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

Nusinersen in treatment-naïve patients with later-onset spinal muscular atrophy (SMA): efficacy results from a phase 1b/2a multicentre study (CS2) and its open-label extension (CS12)

Basil T Darras, MD

8 October, 2016

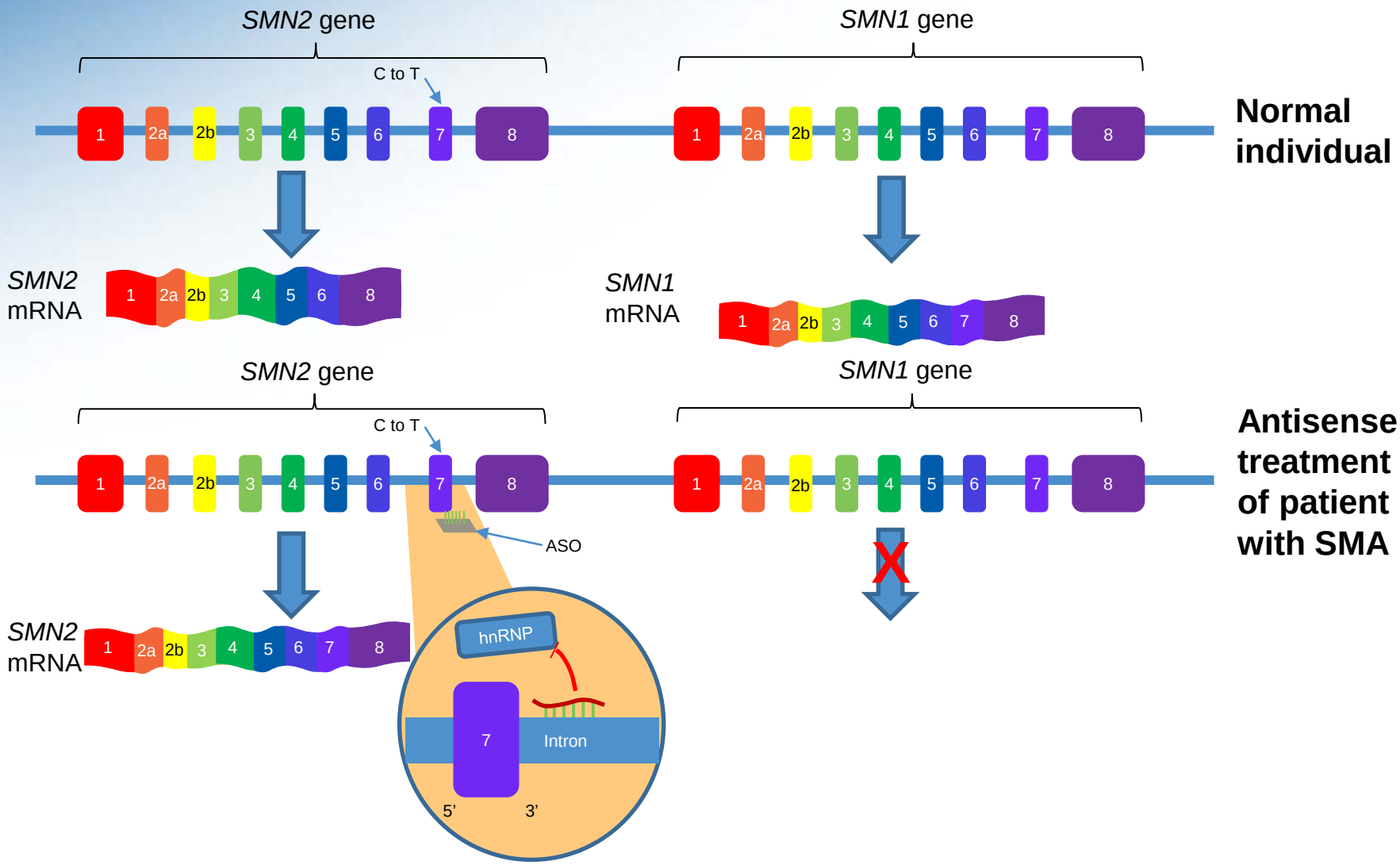
Darras BT,[1*] Chiriboga CA,[2] Montes J,[2] Swoboda KJ,[3] Johnson N,[4] Iannaccone ST,[5] Castro D,[5] Mignon L,[6] Norris D,[6] Gamelin L,[6] Xia S,[6] Fine S,[6] Bennett CF,[6] Bishop K,[6] Foster R,[7] Gheuens S,[7] Sun P,[7] Farwell W,[7] Schneider E,[6] De Vivo DC,[2] on behalf of the CS2 and CS12 study investigators

