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Efficacy and Safety of Nusinersen in Children With Later-Onset Spinal Muscular Atrophy (SMA): End of Study Results From the Phase 3 CHERISH Study

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Disclosures

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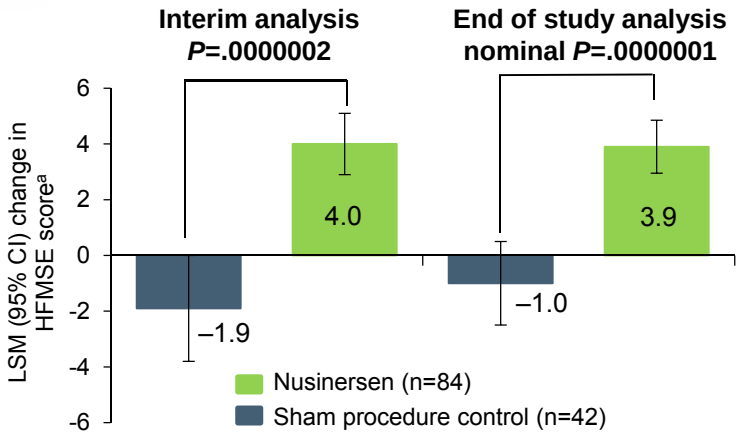
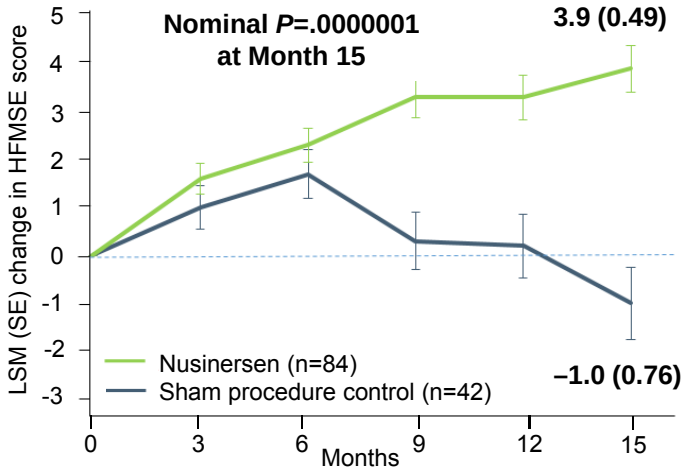
CHERISH: Background and Primary Endpoint

- Nusinersen has demonstrated:
  - Significant and clinically meaningful efficacy on measures of motor function[1-3]
  - Favorable safety across multiple SMA populations[1-3]
  - Greater event-free survival in infants with infantile-onset SMA (vs. sham procedure control)[1]
- CHERISH was a Phase 3, global, randomized, double-blind, sham procedure–controlled study to assess the clinical efficacy and safety of intrathecal nusinersen in children with later-onset SMA
  - Baseline characteristics of children in CHERISH were consistent with the general population of children with later-onset SMA[4]
  - For study design details, see poster P3.184 (presentation on April 25, 5:30–7:00 PM)

