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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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- **JK:** advisory boards for SMA studies for AveXis, Biogen, Ionis Pharmaceuticals, Inc., and Roche
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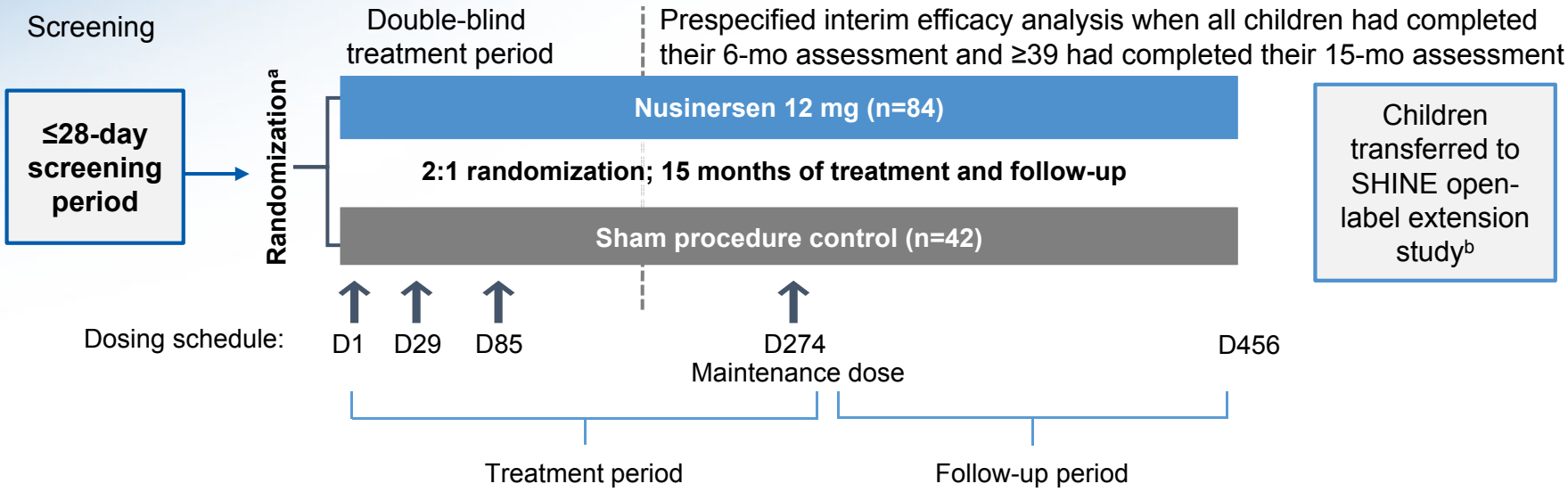
Introduction

- **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]
  - Has demonstrated:
    - Significant and clinically meaningful efficacy on the achievement of motor milestones and measures of motor function across multiple SMA populations, including presymptomatic SMA,3 infantile-onset SMA,[5,6] and later-onset SMA[7,8]
    - Favorable safety across multiple SMA populations[4-8]
    - Significantly greater event-free survival in infants with infantile-onset SMA vs. sham procedure control[6]
  - Resulted in stable or improved motor function over time in children with later-onset SMA for up to ~3 years as measured by HFMSE and ULM scores in open-label studies[8]
- **CHERISH study**
  - 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 (most likely to develop Type II or III)

HFMSE = Hammersmith Functional Motor Scale Expanded; mRNA = messenger RNA; SMN = survival motor neuron; ULM = Upper Limb Module. 1. Lunn MR, Wang CH. *Lancet*. 2008;371(9630):2120-2133. 2. Markowitz JA, *et al*. *Pediatr Neurol.* 2012;46(1):1-12. 3. Hua Y, et al. Genes Dev. 2010;24(15):1634-1644. 4. 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. 5. Finkel RS, *et al. Lancet.* 2016;388(10063):3017-3026. 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. 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. 8. Darras BT, *et al.* Nusinersen in treatment-naïve patients with later-onset spinal muscular atophy (SMA): efficacy results from a phase 1b/2a multicenter study (CS2) and its open-label extension (CS12). Presented at: 21st International Congress of the World Muscle Society; October 4–8, 2016; Granada, Spain.

