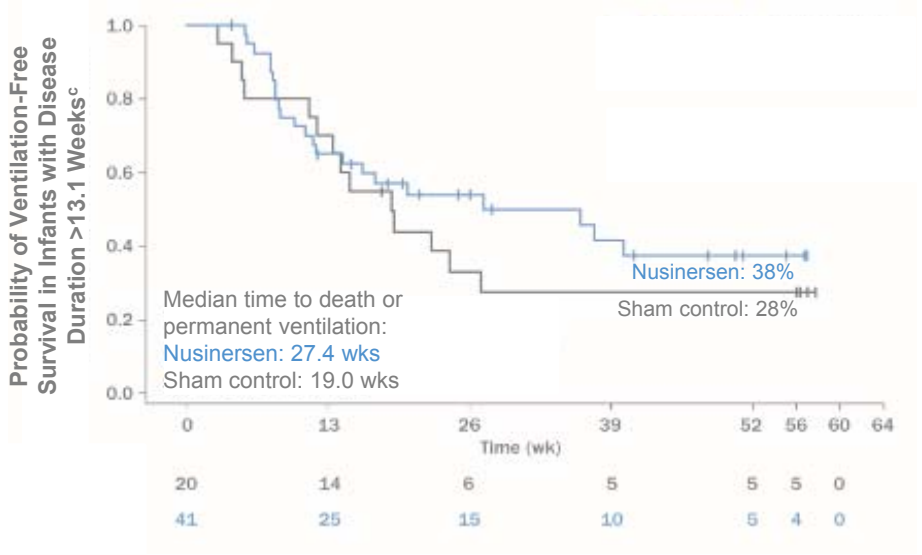


HR = hazard ratio. All infants randomized who received at least one dose of nusinersen or sham procedure were included in the analysis [a]Versus sham control-treated patients. [b]Log-rank statistical test stratified by disease duration. [c]Estimated from the Kaplan-Meier method.

Event-Free Survival in Infants With Disease Duration Below and Above the Study Median

- In infants with a median disease duration ≤13.1 weeks, HR = 0.24[a]; nominal *P*<0.001[b]
- In infants with a median disease duration >13.1 weeks, HR = 0.84[a]; nominal *P*=0.40[b]





Nusinersen — Sham control

A hazard ratio (HR) <1 indicates lower risk of event for the nusinersen group. The HR is calculated based on Cox regression adjusted for each infant's disease duration at screening.
[a]Based on Cox proportional hazards model adjusted for each infant's disease duration at screening. [b]Based on log-rank test. [c]Estimated from the Kaplan-Meier method.

Permanent Ventilation Requirement at End of Study

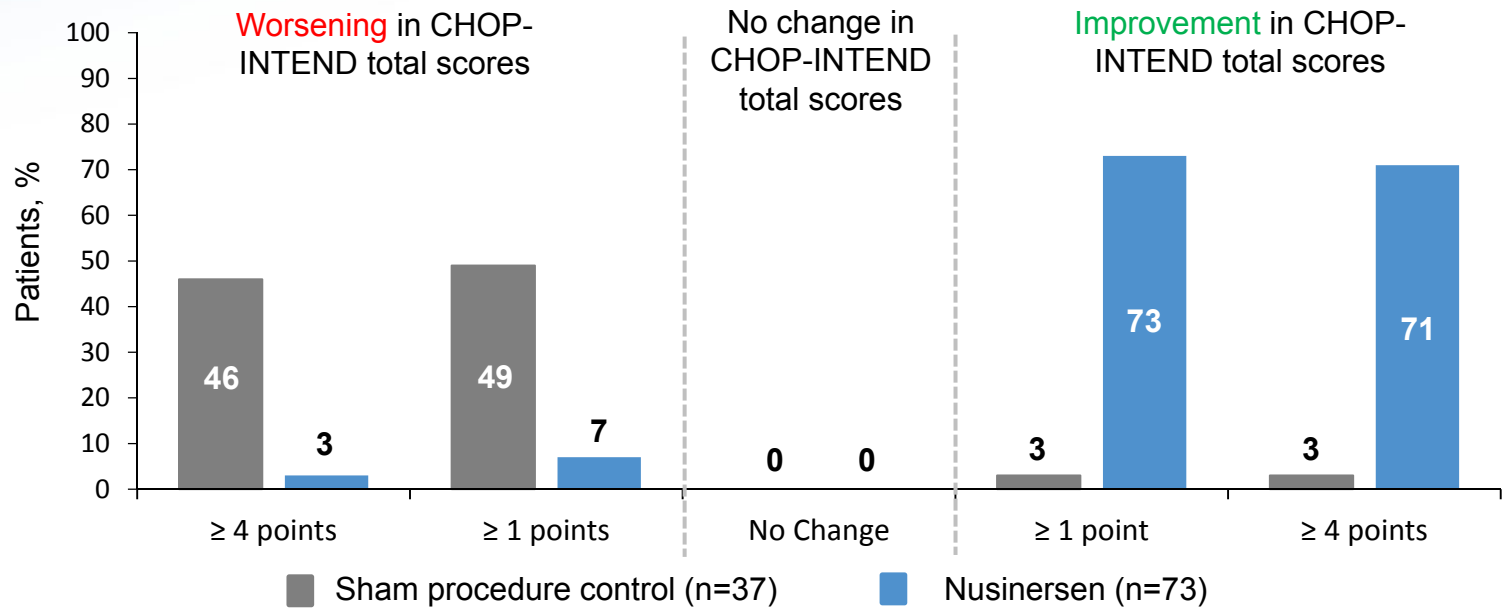
- The risk of permanent ventilation was 34% lower in nusinersen-treated vs. sham control infants (*P*=0.1329)

