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Efficacy and Safety of Nusinersen in Genetically Diagnosed Infants With Presymptomatic Spinal Muscular Atrophy (SMA): Results From the Second Interim Analysis of the Ongoing, Phase 2 NURTURE Study

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Disclosures

- TOC: advisor/consultant to AveXis, Biogen, Catalyst, Cure SMA, Cytokinetics, Marathon, Novartis, Roche, Sarepta, and the Spinal Muscular Atrophy Foundation
- DCD: advisor/consultant for AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Inc., Roche, Sarepta, and the Spinal Muscular Atrophy Foundation, with no financial interests in these companies; grants from the Department of Defense, Hope for Children Research Foundation, the National Institutes of Health, and the Spinal Muscular Atrophy Foundation
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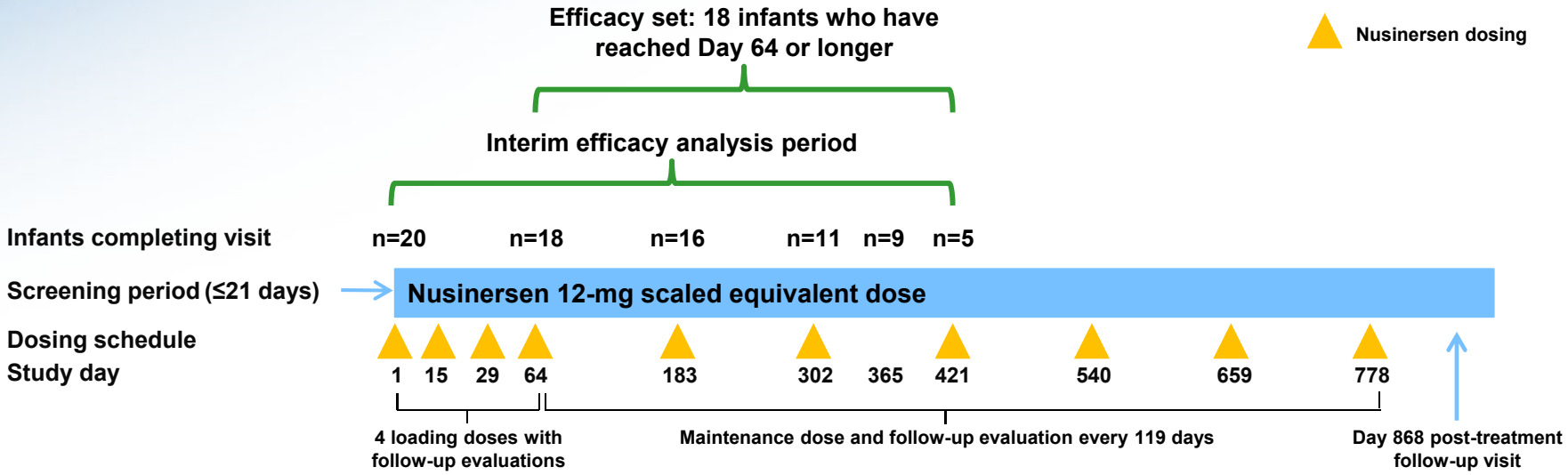
Introduction

- Spinal muscular atrophy (SMA)
  - SMA subtype concordance is high among siblings: 87% of 265 sibling pairs with SMA had a concordant phenotype[1]
- Nusinersen
  - Antisense oligonucleotide[2]
  - Modifies splicing of the paralogous *SMN2* precursor mRNA[2]
  - Increases production of full-length SMN protein[2,3]
- NURTURE
  - Phase 2, open-label, multicenter, multinational, single-arm study
  - Infants with genetically diagnosed and presymptomatic SMA (most likely to develop SMA Type I or II)
  - June 2016 interim analysis[4]: clinically meaningful efficacy on survival and motor milestone achievement over SMA Type I natural history[5]