Study Design and Endpoints

- Key eligibility criteria included age 2–12 years, confirmed 5q SMA, and onset of SMA symptoms at age >6 months



- **ITT set:** all infants who were randomized and received ≥1 dose of study drug/sham procedure control
- **Efficacy set:** subset of infants in the ITT set who were assessed at the Month 15 (D456) visit

ITT= intention-to-treat; RULM = Revised Upper Limb Module. [a]Randomization was stratified based on age at screening (<6 vs ≥6 years). [b]All infants completing the end of study visit for CHERISH had the opportunity to enrol in SHINE. ClinicalTrials.gov, NCT02193074.

CHERISH Hierarchical Endpoints

- Primary endpoint[a,b]
  - Change from baseline in HFMSE score at 15 months
- Secondary endpoints[b]
  - Proportion of children achieving a ≥3-point increase from baseline in HFMSE score at 15 months
  - Proportion of children who achieved any new WHO motor milestone at 15 months
  - Number of new WHO motor milestones achieved per child at 15 months
  - Change from baseline in RULM test at 15 months
  - Proportion of children who achieved standing alone at 15 months
  - Proportion of children who achieved walking with assistance at 15 months
- Safety and tolerability also were assessed

WHO = World Health Organization. [a]Assessed in the interim efficacy analysis when all children had completed their 6-month assessment and ≥39 had completed their 15-month assessment. [b]Primary analyses must reach statistical significance before inferential conclusions can be drawn from the remaining secondary endpoints.

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 the motor milestones, n (%)		
Sat without support	42 (100)	84 (100)
Stood without support	12 (29)	11 (13)
Walked with support	14 (33)	20 (24)
Walked ≥15 ft independently	0	0
***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)**	**19.4 (6.2)**

[a]Baseline is 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 or ≥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 datasets.

Hammersmith Functional Motor Scale Expanded

Type I | Type II SMA | Type III SMA

HFMSE


Sitting


Rolling


Transitions/ Crawling


Standing


Transitions/ Kneeling


Squat/ Jump


Stairs

HFMSE ITEMS

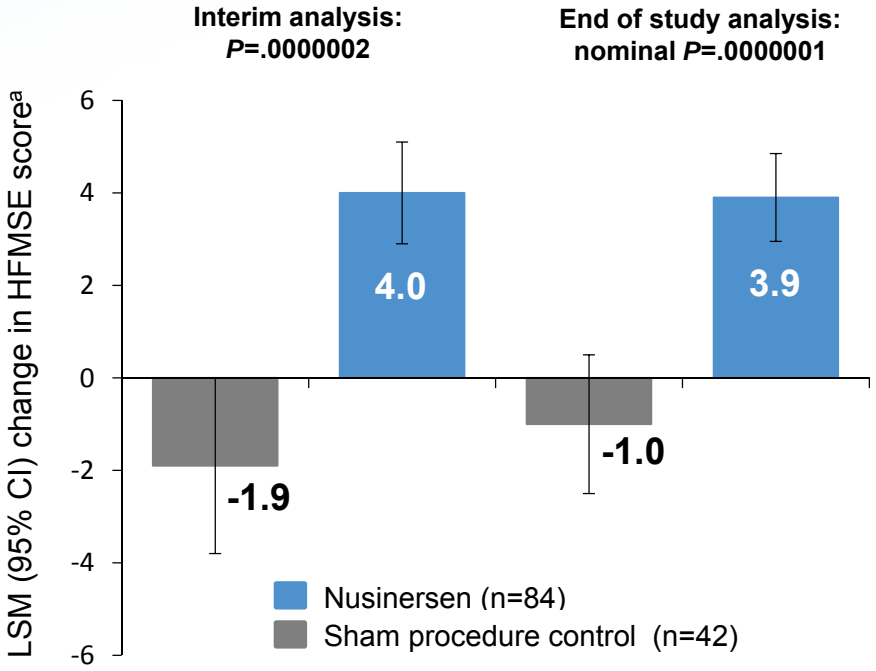
- 33 items
- Hierarchical organization of items permits characterization of patients across the spectrum
- Detailed manual with operational definitions and training videos
- Minimal patient burden requiring only standard equipment; takes less than 15 minutes on average

