21st International Congress of the World Muscle Society
4-8 October, 2016
Granada, Spain

Nusinersen in Pre-symptomatic Infants With Spinal Muscular Atrophy (SMA): Interim Efficacy and Safety Results From the Phase 2 NURTURE Study

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8 October 2016

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Disclosures

- EB: grants from Fondazione Telethon and the Italian Ministry of Health; advisor/consultant for AveXis, Biogen, Edison Pharmaceuticals, Novartis and Roche
- W-LH: grants from Biogen
- SPR, WF, SG, PS and ZJZ: employees of and hold stock/stock options in Biogen
- JS and ES: employees of and hold stock/stock options in Ionis Pharmaceuticals, Inc.
- DCVD: advisor/consultant for AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Roche, Sarepta and the SMA 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 SMA Foundation
- This study was sponsored by Biogen (Cambridge, MA, USA)
- Writing and editorial support for the preparation of this presentation was provided by Excel Scientific Solutions (Southport, CT, USA): funding was provided by Biogen

Introduction

- Spinal muscular atrophy (SMA)
  - Rare autosomal recessive neuromuscular disorder[1]
  - Caused by mutations in the *survival motor neuron 1* (*SMN1*) gene[1]
  - Results in SMN protein deficiency[1]
  - A second gene, *SMN2*, produces limited full-length SMN protein[1]
  - *SMN2* copy number correlates with clinical phenotype[1]
- Preclinical data suggest that proactive treatment of pre-symptomatic patients with SMA may lead to improved clinical outcomes[2]
- Nusinersen
  - Antisense oligonucleotide that modifies the splicing of SMN2 precursor mRNA[3]
  - Increases full-length SMN2 mRNA levels
  - Promotes increased production of functional SMN protein[4,5]
  - Safety and tolerability of nusinersen previously demonstrated (study CS3a)[6]

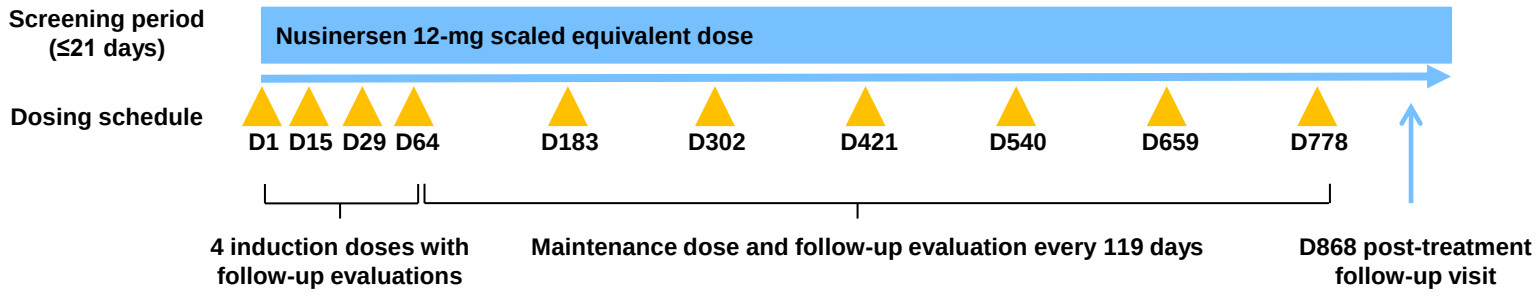
mRNA = messenger RNA. 1. Prior TW. *Curr Opin Pediatr.* 2010;22(6):696-702. 2. Staropoli JF, *et al*. *Genomics.* 2015;105(4):220-228. 3. Hua Y, *et al. Genes Dev.* 2010;24(15):1634-1644. 4. Passini MA, *et al. Sci Transl Med.* 2011;3(72):72ra18. 5. Darras B, *et al. Neuromuscul Disord.* 2014;24(9-10):920. 6. Finkel R, *et al. Neurology.* 2016;86(suppl 16):P5.004.