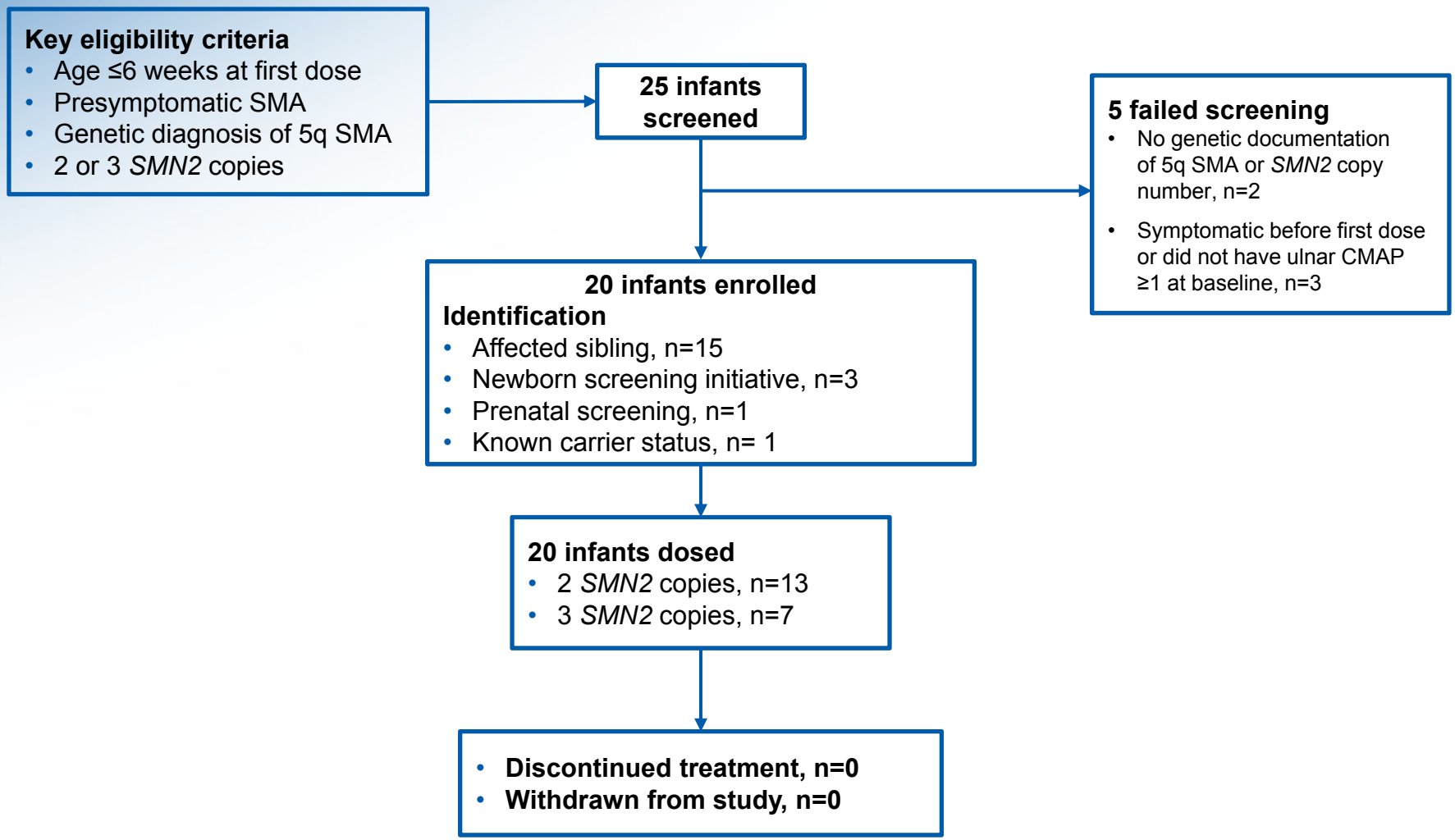
mRNA = messenger RNA; SMN = survival of motor neuron. 1. Jones C, *et al*. SMA subtype concordance in siblings: findings from the Cure SMA cohort. Presented at: 2016 Annual Spinal Muscular Atrophy Conference; June 16–19, 2016; Anaheim, CA. 2. Hua Y, *et al. Genes Dev.* 2010;24(15):1634-1644. 3. Passini MA, *et al. Sci Transl Med.* 2011;3(72):72ra18. 4. Bertini E, *et al*. Nusinersen in presymptomatic 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*. *Neurology*. 2014;83(9):810-817.

Now, Updated Interim Analysis
(as of October 31, 2016)



NURTURE study interim analysis data cut-off date: October 31, 2016.

Participant Disposition: Interim Analysis



CMAP = compound muscle action potential. NURTURE study interim analysis data cut-off date: October 31, 2016.