http://columbiasma.org/docs/cme-2010/Hammersmith%20Functional%20Motor%20Scale%20Expanded%20for%20SMA%20Type%20II%20and%20III%20-%20Manual%20of%20Procedures.pdf. Accessed June 2017

Primary Endpoint: Change in HFMSE Score

- Nusinersen-treated infants demonstrated significant improvements from baseline in HFMSE score at 15 months of treatment

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

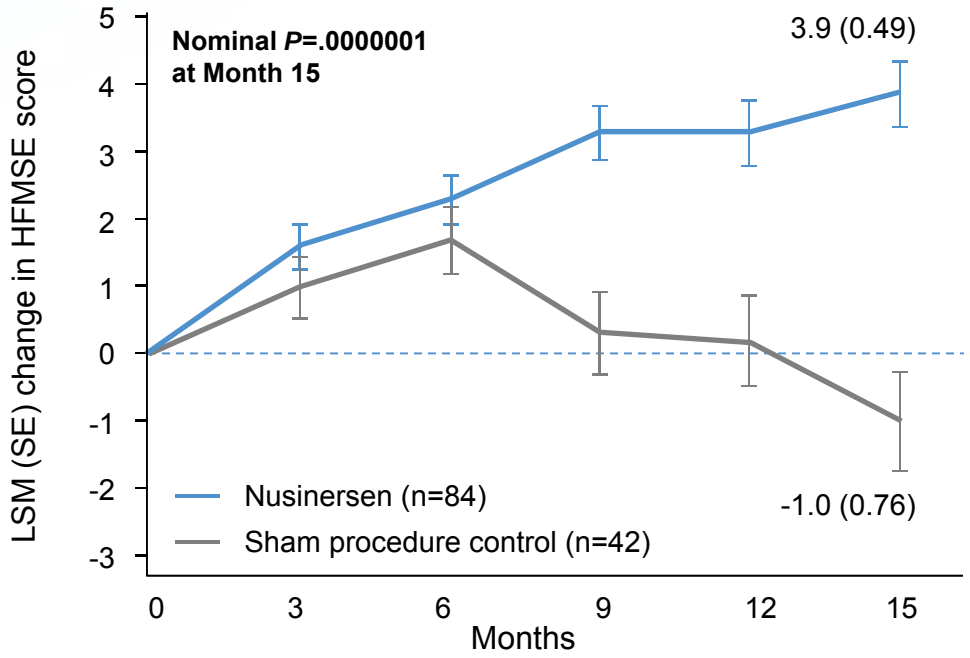


LSM = least squares mean. [a]From baseline to Month 15. Interim analysis: observed: control, n=19; nusinersen, n=35; imputed: control, n=23; nusinersen, n=49. Final analysis: observed: control, n=34; nusinersen, n=66; imputed: control, n=8; nusinersen, n=18.

