ARTICLE   CLASS OF EVIDENCE

Nusinersen in spinal muscular atrophy type 1 patients older than 7 months
A cohort study

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Abstract

Objective
To evaluate the safety and clinical efficacy of nusinersen in patients with spinal muscular atrophy type 1 (SMA1) older than 7 months.

Methods
Patients with SMA1 were treated with nusinersen by intrathecal injections as a part of the Expanded Access Program (EAP; NCT02865109). We evaluated patients before treatment initiation (M0) and at 2 months (M2) and 6 months (M6) after treatment initiation. Survival, respiratory, and nutritional data were collected. Motor function was assessed with the modified Hammersmith Infant Neurologic Examination Part 2 (HINE-2) and physiotherapist scales adjusted to patient age (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders and the Motor Function Measure 20 or 32).

Results
We treated 33 children ranging in age from 8.3 to 113.1 months between December 2016 and May 2017. All patients were alive and were continuing treatment at M6. Median progress on the modified HINE-2 score was 1.5 points after 6 months of treatment ($p < 0.001$). The need for respiratory support significantly increased over time. There were no statistically significant differences between patients presenting with 2 and those presenting with 3 copies of the survival motor neuron 2 (*SMN2*) gene.

Conclusions
Our results are in line with the phase 3 study for nusinersen in patients with SMA1 treated before 7 months of age and indicate that patients benefit from nusinersen even at a later stage of the disease.

ClinicalTrials.gov identifier:
NCT02865109.

Classification of evidence
This study provides Class IV evidence that for patients with SMA1 who are older than 7 months, nusinersen is beneficial.

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CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; **EAP** = Expanded Access Program; **ENDEAR** = A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy; **HINE-2** = Hammersmith Infant Neurologic Examination Part 2; **MFM** = Motor Function Measure; **M0** = before treatment; **M2** = 2 months of treatment; **M6** = 6 months of treatment; **SMA** = spinal muscular atrophy; **SMN** = survival motor neuron.

Spinal muscular atrophy (SMA) is caused by a homozygous mutation in survival motor neuron 1 (*SMN1*) that leads to motor neuron loss and axial and proximal muscle weakness. *SMN2*, a nearly identical gene, also produces SMN protein, but ≈90% of it is nonfunctional.[1] The number of *SMN2* copies is a known disease modifier.[1]

SMA type 1 is the most severe form of the disease. It starts before the age of 6 months, and patients never acquire a stable sitting position. In nearly all cases, there is no motor progress after the onset of symptoms, and the patient declines systematically after diagnosis.[1–3] The median survival is from ≈8 to 13.5 months of age.[3,4] Some patients, who generally have 3 copies of *SMN2*, present with a more chronic disease and may even live into adulthood with nutritional and ventilatory support.[3–7]

Nusinersen (Spinraza, Biogen Inc, Cambridge, MA) is an antisense oligonucleotide that increases production of functional SMN protein from *SMN2*. Patients with SMA1 treated with nusinersen have improved event-free survival and achieve motor milestones that sham-treated patients never do.[8,9] All trials so far have included only children <7 months of age at the time of enrollment.[8,9] Precocity of the treatment appears to predict the success of nusinersen therapy in SMA1[8,9] and SMA2,[10] and the benefit of treatment when initiated in patients >7 months of age was unknown. Here, we present results of safety and clinical efficacy after 6 months of follow-up of a cohort of patients with SMA1 treated with nusinersen beginning after the age of 7 months.

Methods

We prospectively observed all drug-naive patients with SMA1 who started treatment with nusinersen in our center after the age of 7 months between December 2016 and May 2017 and who completed 6 months of observation (EAP; NCT02865109). All patients within standard of care and without tracheostomy could be treated. Treatment was administered as previously reported.[8] Patients were assessed before treatment (M0) and at 2 months (M2) and 6 months (M6) after treatment initiation. We collected clinical history, adverse events, and *SMN2* copy numbers and performed full clinical examinations. We categorized patient respiratory status as no support, support for <16 h/d, or permanent support. Nutritional status was categorized as no support, nasogastric tube, or gastrostomy. We used the modified Hammersmith

Infant Neurologic Examination Part 2 (HINE-2) to evaluate motor milestones.[4,8] Physiotherapists performed Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) in all patients younger than 2 years. Motor Function Measure (MFM) 20 was performed in patients between 2 and 5 years of age and MFM 32 in those >5 years of age. All data were recorded in an ethics review board–approved registry (ANSM 2017-A02291-52, NCT03339830). Parents were informed of this registry and signed an informed consent for procedures outside the standard of care. Changes over time were analyzed with the Friedman and McNemar tests for quantitative and qualitative variables, respectively. Differences between 2 and 3 *SMN2* copies were assessed with Mann-Whitney and χ^2 tests for quantitative and qualitative variables, respectively, and negative results were confirmed with a parametric *t* test and analysis of variance. Missing data were not part of the analysis. We used IBM SPSS Statistics 22 (Armonk, NY) for all analysis.