[1]Department of Neurology, Boston Children's Hospital, Boston, MA, USA; [2]Columbia University Medical Center, New York, NY, USA; [3]Massachussetts General Hospital; Department of Neurology, Boston, MA, USA; [4]Neurology, University of Utah School of Medicine, Salt Lake City, UT, USA; [5]Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA; [7]Biogen, Cambridge, MA, USA

Disclosures

- BTD: consultant at scientific advisory board meetings for Roche, AveXis, PTC Therapeutics, Biogen, Marathon Pharma; advisor for Ionis Pharmaceuticals, Inc.; received research support from SMA Foundation, NIH/NINDS, Slaney Fund for SMA
- CAC: consultant for Roche Pharmaceuticals, AveXis, and Novartis; received grants from SMA Foundation and Department of Defense
- JM: receives support from Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) 1K01HD084690-01A1; consultant for Ionis Pharmaceuticals, Inc.; served on advisory boards for Roche Pharmaceuticals and Biogen
- KJS: receives support from Eunice Kennedy Shriver National Institute for Health and Human Development (NICHD) R01-HD69045, has served as a consultant for Roche Pharmaceuticals, and is on the scientific advisory board for AveXis
- NJ: serves as an Associate Editor for Neurology: Genetics; funded by the NIH, grant #1K23NS091511-01; received research support from the Muscular Dystrophy Association, Myotonic Dystrophy Foundation, Valerion Therapeutics, AMO Pharma, Ionis Pharmaceuticals, Inc., and Biogen
- STI: consultant for Ionis Pharmaceuticals; served on advisory Boards for Biogen, AveXis, Santhera and Sarepta; research grants from NIH and MDA
- DC: served on advisory boards for Sarepta and Marathon Pharmaceuticals
- LM, DN, LG, SX, SF, CFB and ES: employees of and hold stock/stock options in Ionis Pharmaceuticals, Inc.
- KB: full-time employee of Ionis Pharmaceuticals, Inc. from 2009–2015
- RF, SG, SP and WF: employees of and hold stock/stock options in Biogen
- DCD: advisor/consultant for AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Inc., Roche, Sarepta, and the SMA Foundation, with no financial interests in any of these companies; grants from the Department of Defense, Hope for Children Research Foundation, the National Institutes of Health, and the SMA Foundation
- Ionis Pharmaceuticals, Inc. (Carlsbad, CA, USA) and Biogen (Cambridge, MA, USA) funded the studies
- Writing and editorial support for the preparation of this presentation was provided by Excel Scientific Solutions (Horsham, UK): funding was provided by Biogen

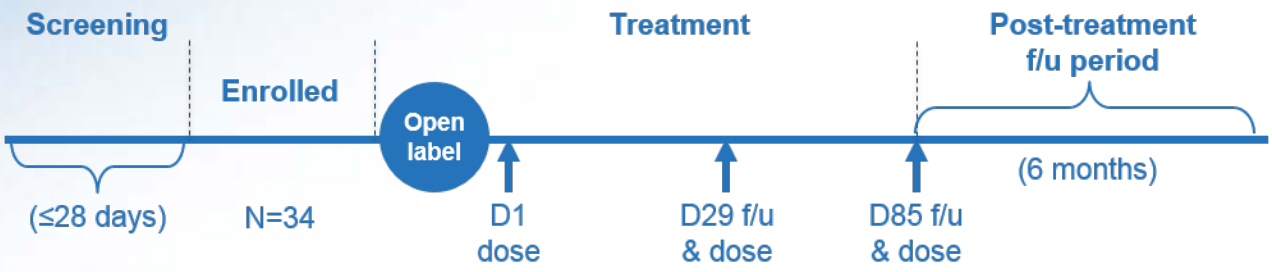
Spinal muscular atrophy and nusinersen



ASO = antisense oligonucleotide; hnRNP = heterogeneous nuclear ribonucleoprotein; mRNA = messenger ribonucleic acid; SMA = spinal muscular atrophy; *SMN* = survival motor neurone. 1. Chiriboga CA, *et al. Neurology*. 2016;86:890-897.