Primary Endpoint: Change in HFMSE Score

- Nusinersen-treated infants demonstrated significant improvements from baseline in HFMSE score at 15 months of treatment

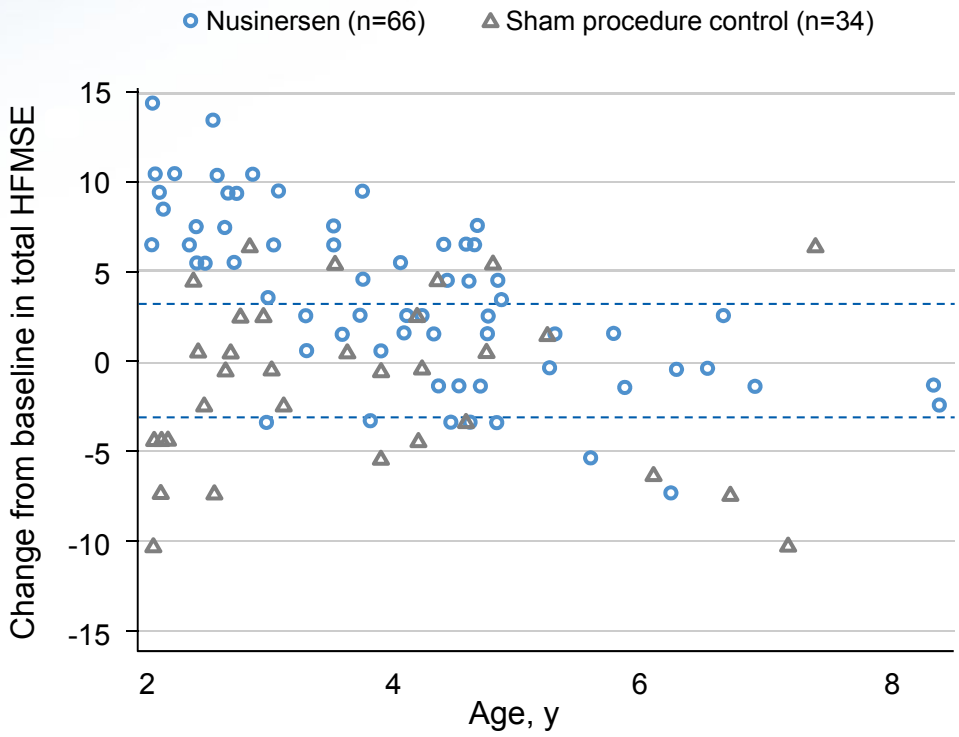
End of study analysis:
mean change over time at end of study



Final analysis: observed: control, n=34; nusinersen, n=66; imputed: control, n=8; nusinersen, n=18.

Change in HFMSE by Age at Screening

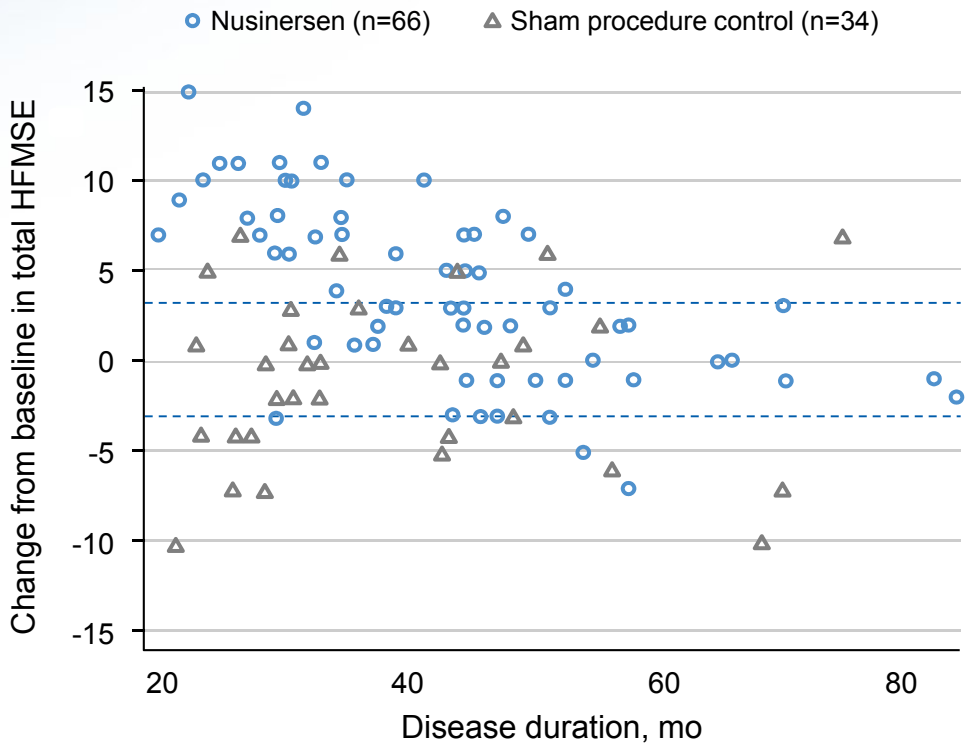
- Nusinersen-treated children who were younger at screening showed greater improvements from baseline in HFMSE scores at 15 months of treatment



