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Nusinersen treatment of infantile-onset spinal muscular atrophy (SMA): study design and initial interim efficacy and safety findings from the phase 3 ENDEAR study

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Disclosures

- NK: reports serving on National Advisory Board for Biogen; outside of the submitted work, NK serves on National Advisory Boards and as consultant for AveXis, Catalyst, Cytokinetics, Marathon, PTC, and Sarepta. NK also serves in an advisory capacity to CureSMA and MGFA
- WF, ZJZ, PS, and SG: full-time employees of Biogen and own stock in Biogen
- ES: full-time employee of Ionis Pharmaceuticals Inc. and owns stock in Ionis Pharmaceuticals Inc
- RF: reports grants and personal fees from Ionis Pharmaceuticals during the conduct of the study; grants and advisor fees from Biogen, grants from Cytokinetics and advisor to Roche, Novartis, and AveXis outside the submitted work. RF serves in an advisory capacity to non-profit organisations: the SMA Foundation, CureSMA, SMA Reach (UK) and SMA Europe, and also serves on the DSMB for the AveXis gene transfer study
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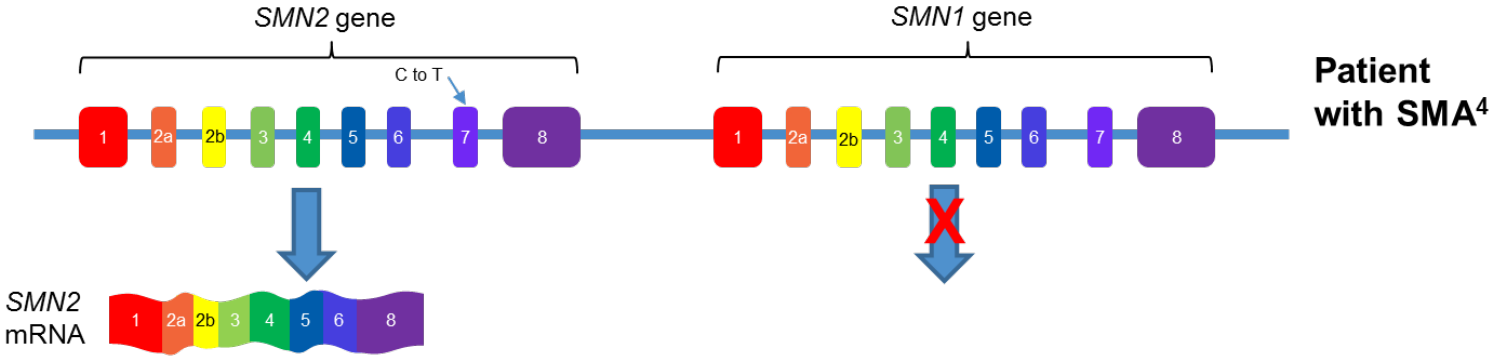
DSMB = data and safety monitoring board

Spinal Muscular Atrophy

SMA is a rare, debilitating, autosomal recessive neuromuscular disorder[1]

- Caused by insufficient levels of SMN protein[2]

SMA subtype	Severity	Age of onset	Natural age of death
Type 1 infantile-onset[3]	Severe	<6 mo	<2 y



The *SMN2* gene produces insufficient levels of SMN protein[1,2]

mo = months; mRNA = messenger ribonucleic acid; SMA = spinal muscular atrophy; SMN = survival of motor neuron; y = years. 1. Lunn MR *et al. Lancet*. 2008;371:2120-2133; 2. Prior TW. *Curr Opin Pediatr.* 2010;22(6):696-702; 3. Markowitz JA, *et al. Pediatr Neurol* 2012;46:1-124; 4. Chiriboga CA, *et al. Neurology*. 2016;86:890-897

Nusinersen

- Antisense oligonucleotide that increases the amount of full-length *SMN2* mRNA[1]
  - Promotes increased production of functional SMN protein[2,3]