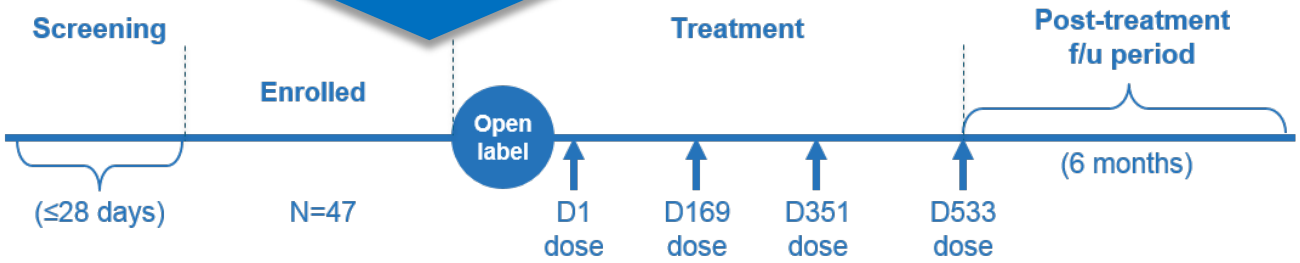
CS2 (phase 1b/2a, open-label study) and CS12 (multiple dose redosing study)

CS2 total cohort	Dose	Total dose	N[a]
1	3 mg	9 mg	8
2	6 mg	18 mg	8
3	9 mg	18 mg	9[b]
4	12 mg	36 mg	9



Interval between studies:
3 mg: ~13 months
6 mg: ~10 months
9 mg: ~10 months
12 mg: ~7 months

CS12 total cohort	Dose	Total dose	N[a]
1	12 mg	48 mg	47



- Primary endpoint:
  - Evaluate the safety and tolerability of nusinersen administered intrathecally
- Exploratory endpoints include:
  - HFMSE
  - ULM test (non-ambulatory patients)
  - 6MWT (ambulatory patients)

6MWT = 6-minute walk test; AE = adverse event; D = day; HFMSE = Hammersmith functional motor scale – expanded; f/u, follow-up; ULM = upper limb module test. N[a] = overall enrollment. [b]Patients received treatment on Days 1 and 85 only. Data cut-off dates: 12 January 2015 (CS2), 07 April 2016 (CS12 interim analysis). Chiriboga CA, et al. AAN 2014; ClinicalTrials.gov NCT01703988; Clinicaltrials.gov NCT02052791.

Baseline demographics for patients who received their first nusinersen dose in CS2

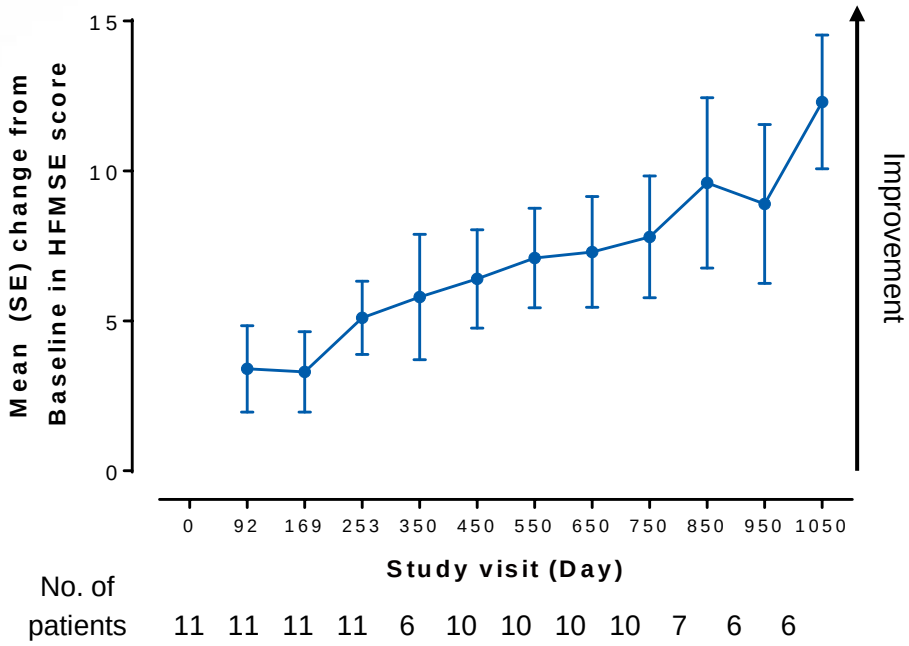
- 6 / 34 patients from CS2 who entered CS12 previously received nusinersen in CS1[a]
- Patients naïve to drug in CS2 were identified and followed into CS12 for this analysis (N=28)