Baseline Characteristics

Characteristic	2 *SMN2* copies n=13[a]	3 *SMN2* copies n=7	Total n=20
Age at first dose, days, n			
≤14	6	2	8
>14 to ≤28	5	3	8
>28	2	2	4
Range	3–41	10–42	3–42
Mean CHOP INTEND total score Median (range)[b]	48.0 50.0 (25–60)[c]	53.8 56.0 (40–60)[d]	49.6 54.0 (25–60)[e]
Mean HINE total motor milestones Median (range)[b]	2.5 3.0 (0–5)[c]	4.2 4.0 (2–7)[d]	3.0 3.0 (0–7)[e]
Mean ulnar CMAP amplitude Median (range), mV[b]	2.62 2.15 (1.0–6.7)[c]	3.96 4.00 (2.7–4.9)[d]	2.99 2.85 (1.0–6.7)[e]
Mean peroneal CMAP amplitude Median (range), mV[b]	2.47 2.65 (0.2–4.2)[f]	4.88 4.40 (4.0–7.0)[d]	3.27 3.20 (0.2–7.0)[g]

Characteristic	Total n=20
Male, %	55
Region, n	
North America	13
Europe	4
Asia-Pacific	3

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination. NURTURE study interim analysis data cut-off date: October 21, 2016. [a]Included 1 set of twins each with 2 *SMN2* copies. [b]Based on efficacy set of patients who completed the Day 64 visit or longer (n=18). [c]n=13. [d]n=5. [e]n=18. [f]n=10. [g]n=15.

Primary Endpoint: Time to Death or Respiratory Intervention[a]

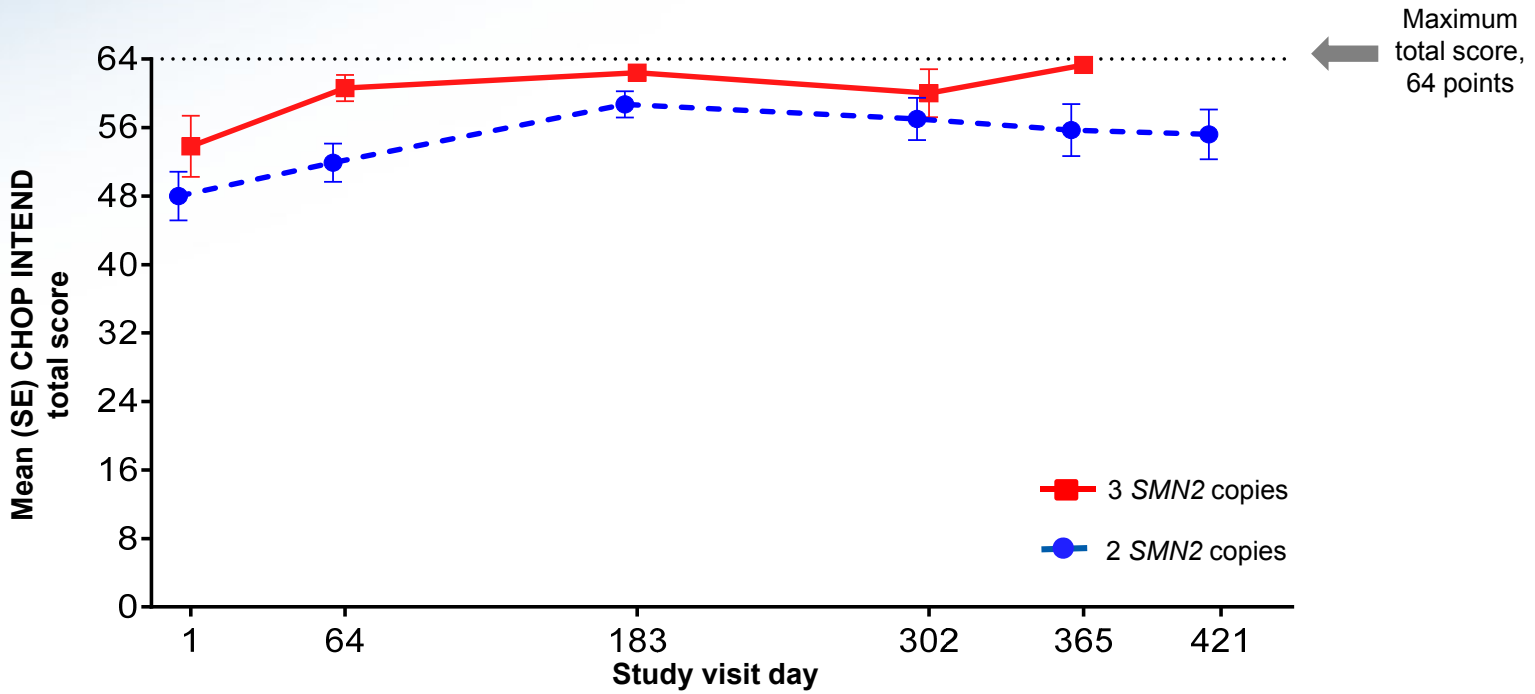
- At the time of the interim analysis, infants had been on study for a median (range) of 317.5 (2–524) days
- All infants were alive and none had required respiratory intervention[a]

Nusinersen-treated infants, n (%)	*2 SMN2* copies n=13	*3 SMN2* copies n=7	Total n=20
Alive	13 (100)	7 (100)	20 (100)
Required invasive ventilation or tracheostomy	0	0	0
Required noninvasive ventilation for ≥6 hours/day continuously for ≥7 days	0	0	0

NURTURE study interim analysis data cut-off date: October 31, 2016. [a]Respiratory intervention was defined as invasive or noninvasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy.