Primary endpoint: change from baseline to Month 15 in HFMSE score



End of study analysis
Mean change over time at end of study

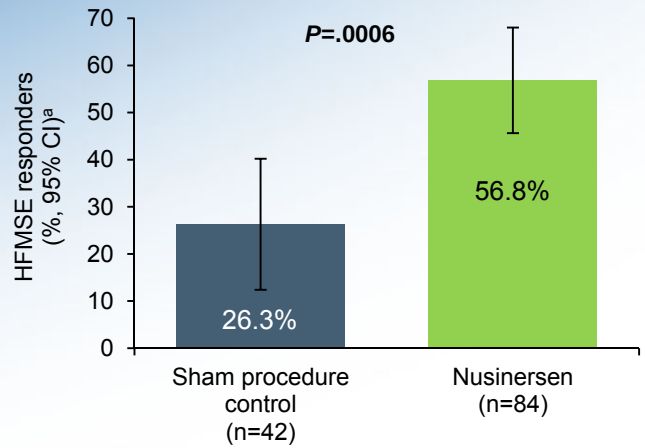


HFMSE = Hammersmith Functional Motor Scale Expanded; LSM = least-squares mean; SMA = spinal muscular atrophy. Descriptions of statistical analyses in notes sections of slide. [a]From baseline to Month 15. Interim analysis: observed: sham procedure control, n=19; nusinersen, n=35; imputed: sham procedure control, n=23; nusinersen n=49. End of study analysis: observed: sham procedure control, n=34; nusinersen, n=66; imputed: sham procedure control n=8, nusinersen n=18.

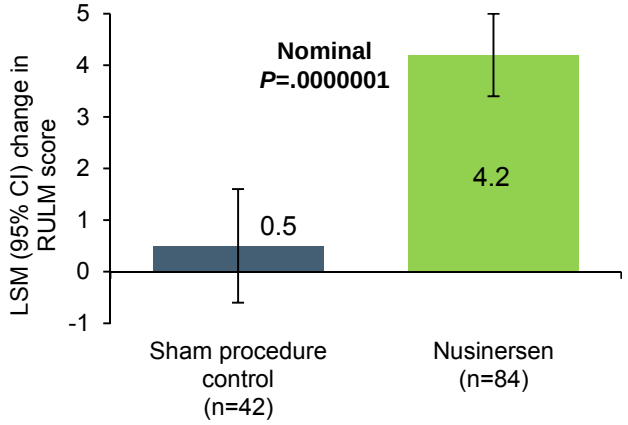
1. Finkel RS, *et al.* Primary efficacy and safety results from the phase 3 ENDEAR study of nusinersen in infants diagnosed with spinal muscular atrophy (SMA). Presented at: 43rd Annual Congress of the British Paediatric Neurology Association; January 11-13, 2017; Cambridge, UK. 2. Finkel RS, *et al. Lancet.* 2016;388(10063):3017-3026. 3. Bertini E, *et al*. Nusinersen in pre-symptomatic infants with spinal muscular atrophy (SMA): interim efficacy and safety results from the phase 2 NURTURE study. Presented at: 21st International Congress of the World Muscle Society; October 4-8, 2016; Granada, Spain. 4. Wang CH *et al.*; Participants of the International Conference on SMA Standard of Care. *J Child Neurol.* 2007;22(8):1027-1049.

CHERISH: Secondary Endpoints and Safety

Proportion of HFMSE responders[a]



Change from baseline in RULM[c]



WHO motor milestones at Month 15

Endpoint	Sham procedure control n=42	Nusinersen n=84	Treatment difference
% (95% CI) who achieved any new motor milestone[b]	5.9 (0.7, 19.7)	19.7 (10.9, 31.3)	***P*=.0811**
LSM (95% CI) no. of new motor milestones achieved per child	–0.2 (–0.4, 0.0)	0.2 (0.1, 0.3)	**Nominal *P*=.0001**
% (95% CI) able to stand alone	2.9 (0.07, 15.3)	1.5 (0.04, 8.2)	**Nominal *P*>.9999**
% (95% CI) able to walk with assistance	0 (0, 10.3)	1.5 (0.04, 8.2)	**Nominal *P*>.9999**

Treatment-emergent AEs

AE, n (%)	Sham procedure control n=42	Nusinersen n=84
Any AE	42 (100)	78 (93)
Severe AE	3 (7)	4 (5)
AE possibly related or related to drug[d]	4 (10)	24 (29)
AE related to drug[d]	0	1 (1)[e]
SAE	12 (29)	14 (17)
Discontinued treatment due to an AE	0	0
AEs observed at a ≥5% higher frequency in nusinersen group 72 h after drug administration		
Back pain	0	19 (23)
Headache	1 (2)	22 (26)
Vomiting	1 (2)	11 (13)
Epistaxis	0	4 (5)

