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Interim Efficacy and Safety Results from the Phase 2 NURTURE Study Evaluating Nusinersen in Presymptomatic Infants With Spinal Muscular Atrophy

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Introduction

- Spinal muscular atrophy (SMA)
  - Autosomal recessive neuromuscular disorder [1]
  - Caused by mutations in the *SMN1* gene[1]
  - SMA Type I: onset by age 6 months, never rolls or sits independently[2]
  - SMA Type II: onset by age 6–18 months, sits, but never walks independently[2]
- Nusinersen
  - Antisense oligonucleotide[3]
  - Modifies splicing of the homologous *SMN2* precursor mRNA[3]
  - Leads to increased production of full-length SMN protein[3,4]
- NURTURE
  - Phase 2, open-label, multicenter, multinational, single-arm study
  - 12-mg scaled equivalent dose of intrathecal nusinersen
  - Infants with genetically diagnosed and presymptomatic SMA (most likely to develop Type I or II)
  - Previous interim analysis:
    - Infants treated were achieving motor milestones generally consistent with normal development[5] in contrast to the natural history of SMA Type I[6]

mRNA = messenger RNA; SMN = survival of motor neuron. 1. Prior TW. *Curr Opin Pediatr.* 2010;22(6):696-702. 2. Finkel R, *et al*; ENMC SMA Workshop Study Group. *Neuromuscul Disord.* 2015;25(7):593-602. 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. 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. 6. Finkel RS, *et al*. *Neurology*. 2014;83(9):810-817.

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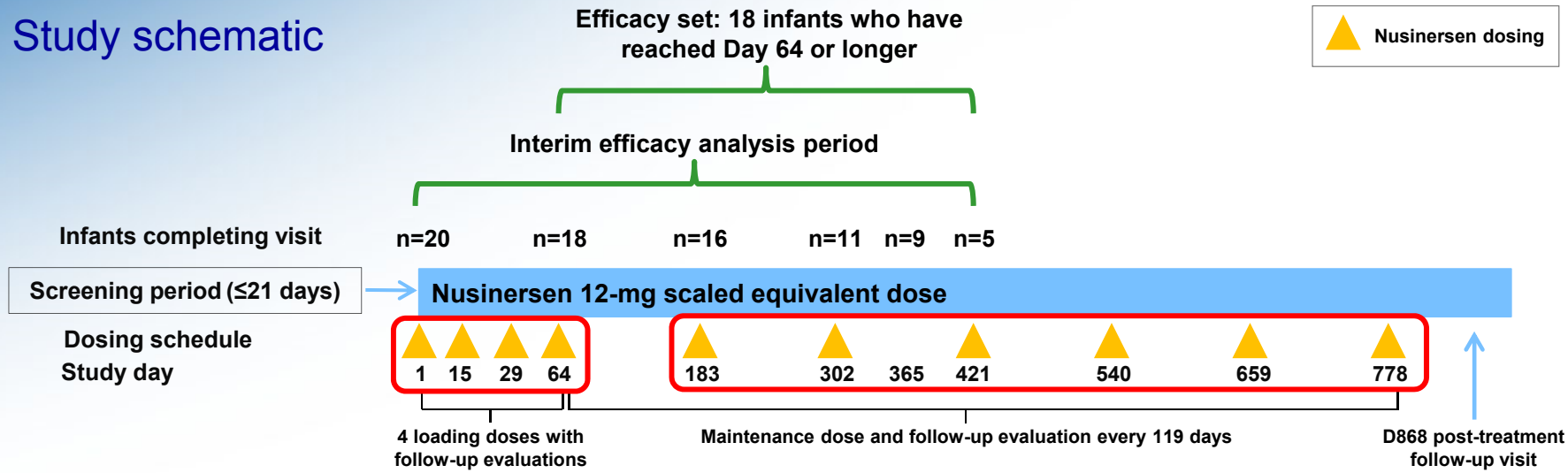
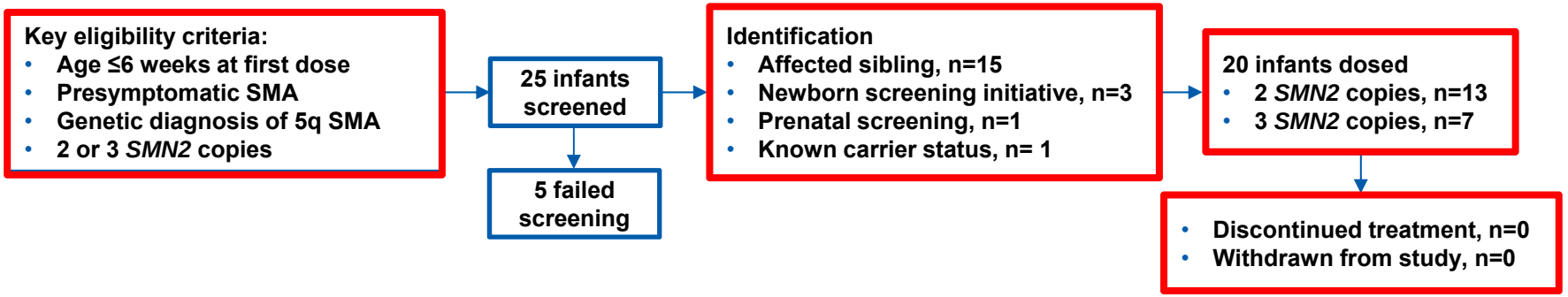
Study Overview: Interim Analysis (Data Cut-off: October 31, 2016)