NURTURE Study Design

- Phase 2, open-label, multicentre, multinational, single-arm study in 10 countries
  - **Objective:** to evaluate the efficacy and safety profile of intrathecal nusinersen in infants with genetically diagnosed and pre-symptomatic SMA
  - **Planned enrolment:** up to 25 infants

Key inclusion criteria:
- Age ≤6 weeks at first dose
- Pre-symptomatic
- Genetic diagnosis of 5q *SMA* gene deletion/ mutation
- Gestational age, 37–42 (34–42 for twins) weeks
- 2 or 3 *SMN2* copies
- Ulnar CMAP amplitude ≥1 mV at Baseline

Key exclusion criteria
- Hypoxemia (O_2 saturation of <96% awake or asleep at sea level)
- Infection during Screening period or ongoing medical condition incompatible with study procedures/ assessments



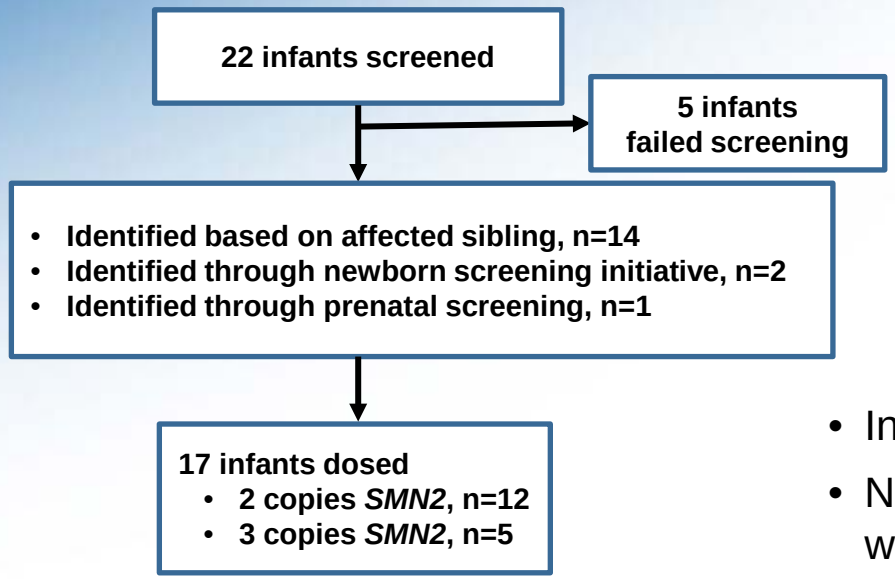
CMAP = compound muscle action potential.

Study Endpoints

- Primary
  - Time to respiratory intervention (invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy) or death
- Secondary
  - Safety, tolerability and pharmacokinetics
  - Effect on development of SMA by assessing clinical milestones
    - Ability to crawl, stand or walk
  - Motor function milestones
    - Assessed using CHOP INTEND,[1] HINE[2] and WHO[3]
  - Survival (proportion of patients alive)
  - Growth parameters

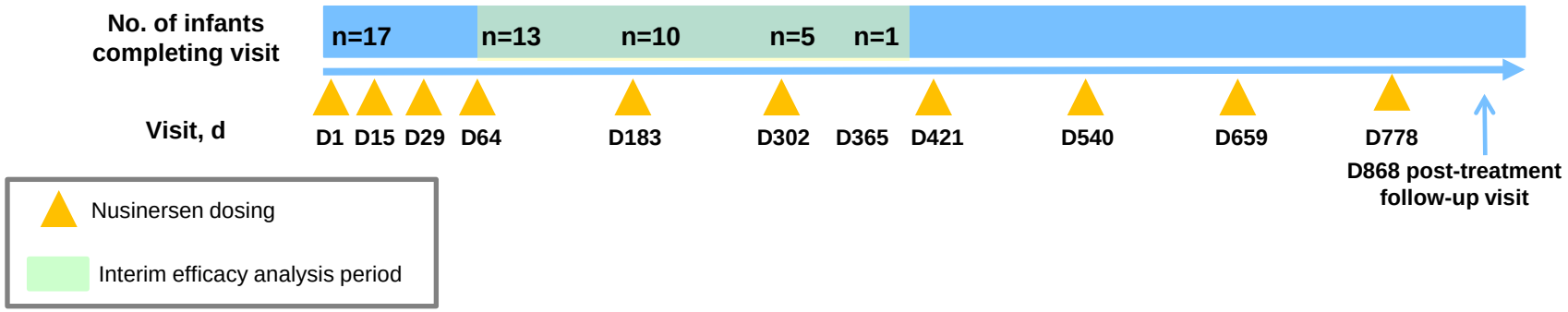
CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; WHO = World Health Organization. 1. Haataja L, *et al*. *J Pediatr.* 1999;135(2 Pt 1):153-161. 2. WHO Multicentre Growth Reference Study Group. *Acta Paediatr Suppl.* 2006;450:86-95. 3. Glanzman AM, *et al*. *Neuromuscul Disord.* 2010;20(3):155-161.