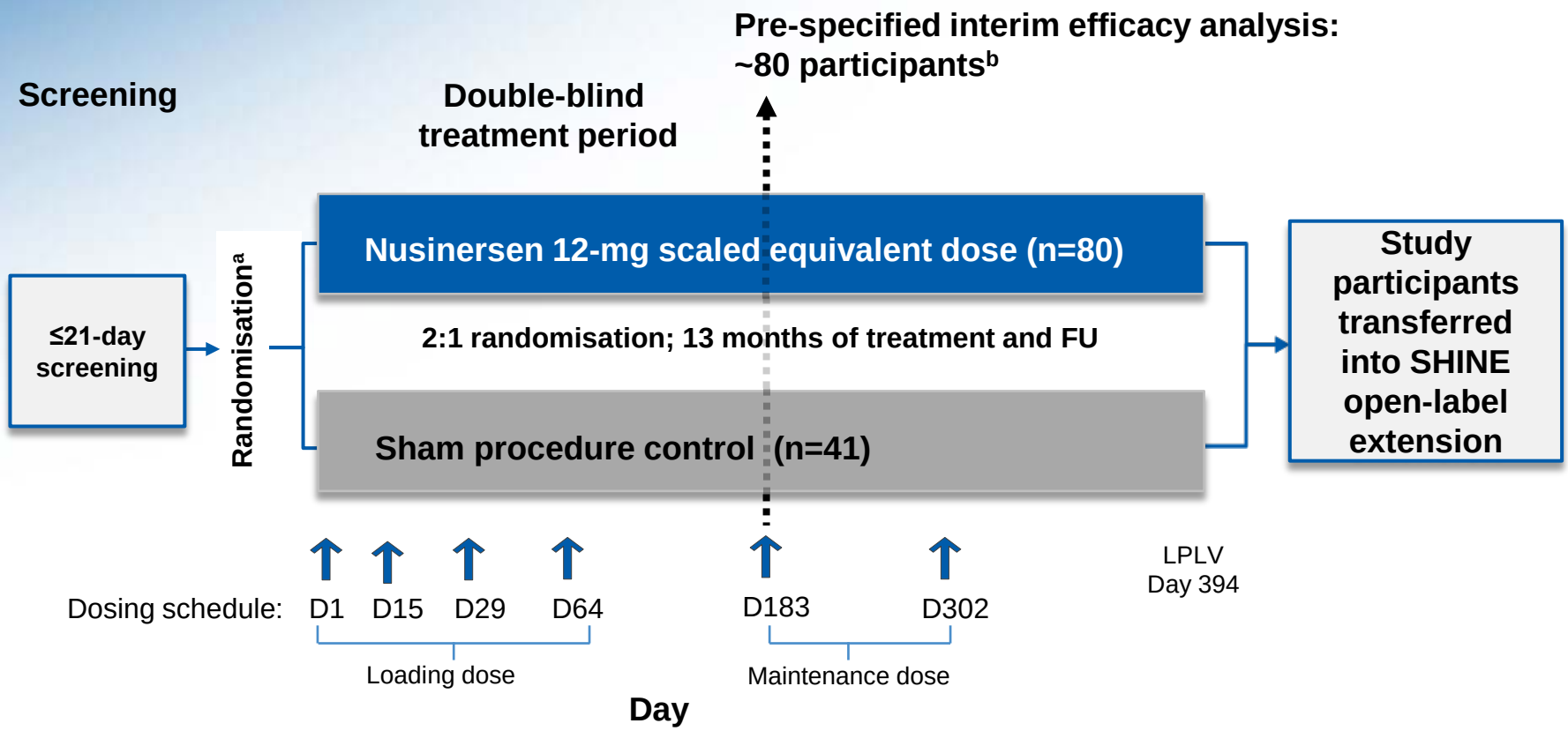
- Phase 2 study (CS3a) interim results[a] in infants with SMA showed promising safety and efficacy[4]
  - No safety or tolerability concerns identified
    - Intrathecal injections were well tolerated
  - Ventilation-free survival of nusinersen-treated infants was divergent from natural history of SMA
  - Achievement of new motor milestones in most treated infants

[a]Interim analysis data cut conducted 26 Jan 2016; 1. Hua Y, *et al. Genes Dev.* 2010;24(15):1634–1644; 2. Passini MA, *et al. Sci Transl Med.* 2011;3(72):72ra18; 3. Darras B, *et al. Neuromusc Disord.* 2014;24(9–10):920; 4. Finkel R, *et al. Neurology.* 2016;86(suppl 16):P5.004