	SMA Type II n=11	SMA Type III n=17	Total N=28
Mean (SD) age at screening in CS2, years	4.4 (4.0)	8.9 (4.4)	7.1 (4.7)
Males, n (%)	8 (73)	7 (41)	15 (54)
Mean (SD) age at symptom onset, months	11.0 (3.4)	22.0 (13.5)	17.7 (11.9)
Mean (SD) age at SMA diagnosis, months	15.4 (6.3)	43.6 (32.4)	32.5 (28.9)
SMN2 copy number, n (%)[b]			
2	0	1 (6)	1 (4)
3	11 (100)	10 (59)	21 (75)
4	0	6 (35)	6 (21)
Ambulatory status, n (%)[b]			
Ambulatory	0	13 (76)	13 (46)
Non-ambulatory	11 (100)	4 (24)	15 (54)
Motor function at screening in CS2, n (%)[b]			
Sitting without support	11 (100)	17 (100)	28 (100)
Standing without support	0	12 (71)	12 (43)
Walking with support	2 (18)	15 (88)	17 (61)
Walking independently	0	13 (76)	13 (46)

[a]CS1 (NCT01494701) was a single ascending-dose, Phase 1, open-label study of nusinersen in patients with later-onset SMA. Patients from CS1 could enrol in CS2. [b]Based on patients dosed with nonmissing data. Data cut-off dates:12 January 2015 (CS2), 07 April 2016 (CS12 interim analysis).

Change in HFMSE score over time: patients with Type II SMA

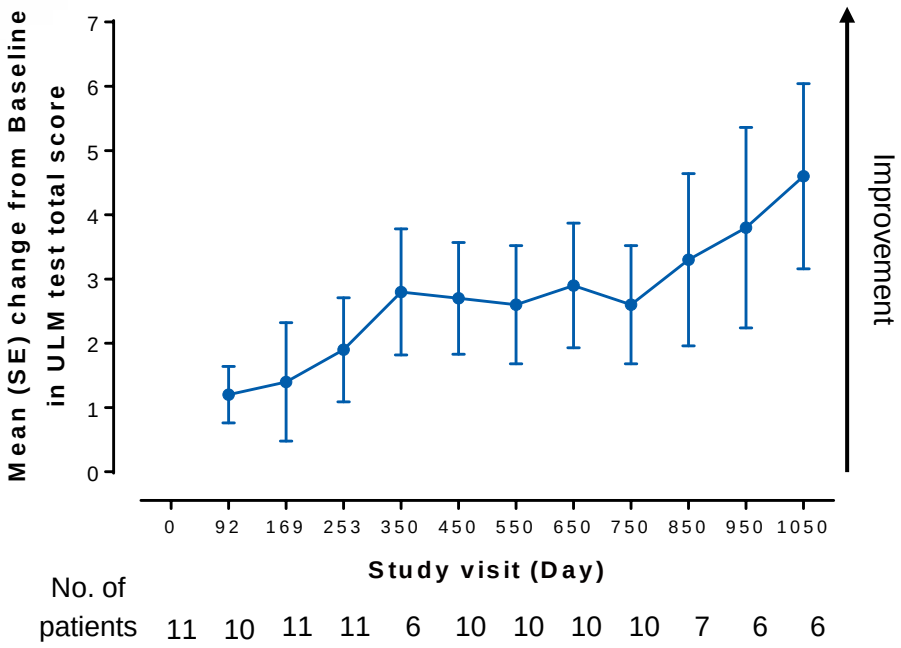
- Maximum possible HFMSE score is 66[1]
- Mean (SE) Baseline HFMSE score: 21.3 (2.9)
- Mean (SE) change with nusinersen of:
  - 5.1 (1.2) points at Day 253
  - 12.3 (2.2) points at Day 1050
- In a natural history cohort of Type II and Type III SMA, mean change was –0.5 point over 24 months (730 days) and –1.7 points over 36 months (1095 days)[2]