Study schematic



Participant disposition



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

Date of presentation: April 27, 2017

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

- At the time of the interim analysis, infants had been enrolled for a median (range) 317.5 (2.0–524.0) days
- All infants were alive and none had required respiratory intervention

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.

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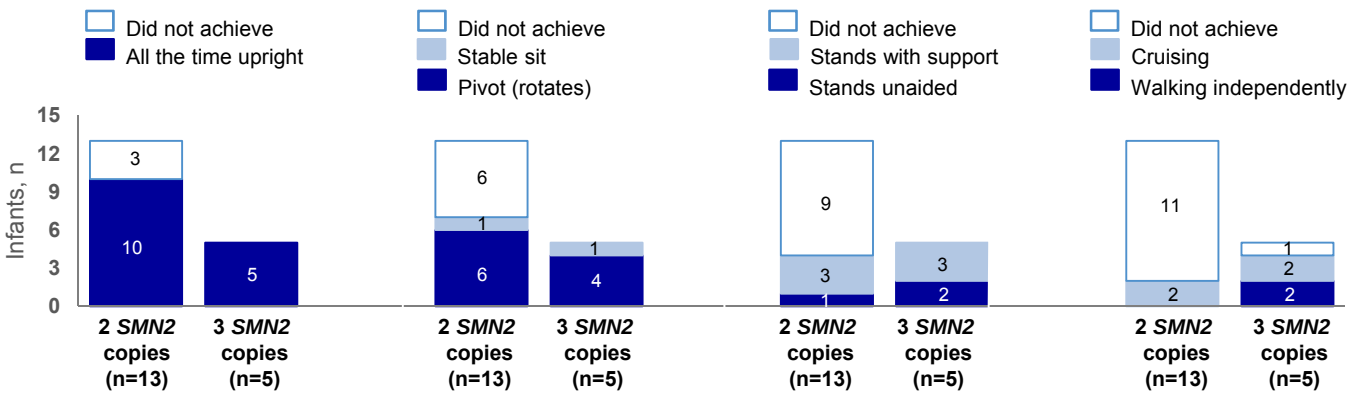
HINE Motor Milestone[1] Achievements[a]

Motor function	Full head control	Independent sitting (stable sit, pivot [rotates])	Stands with support/ Stands unaided	Cruising/ Walking
Total infants achieving, n	15	12	9	6
Expected age of attainment, mo[a]	5	7	8	11
Infants achieving at expected age, n/N (%)	15/**16** (94%)	10/**12** (83%)	7/**11** (64%)	5/**9** (56%)

- Three of **9** infants ≥12 months of age had achieved standing unaided (expected age, 12 months)
- Two infants ~13 months of age had achieved independent walking (expected age, 15 months)

Motor milestone achievement in interim efficacy set (n=18)[a]



HINE = Hammersmith Infant Neurological Examination. [a]Among 18 Infants With Day 64 Assessment. NURTURE study interim analysis data cut-off date: October 31, 2016. [a]In healthy infants. 1. Haataja L, *et al*. *J Pediatr*. 1999;135(2 pt 1):153-161.

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%)
SAE[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 with increased eosinophil count, lymphocyte count, and WBC count	1 (5%)
SAE related to study drug	0
AE leading to treatment discontinuation or withdrawal	0

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse event; 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 from the second interim analysis of NURTURE extend those from a June 2016 interim analysis
  - Continued beneficial effects of nusinersen in infants with presymptomatic SMA on survival and achievement of motor milestones over the expected natural history of SMA Type I[1]
  - All infants are alive without requiring chronic respiratory support and are exhibiting improvements in motor function and/or motor milestones
  - Most infants are achieving motor milestones generally consistent with normal development
  - Achievement of motor milestones not acquired by infants with SMA Type I or II
- Nusinersen was well tolerated and no specific safety concerns were identified

NURTURE study interim analysis data cut-off date: October 31, 2016. 1. Finkel RS, et al. *Neurology*. 2014;83(9):810-817.

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