Mean CHOP INTEND Total Score Over Time

- Sixteen (89%) infants achieved a ≥4-point improvement
- Seven (39%) achieved the maximum total score (64 points)

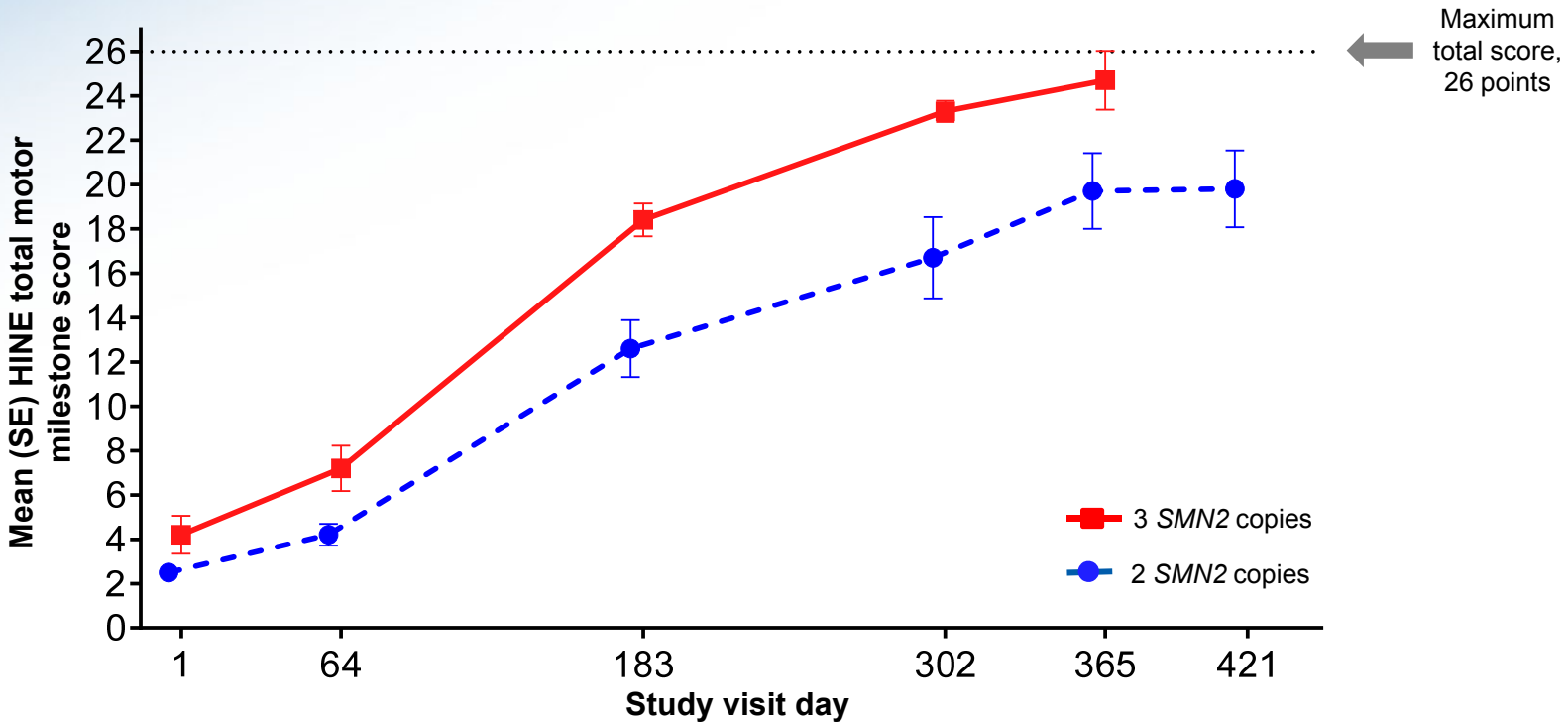


3 *SMN2* copies, n	5	5	5	4	3	
2 *SMN2* copies, n	13	13	11	7	6	5

NURTURE study interim analysis data cut-off date: October 31, 2016.