AE = adverse event; RULM = Revised Upper Limb Module; SAE = serious adverse event; WHO = World Health Organization. For study design details, see poster P3.184 (presentation on April 25, 5:30–7:00 PM). Descriptions of statistical analyses in notes section of slide. [a]HFMSE responder was defined as a child with a ≥3-point increase from baseline in HFMSE score at Month 15. If a child is discontinued due to treatment failure or death, the child is classified as a nonresponder irrespective of imputed value. Observed data: sham procedure control, n=34; nusinersen, n=66. [b]Children who maintained baseline WHO motor milestones at Month 15 and achieved ≥1 new milestone. Children who discontinued due to treatment failure or death before Month 15 were not included. [c]Observed data: sham procedure control, n=34; nusinersen, n=66. [d]Investigator-assessed relation to study drug. [e]One child had postsedation nausea (procedural nausea) considered by the investigator to be related to study treatment.

Conclusions

- Nusinersen-treated children demonstrated significant and clinically meaningful improvements in motor function vs. sham procedure control–treated children
- Nusinersen demonstrated a favorable safety profile
  - The majority of AEs were considered to be related to SMA disease, common events in the general population, or events related to the lumbar puncture procedure
- Children from CHERISH are being transitioned to the SHINE open-label extension[1]

1. ClinicalTrials.gov. A Study for Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies. (SHINE) [NCT02594124]. https://clinicaltrials.gov/ct2/show/NCT02594124. Accessed April 19, 2017.

Efficacy and Safety of Nusinersen in Children With Later-Onset Spinal Muscular Atrophy (SMA): Results of the Phase 3 CHERISH Study

P009

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on behalf of the CHERISH Study Group

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Conclusions

- In the CHERISH study, nusinersen demonstrated significant and clinically meaningful improvements in motor function vs. sham procedure control, as assessed by the HFMSE from baseline to Month 15.
  - Improvements for nusinersen vs. sham procedure control also were observed in the number of new WHO motor milestones achieved per child and in upper limb function.
- Nusinersen demonstrated a favorable safety profile, and no children discontinued treatment due to AEs.
  - The majority of AEs were considered to be related to SMA, common events in the general population, or events related to the LP procedure.
- Children from CHERISH are being transitioned into the SHINE (NCT02594124) open-label extension study.

Introduction

- SMA is an autosomal recessive neuromuscular disorder characterized by severe progressive muscle atrophy and weakness caused by survival of motor neuron (SMN) protein deficiency.[1,2]
  - SMA is categorized into 4 types based on age at symptom onset and maximum motor function achieved.
    - SMA Type II (~27% of SMA cases) typically manifests between 7–18 months of age; affected children are able to sit and may stand independently, but are never able to walk independently.[3]
    - Children with SMA Type III (~12% of SMA cases) typically develop symptoms between 18–36 months of age and may stand and walk independently, but can lose these abilities over time.[4]
- Nusinersen is an antisense oligonucleotide for the treatment of SMA that increases the production of full-length SMN protein.[5]
- Nusinersen has demonstrated significant and clinically meaningful efficacy on the achievement of motor milestones and measures of motor function, as well as favorable safety across multiple SMA populations, and significantly greater event-free survival in infants with infantile-onset SMA (vs. sham procedure control).[6-8]

Objectives

- CHERISH (NCT02292537) was a Phase 3, multicenter, randomized, double-blind, sham procedure–controlled study to assess the efficacy and safety of nusinersen in children with later-onset SMA (most likely to develop SMA Type II or III).