Estimated % of patients who required permanent ventilation[a]	Sham 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 control		0.66[b]

All infants randomized who received ≥1 dose of nusinersen or sham control were included in the analysis. Death was not counted as an event and data were censored at the time of death. Only surviving infants were considered at each time point. [a]Based on the Kaplan-Meier product limit method. [b]*P*=0.1329 based on log-rank test stratified by disease duration.

CHOP INTEND Motor Function Scores at End of Study

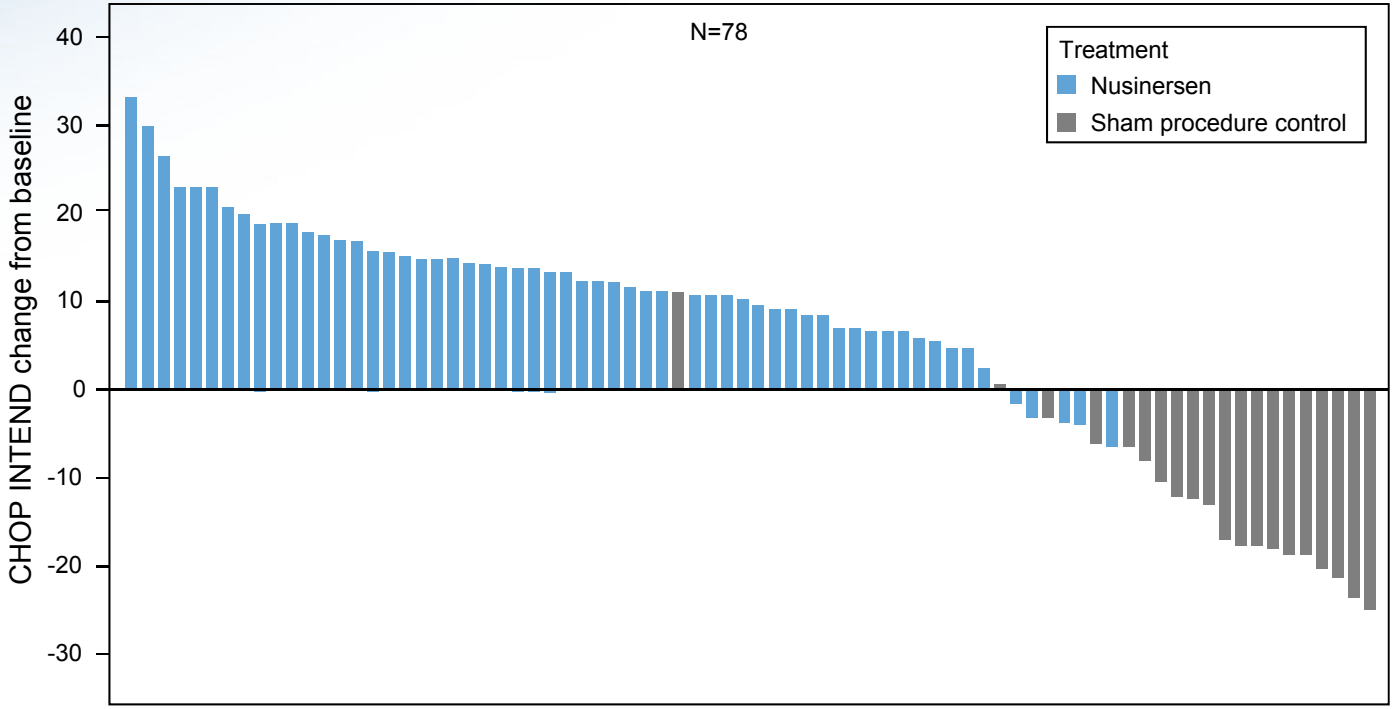
- More improvement and less worsening in nusinersen-treated patients[a]
- A significantly greater proportion of nusinersen-treated patients[a] were CHOP INTEND responders (≥4-point improvement;[b] 71% vs. 3%; *P*<0.0001)



CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. [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

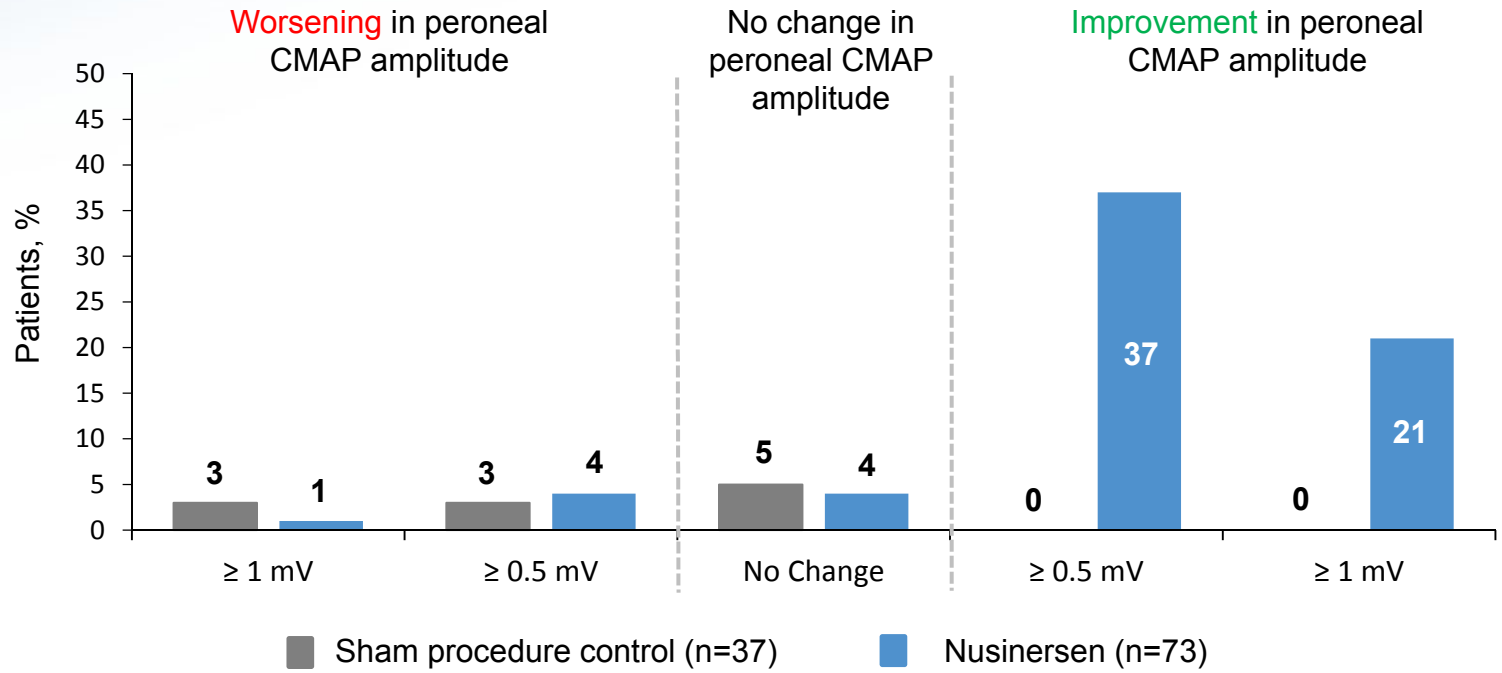
- More improvement and less worsening in motor function assessment (CHOP INTEND) in nusinersen-treated patients[a]



CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders . 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=78. 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.