Mean HINE Total Motor Milestone Score Over Time

- No infants experienced worsening in HINE total motor milestone score from baseline to any visit or from baseline to last study visit



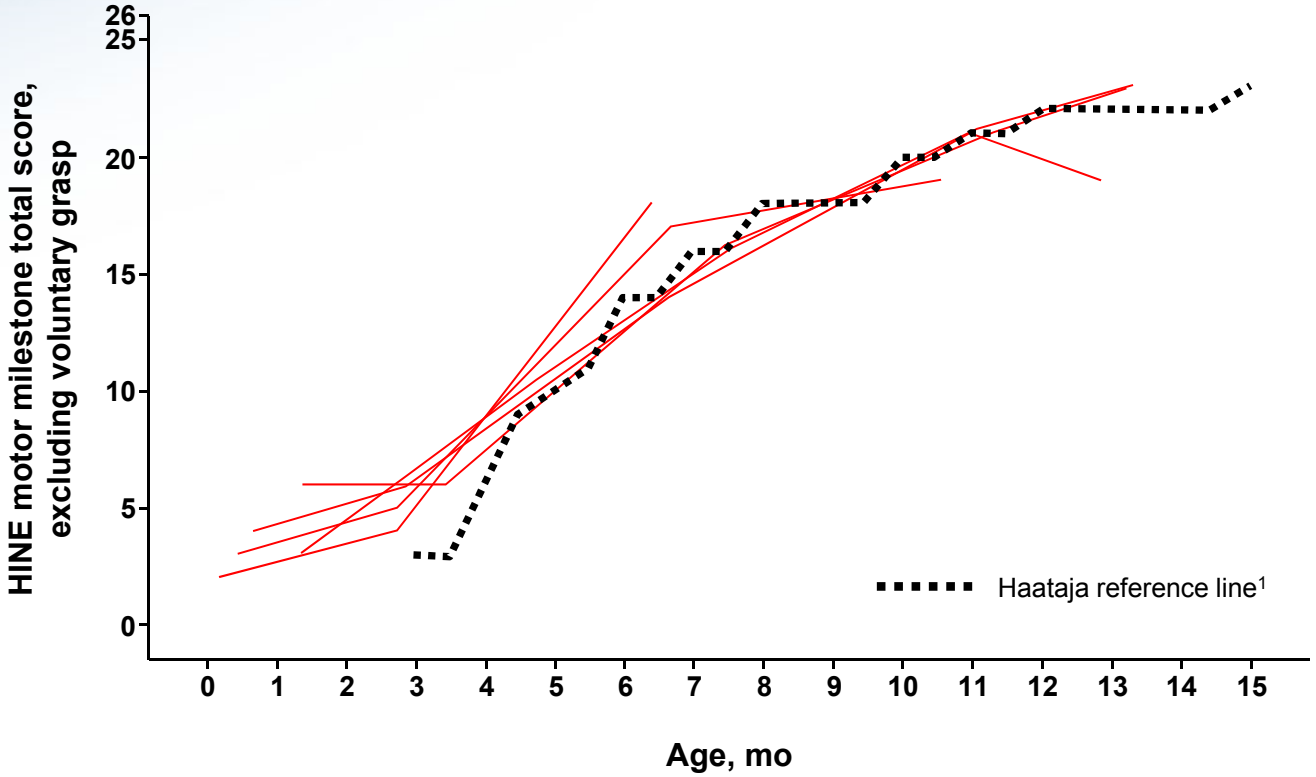
3 *SMN2* copies, n	5	5	5	4	3	
2 *SMN2* copies, n	13	13	11	7	6	5

NURTURE study interim analysis data cut-off date: October 31, 2016.

HINE Motor Milestone Total Score (Excluding Voluntary Grasp)

Infants with 3 *SMN2* copies

- Most infants are achieving motor milestones along timelines consistent with normal development