Methods

- Children with symptomatic SMA 2–12 years of age were randomized 2:1 (stratified based on screening age <6 vs. ≥6 years) to receive 4 doses of intrathecal nusinersen (12 mg nonscaled) or sham procedure control over 9 months during this 15-month study.
- Key inclusion criteria included confirmed 5q SMA and onset of SMA clinical symptoms at ≥6 months of age.
- The primary endpoint was change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) score at Month 15.
  - An interim analysis was prespecified when all children had completed their 6-month assessment and ≥39 children had completed their 15-month assessment.
- Secondary endpoints were sequentially assessed at Month 15 in the following order:
  - Proportion of children who achieved a ≥3.0-point increase from baseline in HFMSE score;
  - Proportion of children who achieved any new World Health Organization (WHO) motor milestone;
  - Number of new WHO motor milestones achieved per child;
  - Change from baseline in Revised Upper Limb Module (RULM) test score;
  - Proportion of children who achieved standing alone;
  - Proportion of children who achieved walking with assistance.
- Safety and tolerability also were assessed.
- For additional study design details, please see poster P3.184 (presentation on April 25 at poster session 3, 5:30–7:00 PM).

Results

- Baseline demographics were generally similar between groups, with slight differences in age, sex, and race (Table 1).
- At the prespecified interim analysis, there was a significant treatment difference of 5.9 points in mean HFMSE score changes from baseline to Month 15 with a 4.0-point mean improvement observed with nusinersen vs. a mean decline of 1.9 points with sham procedure control. (*P*=.0000002; Figure 1A)
- In the end of study analysis, the treatment difference in change from baseline to Month 15 in mean HFMSE score also was highly clinically and statistically significant (4.9 points: nusinersen, 3.9-point improvement; sham procedure control, 1.0-point decline; nominal. *P*=.0000001; Figure 1B–C)
- Treatment-emergent adverse events (AEs), severe AEs, and serious AEs (SAEs) were reported less frequently in nusinersen-treated vs. sham procedure control–treated children. (Table 3)
  - Back pain, headache, and vomiting were observed at a ≥5% higher frequency in the nusinersen group 72 hours following drug administration. These are known complications following lumbar puncture (LP) and appeared to be related to the LP procedure. (Table 3)
- There were no treatment discontinuations due to AEs. (Table 3)
- There was no evidence of adverse effects on platelet counts, renal function, or hepatic enzymes.

Table 1. Baseline characteristics

Characteristic	Sham procedure control n=42	Nusinersen n=84
Female, n (%)	21 (50)	46 (55)
Median (range) age at screening, y	3.0 (2–7)	4.0 (2–9)
Median (range) age at symptom onset, mo	11.0 (6–20)	10.0 (6–20)
Median (range) age at SMA diagnosis, mo	18.0 (0–46)	18.0 (0–48)
Median (range) disease duration, mo	30.2 (10–80)	39.3 (8–94)
Children who have ever achieved motor milestone, n (%)		
Sat without support	42 (100)	84 (100)
Walked with support	14 (33)	20 (24)
Stood without support	12 (29)	11 (13)
Walked ≥15 ft independently	0	0
Children using a wheelchair, n (%)	29 (69)	64 (76)
SMN2 gene copies, n		
2	4 (10)	6 (7)
3	37 (88)	74 (88)
4	1 (2)	2 (2)
Unknown	0	2 (2)
Mean (SD) HFMSE total score[a]	19.9 (7.2)	22.4 (8.3)
Mean (SD) WHO total score[a,b]	1.5 (1.0)	1.4 (1.0)
Mean (SD) RULM total score[a,c]	18.4 (5.7)	19.5 (6.2)

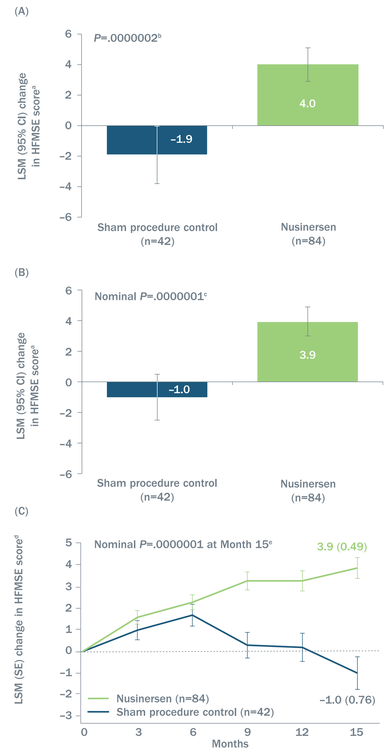
[a]Baseline was defined as the last nonmissing value before the first dose of nusinersen or sham procedure control
[b]If the baseline value as defined above was missing, then baseline was imputed as the median of the nonmissing values of the stratum to which the child belongs: age <6 vs. ≥6 years
[c]One child had a missing value and this was imputed as the median baseline value of the child across all the multiply imputed (MI) datasets