Study Overview: Interim Analysis



- Interim analysis data cutoff date: 8 June 2016
- No infants have discontinued treatment or withdrawn from the study

- Efficacy analyses are based on 13 infants who have reached the first efficacy assessment visit (Day 64, age ~2 months) or longer



Baseline Characteristics

Characteristic	2 *SMN2* copies n=12[a]	3 *SMN2* copies n=5	Total n=17
Age at first dose, d, n (%)			
≤14	5 (42)	1 (20)	6 (35)
>14 to ≤28	5 (42)	2 (40)	7 (41)
>28	2 (17)	2 (40)	4 (24)
Median (range)	17.0 (8–41)	24.0 (12–42)	19.0 (8–42)
Male, n (%)	8 (67)	3 (60)	11 (65)
Female, n (%)	4 (33)	2 (40)	6 (35)
Region, n (%)			
North America	7 (58)	5 (100)	12 (71)
Europe	3 (25)	0	3 (18)
Asia-Pacific	2 (17)	0	2 (12)
Mean CHOP INTEND total score Median (range; n)[b]	48.9 45.0 (39.0–60.0; 9)	53.5 57.0 (40.0–60.0; 4)	50.3 55.0 (39.0–60.0; 13)
Mean HINE total motor milestones Median (range; n)[b]	2.3 3.0 (0–4.0; 9)	4.8 4.5 (3.0–7.0; 4)	3.1 3.0 (0–7.0; 13)
Mean ulnar CMAP amplitude Median (range; n), mV[b]	2.42 2.3 (1.0–4.2; 9)	3.95 4.1 (2.7–4.9; 4)	2.89 3.0 (1.0–4.9; 13)
Mean peroneal CMAP amplitude Median (range; n), mV[b]	2.76 2.8 (1.1–4.2; 7)	4.35 4.2 (4.0–5.0; 4)	3.34 3.4 (1.1–5.0; 11)

NURTURE study interim analysis data cutoff date: 8 June 2016. [a]Included 1 set of twins each with 2 copies of *SMN2*. [b]Based on efficacy set of patients who completed Day 64 visit or longer (n=13).

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

- At the time of the interim analysis, infants had been enrolled for up to ~13 months
- All infants were still alive
- No infants have required invasive ventilation or tracheostomy
- No infants have required non-invasive ventilation for ≥6 hours/day continuously for ≥7 days

NURTURE study interim analysis data cutoff date: 8 June 2016. [a]Respiratory failure was defined as invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy.

Summary of HINE Motor Milestone[1] Achievements

Milestone	Total no. of infants achieving milestone n=13[a]	2 copies of *SMN2* n=9	3 copies of *SMN2* n=4
Head control (Full)	9	5	4
Sitting (Independent: stable, pivot)	5	4	1
Standing (Stands with support, unaided)	3	2	1
Walking (Cruising, walking)	1	1	–

1. Haataja L, *et al*. *J Pediatr*. 1999;135(2 Pt 1):153-161. NURTURE study interim analysis data cutoff date: 8 June 2016. [a]Efficacy analyses are based on 13 infants who have reached the first efficacy assessment visit (Day 64, age ~2 months) or longer.