The ENDEAR Study

- ENDEAR is a Phase 3, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy, safety, and tolerability of intrathecal nusinersen in infants with SMA

ENDEAR Study Design



ITT and Safety population: randomised and received ≥1 dose of study drug

Interim Efficacy population: ITT participants who received nusinersen dose/sham-procedure ≥6 months before cut-off date for interim efficacy analysis, and/or were assessed at any of the Day 183, 302 or 394 visits

D = day; FU = follow-up; ITT = intent to treat; LPLV = last patient last visit; [a]Randomisation was stratified by disease duration during screening (age at screening minus age at symptom onset): ≤12 vs. >12 weeks; [b]Interim efficacy analysis was conducted on 15 June 2016, once ~80 participants had the opportunity to be assessed at Day 183 visit. Final efficacy analysis of ENDEAR will occur when the last surviving participant completes the Day 394 assessment or earlier, as per ethical considerations. Clinicaltrials.gov NCT02193074

Key Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age	Hypoxemia (oxygen saturation of <96% awake or asleep without ventilation support)
Genetic diagnosis of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation	Signs or symptoms of SMA present at birth, or within ≤1 week after birth
≤7 months of age at screening[a]	Untreated or treated active infection
2 *SMN2* copies	Previous use of an investigational drug for the treatment of SMA

[a]Additionally, a gestational age of 37–42 weeks was required

ENDEAR Hierarchical Endpoints[a]

- Primary
  - Proportion of motor milestone responders
    - Assessed using modified section 2 of the HINE[1]
    - Interim efficacy analysis conducted once ~80 participants had the opportunity to be assessed at Day 183 visit
  - Time to death or permanent ventilation *[Not tested at the interim efficacy analysis]*
    - Permanent ventilation: tracheostomy or ≥16 hours ventilatory support per day for >21 days

HINE = Hammersmith Infant Neurological Exam. [a]Primary analyses must reach statistical significance before inferential conclusions can be drawn from the remaining secondary and tertiary endpoints; 1. Haataja L, *et al*. *J Pediatr.* 1999;135(2 Pt 1):153–161

ENDEAR Primary Endpoint: Definition of HINE Motor Milestone Responders

Modified section 2 of the HINE[1]

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

Improvement

Improvement

Improvement: ≥2-point improvement in ability to kick (or maximal score), OR ≥1-point improvement in any other milestone excluding voluntary grasp

Worsening: ≥2-point worsening in ability to kick (or zero score), OR ≥1-point worsening in any other milestone excluding voluntary grasp

Motor Milestone Responder definition[a]: More HINE categories with improvement than worsening

- Participants who die or withdraw are counted as non-responders

[a]Study participants on permanent ventilation will be assessed; 1. Haataja L, *et al*. *J Pediatr.* 1999;135(2 Pt 1):153–161

Other ENDEAR Study Endpoints[a]

Not tested at interim efficacy analysis

- Secondary endpoints include:
  - CHOP-INTEND responders
    - ≥4-point improvement from Baseline in total score from Day 183+
  - Survival rate
  - Participants (%) not requiring permanent ventilation
  - Proportion of CMAP responders (peroneal nerve)
    - Maintenance or increase by ≥1 mV vs. Baseline from Day 183+

- Additional endpoints include:
  - Growth parameters from Baseline
  - Safety and tolerability
  - Pharmacokinetics[b] and immunogenicity

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential;
[a]Primary analyses must reach statistical significance before inferential conclusions are drawn from other endpoints; [b]Pharmacokinetics will be assessed using plasma and cerebrospinal fluid samples

Baseline Demographics: ITT population

- Baseline demographics were balanced except for age and geographic region
  - The nusinersen group was younger than the sham controls group
  - A higher percentage of nusinersen–treated patients were from Asia-Pacific region; more sham-procedure control patients were from Europe