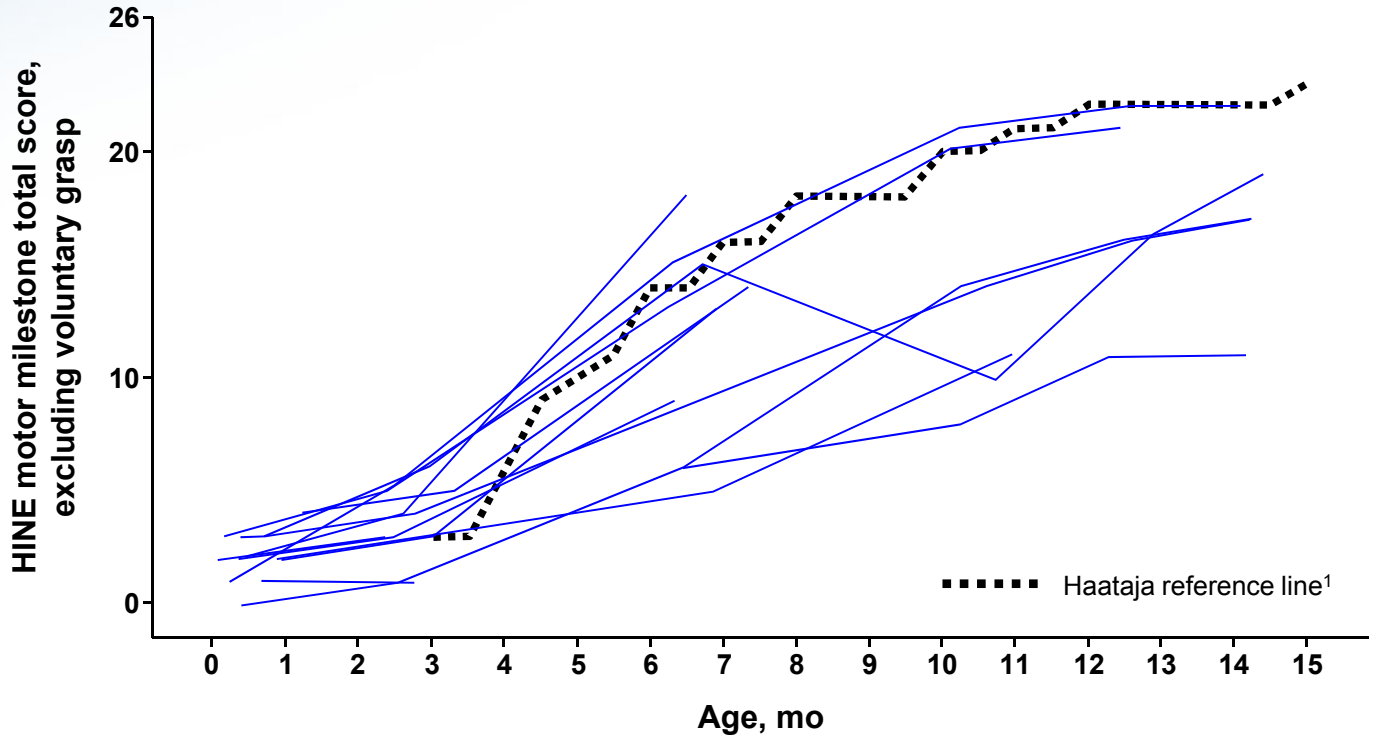
One infant attended the Day 64 assessment on study day 98. NURTURE study interim analysis data cut-off date: October 31, 2016.

1. Haataja L, *et al*. *J Pediatr*. 1999;135(2 pt 1):153-161.

HINE Motor Milestone Total Score (Excluding Voluntary Grasp)

Infants with 2 *SMN2* copies

- Some infants are achieving motor milestones along timelines consistent with normal development
- Among those who are not, the infants are trending up and achieving new motor milestones along timelines near normal development