Dotted lines represent ±3-point change in HFMSE.

Change in HFMSE by Disease Duration at Screening

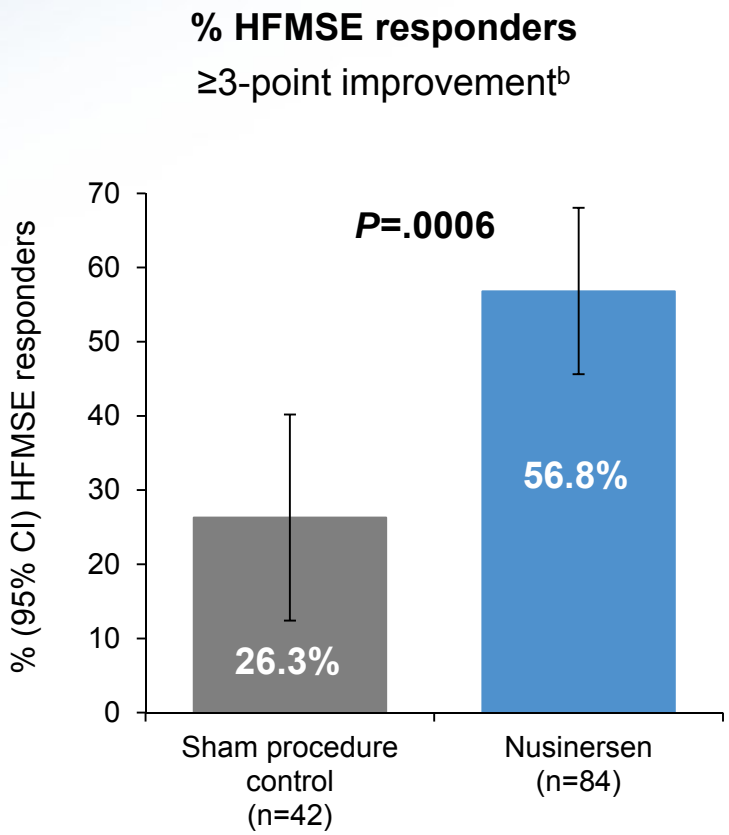
- Nusinersen-treated children with shorter disease durations at screening showed greater improvements from baseline in HFMSE scores at 15 months of treatment



Dotted lines represent ±3-point change in HFMSE.

Proportion of HFMSE Responders

- Significantly more nusinersen-treated children[a] were HFMSE responders[b]



[a]Vs. sham procedure control. [b]HFMSE responder was defined as a child with ≥3-point increase from baseline in HFMSE 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. Observed data: control, n=34; nusinersen, n=66.

Achievement of WHO Motor Milestones

- Achievement of any new WHO motor milestone at Month 15 trended higher in nusinersen-treated children[a]

Endpoint	Sham procedure control n=34	Nusinersen n=66	Treatment difference
% (95% CI) who achieved any new motor milestone[b]	5.9 (0.7 to 19.7)	19.7 (10.9 to 31.3)	*P*=.0811
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

[a]Vs. sham procedure control. [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. [b]Based on analysis of covariance with treatment as a fixed effect and adjustment for each child's age at screening and number of milestones at baseline. Observed data: control, n=34; nusinersen, n=66.