Table 3. Overall summary of treatment-emergent AEs

AE, n (%)	Sham procedure control n=42	Nusinersen n=84
Any AE	42 (100)	78 (93)
Moderate or severe AE	23 (55)	39 (46)
Severe AE	3 (7)	4 (5)
AE possibly related or related to study drug[a]	4 (10)	24 (29)
AE related to study drug[a]	0	1 (1)[b]
SAE	12 (29)	14 (17)
Most frequent AEs[c]		
Pyrexia	15 (36)	36 (43)
Upper respiratory tract infection	19 (45)	25 (30)
Headache	3 (7)	24 (29)
Vomiting	5 (12)	24 (29)
Back pain	0	21 (25)
Cough	9 (21)	21 (25)
Nasopharyngitis	15 (36)	20 (24)
Most frequent SAEs[d]		
Pneumonia	6 (14)	2 (2)
Influenza	2 (5)	0
Respiratory distress	2 (5)	2 (2)
Fecaloma	2 (5)	0
Dehydration	2 (5)	0
SAE related to study drug[a]	0	0
Discontinued treatment due to a AE	0	0
AEs observed at ≥5% higher frequency in nusinersen group 72 h after drug administration		
Back pain	0	19 (23)
Headache	1 (2)	22 (26)
Vomiting	1 (2)	11 (13)
Epistaxis	0	4 (5)

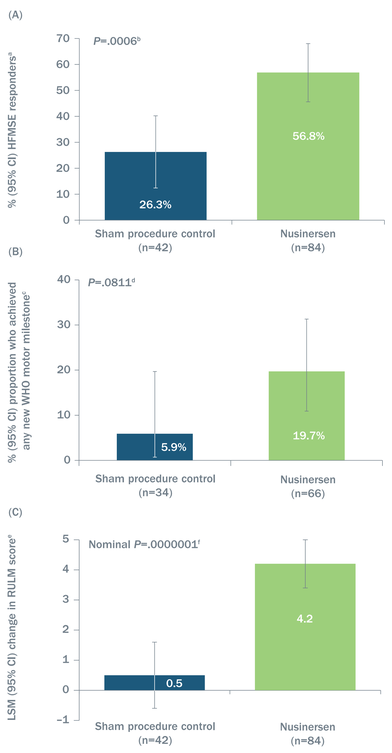
[a]Investigator assessed relation to study drug
[b]One child had postsedation nausea (procedural nausea) considered by the investigator to be related to study treatment
[c]Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) in ≥20% of children in either treatment group
[d]MedDRA PT in ≥5% of children in either treatment group

Figure 1. Mean change from baseline in HFMSE score at: **(A)** prespecified interim analysis (primary endpoint); **(B)** end of study; and **(C)** over time at end of study



LSM = least squares mean
[a]From baseline to Month 15. Based on MI data. From MI procedure, based on analysis of covariance (ANCOVA) with treatment as a fixed effect and adjustment for each child's age at screening and HFMSE score at baseline. These estimates were constructed from fitting the ANCOVA model to each of the imputed datasets. Interim analysis: observed: sham procedure control, n=19; nusinersen, n=35; imputed: sham procedure control, n=23; nusinersen, n=49. Final analysis: observed: sham procedure control, n=34; nusinersen, n=66; imputed: sham procedure control, n=8; nusinersen, n=18
[b]LSM difference: 5.9 (95% CI, 3.7 to 8.1)
[c]LSM difference: 4.9 (95% CI, 3.1 to 6.7)
[d]Change from baseline to each visit was analyzed using an ANCOVA model and MI. LSM and LSM mean differences for treatment comparison based on MI procedure with ANCOVA fitted to each time point with treatment as a fixed effect and adjustment for each child's age at screening and HFMSE at baseline
[e]LSM difference: 4.9 (95% CI, 3.1 to 6.7)