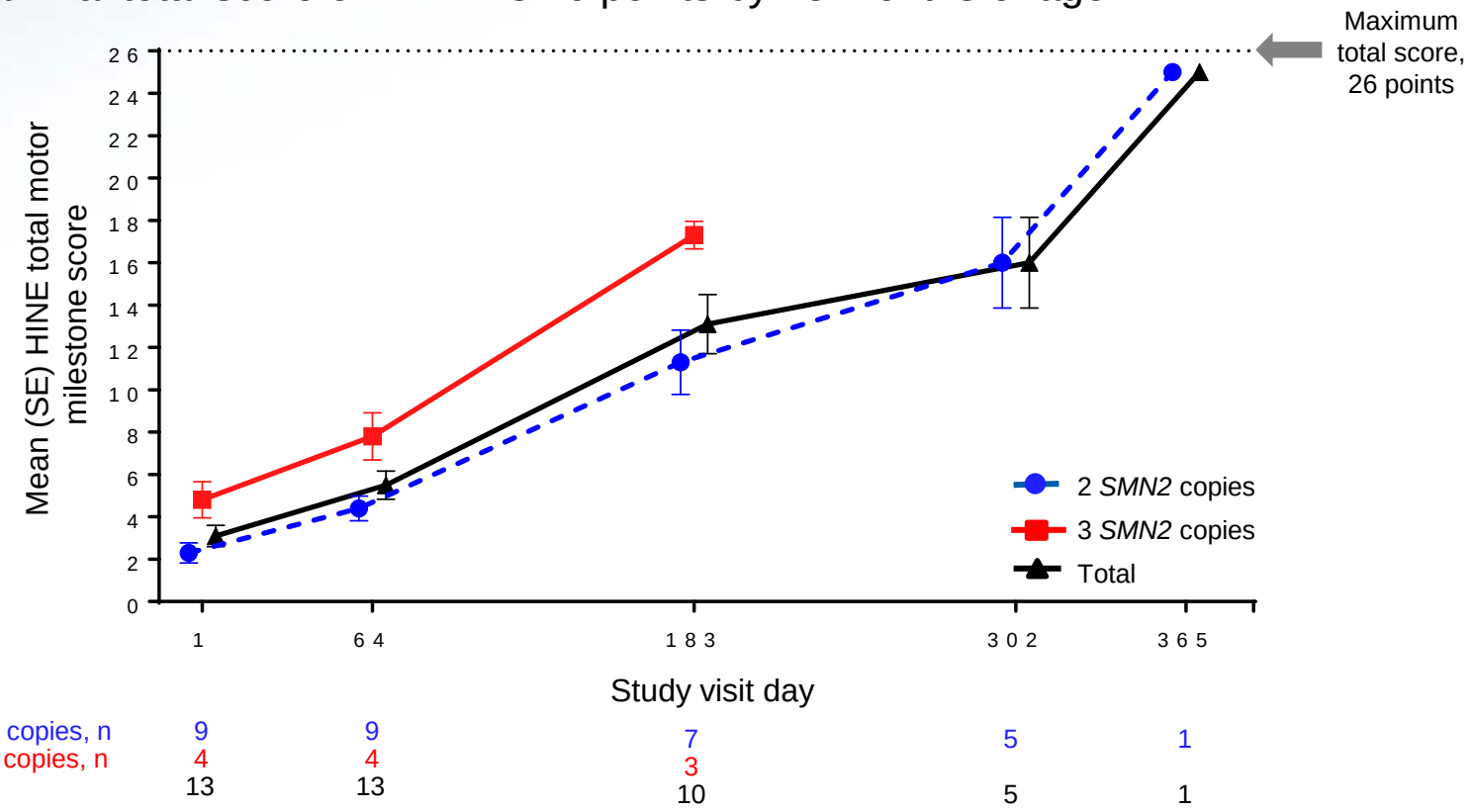
Age-Appropriate Motor Milestone Development Based on HINE

Milestone attainment in nusinersen-treated infants	Motor milestone	Expected age of attainment in healthy infant[1]
8/10 infants Age ≥5 mo	 Full head control	Age 5 mo
5/7 infants Age ≥7 mo	 Independent sitting	Age 7 mo
1/1 infant Age ≥11 mo	 Walking with support (cruising)	Age 11 mo
1/1 infant Age ≥12 mo	 Standing unaided[a]	Age 12 mo

1. Haataja L, *et al*. *J Pediatr*. 1999;135(2 Pt 1):153-161. NURTURE study interim analysis data cutoff date: 8 June 2016. [a]Two infants <8 months of age were standing with support (expected age of attainment: 8 months of age[1]).

Mean HINE Total Motor Milestone Score Over Time

- In general, all enrolled infants demonstrated increased motor milestone scores from Baseline to last evaluation
  - Milestone gain followed a similar trajectory for infants with 2 and 3 copies of the *SMN2* gene
  - Maximal total score on HINE is 26 points by 15 months of age