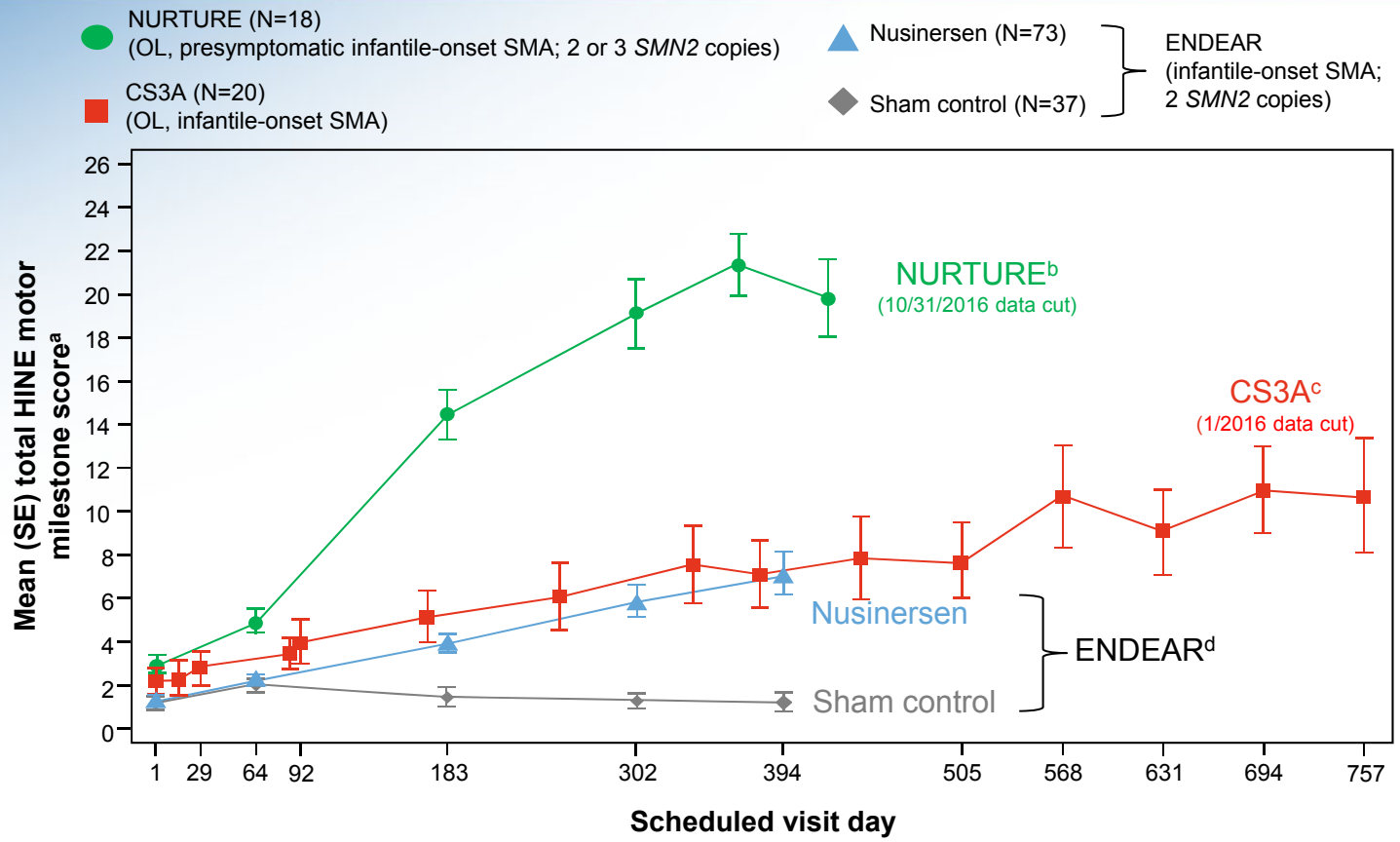
NURTURE study interim analysis data cut-off date: October 31, 2016. 1. Haataja L, *et al*. *J Pediatr*. 1999;135(2 pt 1):153-161.

WHO Motor Milestone Achievement

WHO motor milestone[1] (definition of milestone)[2]	Infants achieving milestone		
	2 SMN2 copies	*3 SMN2* copies	Total
Sitting without support (sits up straight for ≥10 seconds)	7	5	12
Standing with assistance (stands with assistance for ≥10 seconds)	5	5	10
Hands and knees crawling (stomach does not touch surface during ≥3 continuous movements)	2	4	6
Walking with assistance (child takes ≥5 supported steps)	2	3	5
Standing alone (child stands alone for ≥10 seconds)	1	2	3
Walking alone (child takes ≥5 independent steps)	0	2	2

WHO = World Health Organization. NURTURE study interim analysis data cut-off date: October 31, 2016. 1. WHO Multicentre Growth Reference Study Group. *Acta Paediatr Suppl.* 2006;450:86-95. 2. Wijnhoven TMA, *et al*.; WHO Multicentre Growth Reference Study Group. *Food Nutr Bull*. 2004;25(suppl 1):S37-S45.

HINE Motor Milestone Scores Across Studies



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

OL = open label. 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 enrollment: 155 (36–210) days. [d]Median (range) age at first dose: 175.0 (30–262) days.

Growth Parameters: Efficacy Set

- All but 1 infant gained weight over time
- 25% of infants met the "growth failure"* criteria at Day 183 (*SMN2* copies [2/3]: 3/1)
  - 1 infant with gastric tube placed at Day 155 (2 *SMN2* copies)
  - Infants meeting "growth failure" criteria continued to grow over time

**** Growth failure criteria:***

Weight for age <5th percentile (WHO growth charts) or *weight for age failing ≥2 major percentiles over a 6-month period*

NURTURE study interim analysis data cut-off date: October 31, 2016.

Discordant Motor Milestone Achievement in Sibling Pairs

- 13 infants[a] in NURTURE had ≥1 sibling with SMA
- 8 NURTURE infants had a sibling who had not achieved independent sitting[b]
  - 6 infants were ≥7 months of age, 5 had achieved independent sitting
- 5 NURTURE infants had a sibling who achieved independent sitting but not walking
  - 2 infants had achieved independent walking

[a]Among infants with a Day 183 assessment. [b]Defined as HINE categories of stable sit or pivot (rotates). NURTURE study interim analysis data cut-off date: October 31, 2016.