Figure 2. Secondary endpoints at Month 15: **(A)** HFMSE responders; **(B)** proportion of children who achieved any new WHO motor milestone; and **(C)** change from baseline in RULM



[a]HFMSE responder was defined as a child with a ≥3-point increase from baseline in HFMSE score at Month 15. If a child discontinued due to treatment failure or death then the child was classified as a nonresponder irrespective of imputed value. Based on MI data. Estimates from the MI procedure were based on binomial proportions. Odds ratio based on logistic regression with treatment effect and adjustment for each child's baseline age and HFMSE score. Observed data: sham procedure control, n=34; nusinersen, n=66
[b]Odds ratio: 5.59 (95% CI, 2.09 to 14.91)
[c]Children who maintained baseline WHO milestones at Month 15 and achieved ≥1 new milestone. Children who discontinued due to treatment failure or death before Month 15 were not included. Based on imputed data when there was missing data. Proportion of responders based on exact CI. Difference in proportions based on exact unconditional CI. *P* value based on Fisher's exact test
[d]Treatment difference: 13.8 (95% CI, −6.6 to 34.2)
[e]Based on MI data. From MI procedure, based on ANCOVA with treatment as a fixed effect and adjustment for each child's age at screening and derived total score at baseline. Estimates were constructed from fitting the ANCOVA model to each of the imputed datasets. Observed data: sham procedure control, n=34; nusinersen, n=66
[f]LSM difference: 3.7 (95% CI, 2.3 to 5.0)

Table 2. Secondary endpoints: WHO motor milestones at Month 15

Endpoint	Sham procedure control n=42	Nusinersen n=84	Treatment difference
LSM (95% CI) no. of new motor milestones achieved per child[a]	−0.2 (−0.4 to 0.0)	0.2 (0.1 to 0.3)	Nominal *P*=.0001[b]
% (95% CI) of children achieving standing alone[c]	2.9 (0.07 to 15.3)	1.5 (0.04 to 8.2)	Nominal *P*>.9999[d]
% (95% CI) of children achieving walking with assistance[c]	0 (0 to 10.3)	1.5 (0.04 to 8.2)	Nominal *P*>.9999[e]

[a]Based on ANCOVA with treatment as a fixed effect and adjustment for each child's age at screening and number of motor milestones at baseline
[b]LSM difference: 0.4 (95% CI, 0.2 to 0.7)
[c]Proportion of responders based on exact CI. Difference in proportions based on exact unconditional CI. *P* value based on Fisher's exact test
[d]Difference in proportions: −1.4 (95% CI, −21.8 to 19.3)
[e]Difference in proportions: 1.5 (95% CI, −19.1 to 22.1)

References 1. Lunn MR, Wang CH. *Lancet*. 2008;371(9630):2120-2233. 2. Markowitz JA, *et al*. *Pediatr Neurol*. 2012;46(1):1-12. 3. Finkel RS, *et al*.; ENMC SMA Workshop Study Group. *Neuromusc Disord*. doi: 10.1016/j.nmd.2017.02.014. 4. Darras BT. *Pediatr Clin North Am*. 2015;62(3):743-766. 5. Hua Y, *et al*. *Genes Dev*. 2010;24(15):1634-1644. 6. 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. 7. Finkel RS, *et al*. *Lancet*. 2016;388(10063):3017-3026. 7. Bertini E, *et al*. Nusinersen in pre-symptomatic infants with spinal muscular atrophy (SMA): interim efficacy and safety results from the phase 2 NURTURE study. Presented at: 21st International Congress of the World Muscle Society; October 4–8, 2016; Granada, Spain.
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