Data cut-off date: 07 April 2016 (CS12 interim analysis). 1. O'Hagen JM, *et al. Neuromuscul Disord*. 2007:17:693-697; 2. Kaufman P, *et al. Neurology*. 2012;79:1889–1897.

Change in ULM test total score over time: patients with Type II SMA

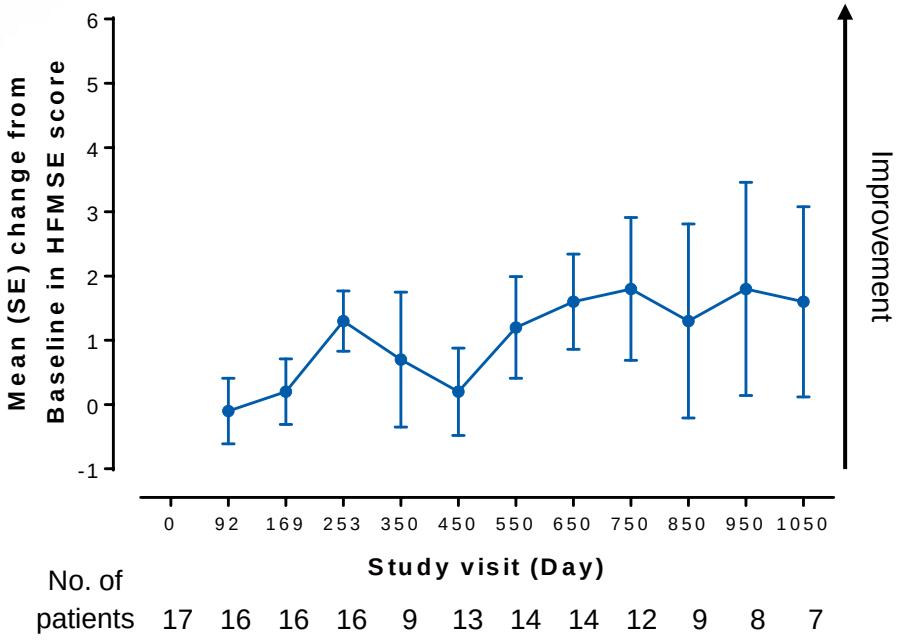
- Maximum possible ULM test total score is 18 in nonambulant patients with SMA[1]
- Mean (SE) Baseline ULM test total score: 11.9 (0.9)
- Mean (SE) change with nusinersen of:
  - 1.9 (0.8) points at Day 253
  - 4.6 (1.4) points at Day 1050
- In a natural history, mean change was 0.04 points over 12 months[2]



Data cut-off date: 07 April 2016 (CS12 interim analysis). 1. Mazzone E, *et al. Neuromuscul Disord*. 2011;21:406-412; 2. Sivo S, *et al. Neuromuscul Disord*. 2015;25(3):212-215.