Summary of Safety

- The lumbar puncture procedure was generally well tolerated
- There were no clinically significant adverse changes in laboratory or neurological examinations considered related to nusinersen
- All AEs considered by the investigator to be possibly related to study drug resolved during study follow-up

AE, n (%)	Total n=20
Any AE	16 (80)
Serious AE[a]	6 (30)
Severe AE	2 (10)
AE related to study drug[b]	0
AE possibly related to study drug[b]	3 (15)
Muscular weakness and weight-bearing difficulty	1 (5)
Hyperreflexia and tachycardia	1 (5)
Pyrexia, increased ALT, increased AST, increased eosinophil, lymphocyte, and WBC counts	1 (5)
Serious AE related to study drug	0
AE leading to treatment discontinuation or withdrawal	0

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cell. NURTURE study interim analysis data cut-off date: October 31, 2016. [a]SAEs were bronchitis, choking, and pneumonia (n=1); pneumonia (n=1); urinary tract (n=1); failure to thrive (n=1); pyrexia (n=1); and abdominal distension, respiratory distress, dehydration, and rhinovirus infection (n=1). [b]Assessed by the investigator.

Conclusions

These results extend the positive results from the June 2016 interim analysis[1]

- All infants alive without requiring chronic respiratory support and are exhibiting improvements in motor function and/or motor milestones
- Continued beneficial effects of nusinersen in infants with presymptomatic SMA on survival and achievement of motor milestones not regularly acquired by infants with SMA Type I or II[2,3]
- Nusinersen-treated infants achieved motor milestones beyond those achieved by their sibling with SMA Type I or II
  - These results are inconsistent with the natural history of sibling pairs with SMA in which most siblings (87%) have concordant phenotypes[4]
- Nusinersen was well tolerated and no specific safety concerns were identified

NURTURE study interim analysis data cut-off date: October 31, 2016. 1. Bertini E, *et al*. Nusinersen in presymptomatic 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; 2. Finkel RS, *et al*. *Neurology*. 2014;83(9):810-817. 3. Finkel R, *et al*.; ENMC SMA Workshop Study Group. *Neuromuscul Disord*. 2015;25(7):593-602. 4. Jones C, *et al*. SMA subtype concordance in siblings: findings from the Cure SMA cohort. Presented at: 2016 Annual Spinal Muscular Atrophy Conference; June 16–19, 2016; Anaheim, CA.

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- The authors also thank the people who are contributing to this study, including the study site principal investigators, clinical monitors, study coordinators, physical therapists, and laboratory technicians

Backup

Study Endpoints

- Primary
  - Time to respiratory intervention (invasive or noninvasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy) or death
- Secondary
  - Proportion of infants developing clinically manifested SMA by 13 and 24 months of age defined as:
    - Age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support
    - Failure to achieve age-appropriate attainment of the 6 WHO motor milestones
  - Survival (proportion of patients alive)
  - Attainment of motor milestones assessed HINE Modified Section 2[1]
  - Change from baseline in CHOP INTEND motor function scale[2]
  - Attainment of motor milestones assessed by WHO criteria[3]
  - Change from baseline in growth parameters
- Safety

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. WHO = World Health Organization. 1. Haataja L, *et al*. *J Pediatr.* 1999;135(2 pt 1): 153-161. 2. Glanzman AM, *et al*. *Neuromuscul Disord.* 2010;20(3):155-161. 3. WHO Multicentre Growth Reference Study Group. *Acta Paediatr Suppl.* 2006;450:86-95. NURTURE study interim analysis data cut-off date: October 31, 2016.

Modified Section 2 of the HINE Scoring and Normal Age of Achievement[a]

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); 3 mo	Touches leg; 4–5 mo	Touches toes; 5–6 mo
Head control	Unable to maintain upright; <3 mo	Wobbles; 4 mo	All the time upright; 5 mo		
Rolling	No rolling	Rolling to side; 4 mo	Prone to supine; 6 mo	Supine to prone; 7 mo	
Sitting	Cannot sit	Sit with support at hips; 4 mo	Props; 6 mo	Stable sit; 7 mo	Pivots (rotates); 10 mo
Crawling	Does not lift head	On elbow; 3 months	On outstretched hand; 4–5 mo	Crawling flat on abdomen; 8 mo	On hands and knees; 10 mo
Standing	Does not support weight	Supports weight; 4–5 mo	Stands with support; 8 mo	Stands unaided; 12 mo	
Walking	No walking	Bouncing; 6 mo	Cruising (walks holding on); 11 mo	Walking independently; 15 mo	

Overall maximum total score = 26
(higher score indicates milestone attained)

Haataja L, *et al*. *J Pediatr.* 1999;135(2 pt 1):153-161. [a]Ages (months) are considered to be the normal age of achievement in individuals without SMA.