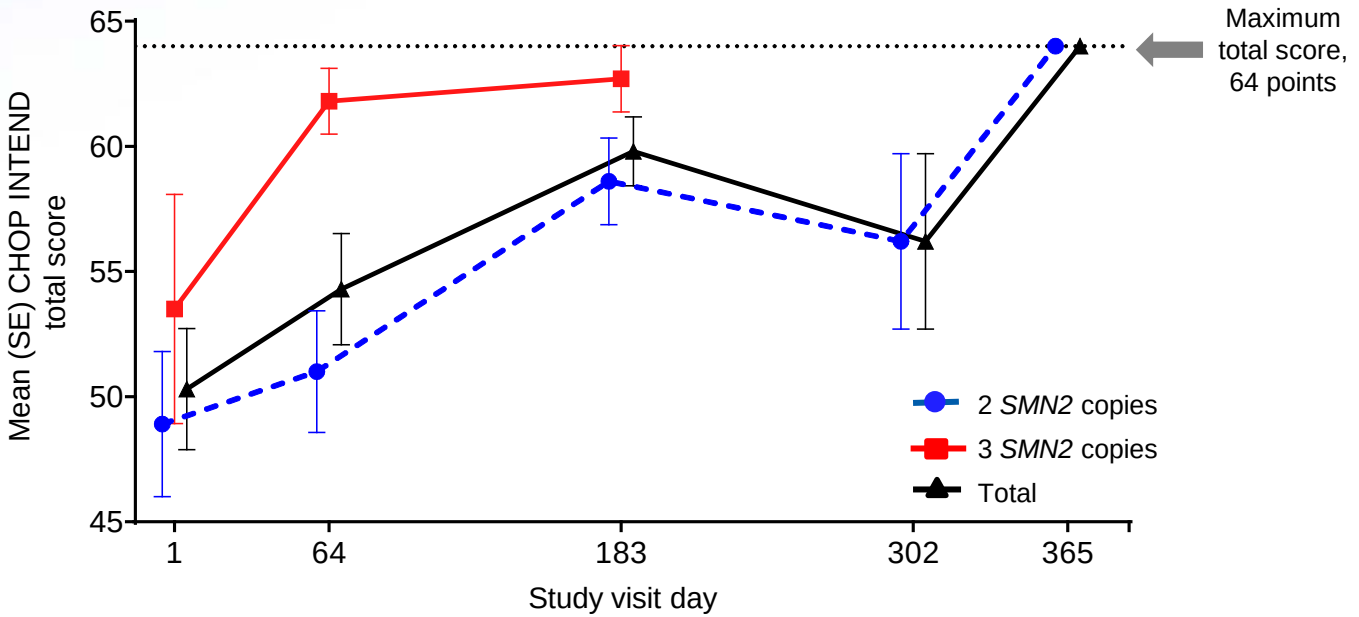


2 *SMN2* copies, n	9	9	7	5	1
3 *SMN2* copies, n	4	4	3		
Total, n	13	13	10	5	1

NURTURE study interim analysis data cutoff date: 8 June 2016.

Mean CHOP INTEND Total Score Over Time

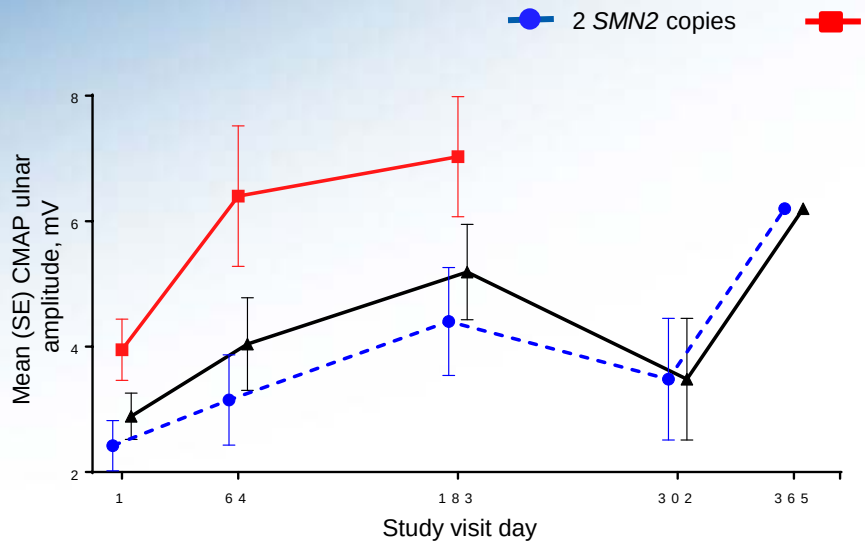
- 10/13 (77%) infants achieved increases (range, 4–20 points)
- 3/13 (23%) experienced decreases (range, 2–3 points)
- Baseline median (range) CHOP INTEND total score was 55.0 (39–60) points in the total efficacy population
  - CHOP INTEND total scores in infants with SMA ≤6 months of age from a natural history study ranged from 10–52 points[1]