Characteristic	Sham-procedure control (n=41)	Nusinersen (n=80)
Female, n (%)	**24** (59)	**43** (54)
Gestational median age, weeks	**40**	**39**
Median age at screening, days	**190**	**152**
Median age at first dose, days	**205**	**165**
Geographic region, n (%) North America Europe Asia-Pacific	 **22** (54) **17** (41) **2** (5)	 **38** (48) **30** (38) **12** (15)
Ethnicity, n (%) Hispanic or Latin-American White	 **4** (10) **37** (90)	 **12** (15) **68** (85)

Baseline Disease Characteristics: ITT Population

- Disease duration and *SMN2* copy number were similar between groups

Characteristic	Sham-procedure control (n=41)	Nusinersen (n=80)
Age at symptom onset, weeks, n (%) ≤12 weeks >12 weeks	 **32** (78) **9** (22)	 **72** (90) **8** (10)
Median age at symptom onset, weeks	**8.0**	**6.5**
Disease duration, weeks, n (%) ≤12 weeks >12 weeks	 **18** (44) **23** (56)	 **34** (43) **46** (58)
Median disease duration, weeks	**12.7**	**13.1**
Median age of SMA diagnosis, weeks	**20.0**	**11.0**
SMA symptoms, n (%) Hypotonia Developmental motor delay Paradoxical breathing Pneumonia or respiratory symptoms Limb weakness Swallowing or feeding difficulties Other	 **41** (100) **39** (95) **27** (66) **9** (22) **41** (100) **12** (29) **14** (34)	 **80** (100) **71** (89) **71** (89) **28** (35) **79** (99) **41** (51) **20** (25)
Participants requiring ventilation support, n (%)	**6** (15)	**21** (26)
Mean (SD) time on ventilation support at Baseline, h	**6.8** (4.2)	**8.4** (4.3)

ENDEAR Interim Efficacy Analysis Results[a]

- Significant improvement in the proportion of nusinersen–treated motor milestone responders versus sham-procedure control (*P*<.0001)
  - Highly clinically and statistically significant percentage of motor milestone responders

- Interim analysis represents 44.89 patient-years of exposure to nusinersen treatment

[a]The interim efficacy analysis was conducted on 15 June 2016, once ~80 participants had the opportunity to be assessed at Day 183 visit

Summary of Adverse Events (AEs)

- No AEs or serious AEs were considered related to treatment
  - 11% nusinersen–treated versus 15% sham-procedure control participants had AEs possibly related to treatment

	Sham-procedure control n=41	Nusinersen n=80
Any AE, %	93	90
Treatment-related AE,[a] %	0	0
Possibly treatment-related AE, %	15	11
Severe or moderate AE, %	85	78
Severe AE, %	66	55
Serious AE, %	80	70

AE = adverse event. [a]Investigators assessed whether the AE was related to study drug.
A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalisation/prolonged hospitalisation, persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. Severe AEs were defined as symptoms causing severe discomfort, incapacitation or significant impact on daily life; participants reporting >1 AE were counted once for total incidence, using the highest severity.

Adverse Event Summary

- Nusinersen was generally well-tolerated
  - Commonly-reported AEs were consistent and age appropriate with those expected in the general population of infants with SMA

	Sham control n=41	Nusinersen n=80
Common AE (>20% in study participants) by MedDRA PT, %		
Pyrexia	54	49
Constipation	22	30
Upper respiratory tract infection	22	25
Respiratory distress	34	24
Pneumonia	15	21
Respiratory failure	34	21
Atelectasis	22	19
Oxygen saturation decreased	22	10
Treatment-emergent AE, %	93	90

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

Conclusions

- ENDEAR is a Phase 3, double-blind, sham-procedure controlled study in infants with SMA
- Nusinersen met the primary endpoint pre-specified for the interim efficacy analysis
  - Clinically and statistically significant percentage of motor milestone responders
  - Acceptable safety profile and well tolerated
- Participants from ENDEAR will be transitioned into the SHINE open-label extension[1]
  - SHINE to enrol all participants with SMA who were previously entered into nusinersen investigational studies
  - Safety, efficacy and tolerability will be assessed
- Final results will be presented at a future medical congress

1. An Open-Label Study (SHINE) for Patients With Spinal Muscular Atrophy (SMA) Who Participated in Studies With IONIS-SMNRx, available at: https://clinicaltrials.gov/ct2/show/NCT02594124?term=NCT0259412

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