Peroneal CMAP Amplitude at End of Study

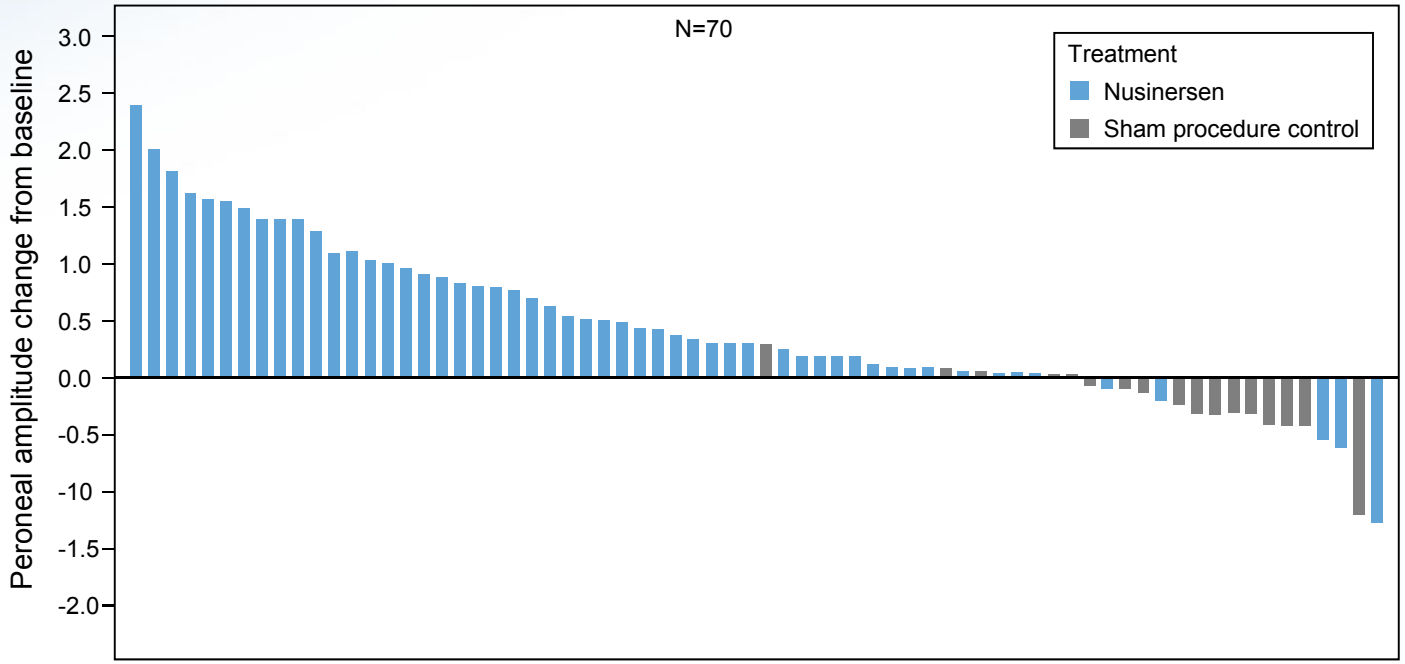
- More improvement was observed in nusinersen-treated patients[a]
- A significantly greater proportion of nusinersen-treated patients[a] were peroneal CMAP responders[b] (36% vs. 5%; nominal *P*=0.0004)



CMAP = compound muscle action potential. [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



CMAP = compound muscle action potential. 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 (nusinersen, n=5; sham procedure control, n=3) and were not included in this analysis. [a]Versus sham-control treated infants.

AE Summary: End of Study Analysis (cont)

AE, n (%)	Sham 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)

AE = adverse event.