Achievement of WHO Motor Milestones

- The percentage of nusinersen-treated children who attained each WHO motor milestone increased from baseline to Month 15

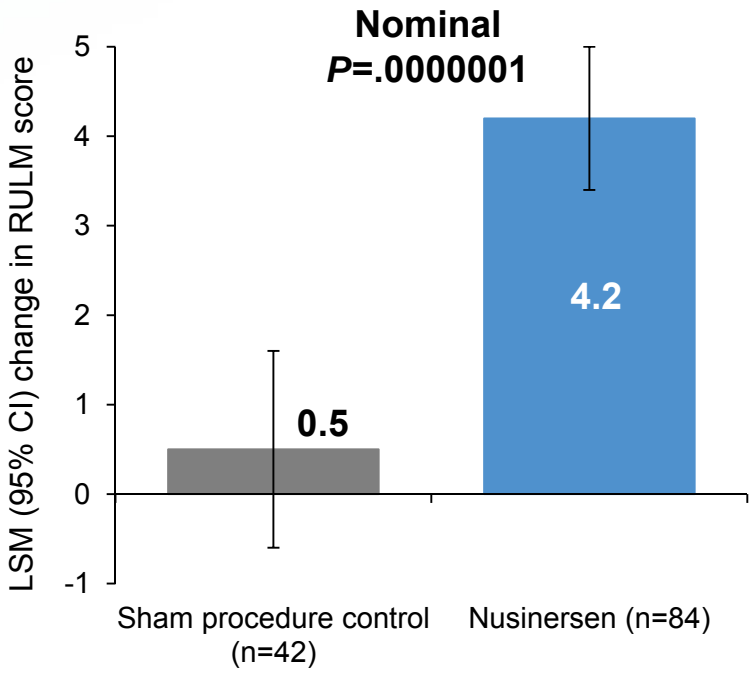
WHO motor milestone	Sham procedure control n=34			Nusinersen n=66			Difference in % change at Month 15 (nusinersen minus sham procedure control)
	Baseline, n (%)	Month 15, n (%)	Change at Month 15, %	Baseline, n (%)	Month 15, n (%)	Change at Month 15, %	
Sitting without support	34 (100)	34 (100)	0	65 (98)	66 (100)	+2	+2
Hands and knees crawling	7 (21)	1 (3)	-18	13 (20)	20 (30)	+10	+28
Standing with assistance	6 (18)	4 (12)	-6	5 (8)	9 (14)	+6	+12
Walking with assistance	2 (6)	2 (6)	0	4 (6)	5 (8)	+2	+2
Standing alone	1 (3)	2 (6)	+3	2 (3)	3 (5)	+2	-1
Walking alone	0	0	0	0	1 (2)	+2	+2

- There were no significant between-group differences in the proportions of children who achieved standing alone or walking with assistance at Month 15 (secondary endpoints)

Improvement in RULM

- Nusinersen-treated children demonstrated greater improvements from baseline in RULM score at 15 months of treatment
  - Maximum score = 18; ≥2-point increase was considered clinically meaningful[1]

Change from baseline in RULM score[b]



[a]Vs. sham procedure control. [b]Observed data: control n=34; nusinersen n=66. [1]OptumRx. Therapeutic class overview. Agent for spinal muscular atrophy: SPINRAZA (nusinersen). https://www.medicaid.nv.gov/Downloads/provider/Spinraza_2017-0314.pdf. Accessed on May 1, 2017.

Safety Results

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]
Serious AE	12 (29)	14 (17)
Serious AE related to study drug[a]	0	0
Discontinued treatment due to an AE	0	0

AE = adverse event. [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.