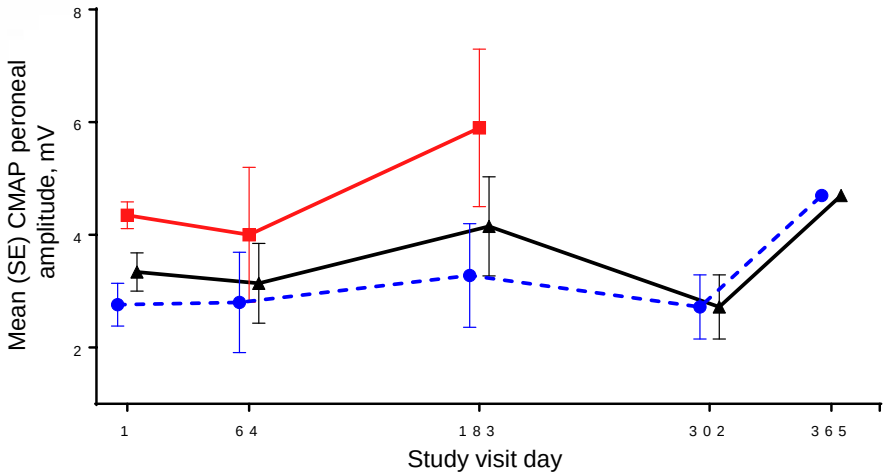


1. Kolb SJ, *et al*; NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. *Ann Clin Transl Neurol*. 2016;3(2):132-145. NURTURE study interim analysis data cutoff date: 8 June 2016.

Mean Ulnar and Peroneal Nerve CMAP Amplitude Over Time

- Overall, mean CMAP amplitude appears to be increasing





2 *SMN2* copies, n	9	8	7	5	1	7	5	4	5	1
3 *SMN2* copies, n	4	3	3			4	2	2		
Total, n	13	11	10	5	1	11	7	6	5	1

Age	CMAP amplitude in healthy infants, mV[1]	
	Ulnar nerve	Peroneal nerve
Neonate	1.6–7.0	1.8–4.0
1–6 mo	2.5–7.4	1.6–8.0
7–12 mo	3.2–10.0	2.3–6.0

1. Miller RG, Kuntz NL. *J Child Neurol*. 1986;1(1):19-26. NURTURE study interim analysis data cutoff date: 8 June 2016.

Growth Parameters

- The majority of infants gained weight over time, consistent with normal development
- Four of 10 infants met the criteria for growth failure at Day 183[a]
  - Three of the 4 infants continued to gain weight over time
  - One infant had a percutaneous gastric tube inserted to assist with feeding

NURTURE study interim analysis data cutoff date: 8 June 2016. [a]Growth failure was defined as weight for age below the fifth percentile (based on WHO growth charts) or a decreased growth velocity resulting in weight for age failing ≥2 major percentiles over a 6-month period. The 4 infants were determined to have growth failure because their weight for age decreased by ≥2 major percentiles over a 6-month period.

Summary of Safety

- Five (29%) infants experienced an SAE. There were no SAEs considered related to study drug
- No severe AEs were reported
- Three (18%) infants experienced AEs considered by the investigator to be possibly related to study drug.
  - Muscular weakness and weight-bearing difficulty (n=1), hyperreflexia and tachycardia (n=1) and increased ALT and AST and pyrexia (n=1)
  - All AEs considered by the investigator to be possibly related to study drug resolved during study follow-up
- No infants experienced AEs that led to discontinuation of study drug or withdrawal from the study
- The lumbar puncture procedure was generally well tolerated
- No clinically significant adverse changes in laboratory or neurological examinations considered related to nusinersen

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse event. NURTURE study interim analysis data cutoff date: 8 June 2016.

Conclusions

- Findings from the NURTURE interim analysis show that all the pre-symptomatic infants with SMA treated with nusinersen are alive without requiring chronic respiratory support and are exhibiting improvements in function and motor milestones
- Most infants are achieving motor milestone and growth parameter gains generally consistent with normal development
- The majority of infants are gaining weight
- To date, no new safety concerns have been identified

NURTURE study interim analysis data cutoff date: 8 June 2016.

Acknowledgements

- 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 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

Back up

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

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.