Change in HFMSE score over time: patients with Type III SMA

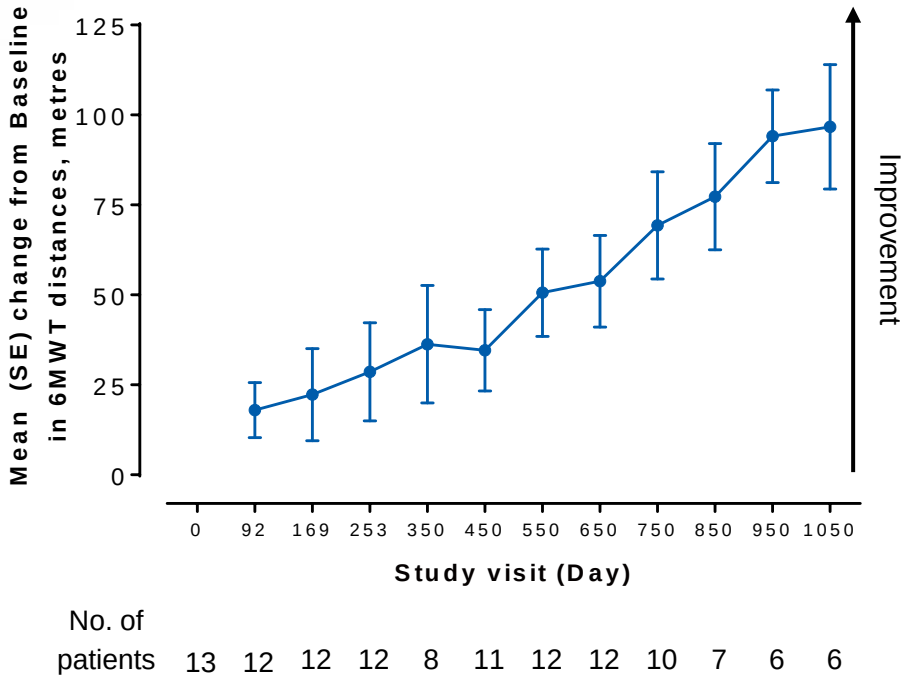
- Maximum possible HFMSE score is 66[1]
- Mean (SE) Baseline HFMSE score: 48.9 (3.0)
- Mean (SE) change with nusinersen of:
  - 1.3 (0.5) points at Day 253
  - 1.6 (1.5) points at Day 1050
- In a natural history cohort of Type II and Type III SMA, mean change was –0.5 points over 24 months (730 days) and –1.7 points over 36 months (1095 days)[2]



Data cut-off date: 07 April 2016 (CS12 interim analysis). 1. O'Hagen JM, *et al. Neuromuscul Disord*. 2007:17:693-697; 2. Kaufman P, *et al. Neurology*. 2012;79:1889–1897.

Change in 6MWT distances over time: patients with Type III SMA

- Mean (SE) Baseline 6MWT distance: 253.3 (50.7) metres
- Mean (SE) change with nusinersen of
  - 28.6 (13.6) metres at Day 253
  - 96.7 (17.3) metres at Day 1050
- Natural history is mean –1.5 metre change over 12 months[1]
- One patient with Type II SMA gained the ability to walk independently
- Two patients with Type III SMA re-gained the ability to walk independently



Data cut-off date: 07 April 2016 (CS12 interim analysis). 1. Mazzone E, *et al. Neuromuscul Disord*. 2013;23(8):624-628.

Safety and tolerability for CS2 and CS12

- In the 28 patients who first received nusinersen in CS2, median (min, max) number of intrathecal doses was 6 (1, 7)
  - Mean (SD) time on study was 880.5 (328.5) days
- Overall, most AEs were mild to moderate and considered not related to study drug
  - No SAEs were reported as related to study drug
- The LP procedure was generally well tolerated
  - Some AEs (e.g., PLPS, headache, back pain) were possibly associated with the LP and are expected in the context of this procedure[1,2]
- No clinically significant adverse changes in laboratory or neurological examinations considered related to nusinersen

LP = lumbar puncture; PLPS = post-lumbar puncture syndrome; SAE = serious AE. Data cut-off dates: 12 January 2015 (CS2), 07 April 2016 (CS12 interim analysis).

1. Ellenby MS, *et al. N Engl J Med*. 2006;355(13)e12; 2. Morgenlander JC. *Postgrad Med*. 1994;95(8):125-128,131.

Summary

- Baseline characteristics for this cohort were consistent with expected natural history
- For patients with Type II SMA with up to ~3 years of treatment:
  - Improvements were observed in motor function over time, as measured by HFMSE scores and ULM test
  - One patient with Type II SMA gained the ability to walk independently
- For patients with Type III SMA with up to ~3 years of treatment:
  - HFMSE scores were stable over time
  - Increases were observed in 6MWT distances
  - Two patients with Type III SMA re-gained the ability to walk independently
- No new safety findings were reported during longer-term treatment with nusinersen

Data cut-off dates: 12 January 2015 (CS2), 07 April 2016 (CS12 interim analysis).

Acknowledgments

- 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