Safety Results

AE, n (%)	Sham procedure control n=42	Nusinersen n=84
Most frequent AEs[a]		
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)
AEs observed at a ≥5% higher frequency in the nusinersen group 72 hours after drug administration		
Back pain	0	19 (23)
Headache	1 (2)	22 (26)
Vomiting	1 (2)	12 (14)
Epistaxis	0	4 (5)

AE = adverse event. [a]Medical Dictionary for Regulatory Activities Preferred Term in ≥20% of children in either treatment group.

Conclusions

- Nusinersen-treated children demonstrated significant and clinically meaningful improvements in motor function vs. those treated with sham procedure control, as assessed by the HFMSE from baseline to Month 15
  - Nusinersen-treated children who were younger and had shorter disease durations generally showed the greatest improvements in HFMSE from baseline; older children and those with longer disease durations demonstrated stabilization of HFMSE scores
- The number of new WHO motor milestones achieved per child and the change from baseline to Month 15 in RULM score trended higher in nusinersen-treated 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 have been transitioned to the SHINE open-label extension[1]

1. ClinicalTrials.gov, NCT02594124

Acknowledgments

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- The authors thank the CHERISH study investigators
- The authors also thank all the contributors to the CHERISH study, including the clinical monitors, study coordinators, physical therapists, pharmacists, and laboratory technicians
- Patient advocacy groups assisted in promoting awareness of this study

Backup

HFMSE[1]

- Validated instrument used to assess motor function in children with SMA
  - High reliability, consistency, and correlation with the full Gross Motor Function Measure[1]
  - A 3-point change in the HFMSE has been previously identified as clinically meaningful[2]

Motor function	Items	Score range
Sitting	1–4	Item scores: 0 = unable to 2 = able without modification
Rolling	5–9	
Transitions/crawling	10–17	
Standing/stepping	18–20	
Transitions/kneeling	21–27	
Squat/jump	28–29	
Stairs	30–33	
Total	**33**	**Total score: 0–66** **Higher score indicates better function**

Child depicted in graph above is ≥2 years of age. Figure adapted from: Together in SMA™ with Biogen. https://www.togetherinsma-hcp.com/en_us/home/disease-education/sma-symptoms.html. Accessed March 29, 2017. 1. O'Hagan JM, *et al*. *Neuromuscul Disord*. 2007;17(9-10): 693-697. 2. Swoboda KJ, *et al*. *PLoS One*. 2010;5(8):e12140.

Achievement of WHO Motor Milestones

WHO motor milestone achievement, n (%)	Sham procedure control n=34	Nusinersen n=66
Sitting without support		
Baseline	34 (100)	65 (98)
Month 15	34 (100)	66 (100)
Hands and knees crawling		
Baseline	7 (21)	13 (20)
Month 15	1 (3)	20 (30)
Standing with assistance		
Baseline	6 (18)	5 (8)
Month 15	4 (12)	9 (14)
Walking with assistance		
Baseline	2 (6)	4 (6)
Month 15	2 (6)	5 (8)
Standing alone		
Baseline	1 (3)	2 (3)
Month 15	2 (6)	3 (5)
Walking alone		
Baseline	0	0
Month 15	0	1 (2)

LSM = least squares means; WHO = World Health Organization. [a]Vs. sham procedure control. [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. [b]Based on analysis of covariance with treatment as a fixed effect and adjustment for each child's age at screening and number of milestones at baseline. Observed data: sham procedure control, n=34; nusinersen, n=66.

Achievement of WHO Motor Milestones

- The percentage of nusinersen-treated children who attained each WHO motor milestone increased from baseline to Month 15

Change from baseline to Month 15 in percentage of children achieving WHO motor milestone, (%)	Sham procedure control n=34	Nusinersen n=66
Sitting without support	0%	+2%
Hands and knees crawling	-18%	+10%
Standing with assistance	-6%	+6%
Walking with assistance	0%	+2%
Standing alone	+3%	+2%
Walking alone	0%	+2%

WHO = World Health Organization.