Primary research question

Is nusinersen safe and efficient in patients with SMA1 older than 7 months?

Classification of evidence

This study provides Class IV evidence that nusinersen is safe and efficient on motor symptoms in this population.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

We collected and included all data on 33 patients (table). At M6, all patients were alive and continuing the treatment. The need for ventilatory support significantly increased over time (figure 1). Eight patients had worsened respiratory status at M6 compared to M0. Three patients (2 patients with 3 *SMN2* copies) started nighttime ventilation as a preventive treatment and were motor-milestones responders. Three patients with 2 *SMN2* copies were placed on full-time ventilation and had no significant motor progress. Two patients with 2 *SMN2* copies started noninvasive ventilation between M0 and M2 for curative reasons but presented motor-milestones response between M2 and M6. There was no significant change in nutritional support. *SMN2* copy number did not influence the need for ventilatory or nutritional support. Median progress in modified HINE-2 was 1.5 points at M6 (n = 30) (table and figure 1A),

Table Characteristics at baseline and evolution of the patients according to *SMN2* copy number

Characteristics	Total (n = 33)	2 Copies of *SMN2* (n = 15)	3 Copies of *SMN2* (n = 17)
Sex, M/F, n	18/15	6/9	11/6
Age at first symptoms, median (range), mo	4 (1.5 to 6)	3 (1.5 to 5)	4 (2 to 6)
Age at first injection, median (range), mo	21.3 (8.3 to 113.1)	19.8 (8.3 to 42.0)	27.7 (8.8 to 113.1)
Duration since onset, median (range), mo	26.0 (4.3 to 109.1)	16.0 (4.3 to 40)	24.7 (4.8 to 109.6)
Modified HINE-2 score, median (range), n			
M0	1 (0 to 6), n = 33	1 (0 to 6), n = 15	2 (0 to 6), n = 17
M2	2 (0 to 8), n = 31	2 (0 to 8), n = 14	2 (0 to 7), n = 16
M6	3.5 (0 to 11), n = 30	3 (0 to 10), n = 14	4 (0 to 11), n = 16
Time-effect *p* value[a]	0.000	0.058	0.000
Delta M2−M0	0 (−1 to 5), *p* = 0.001	0 (−1 to 4), *p* = 0.033	0 (0 to 5), *p* = 0.017
Delta M6−M0[b]	1.5 (−1 to 9), *p* = 0.000	1.5 (−1 to 4), *p* = 0.016	1.5 (0 to 9), *p* = 0.001
CHOP INTEND score, median (range), n			
M0	31.5 (6 to 45), n = 20	30.5 (19 to 36), n = 10	32 (6 to 45), n = 10
M2	34 (17 to 48), n = 19	35 (21 to 40), n = 9	33 (17 to 48), n = 10
M6	35 (19 to 51), n = 22	36.5 (20 to 45), n = 12	34.5 (19 to 51), n = 10
Time-effect *p* value[a]	0.001	0.014	0.040
Delta M2−M0[b]	2 (−3 to 11), *p* = 0.022	2 (−3 to 7), *p* = 0.173	2 (1 to 10), *p* = 0.048
Delta M6−M0[b]	4 (−2 to 14), *p* = 0.001	3.5 (−2 to 11), *p* = 0.011	4 (−2 to 14), *p* = 0.024
MFM 20 score, median (range), n			
M0	22.5 (16.67 to 25), n = 4	25, n = 1	21.67 (16.67 to 23.33), n = 3
M2	28.33 (11.67 to 40), n = 8	30 (26.7 to 40), n = 3	28.33 (11.67 to 31.66), n = 5
M6	30 (13.33 to 48.33), n = 9	32.35 (28.30 to 48.33), n = 4	30 (13.33 to 36.66), n = 5
Time-effect *p* value[a]	0.039	0.368	0.097
MFM 32 score, median (range), n			
M0	25 (19.79 to 30.2), n = 2	—	25 (19.79 to 30.2), n = 2
M2	27.61 (19.79 to 35.42), n = 2	—	27.61 (19.79 to 35.42), n = 2

Table Characteristics at baseline and evolution of the patients according to *SMN2* copy number *(continued)*

| Characteristics	Total (n = 33)			2 Copies of *SMN2* (n = 15)			3 Copies of *SMN2* (n = 17)		
M6	4.16, n = 1			—			4.16, n = 1		
Ventilation	No	NIV	IV	No	NIV	IV	No	NIV	IV
M0, n	16	17	0	6	9	0	10	7	0
M2, n	12	18	3	4	8	3	8	9	0
M6, n	10	20	3	2	10	3	8	9	0
p Value[a]	0.002			0.009			0.135		
Nutritional status	No	NG	PEG	No	NG	PEG	No	NG	PEG
M0	24	3	6	11	2	2	12	1	4
M2	22	5	6	9	4	2	12	1	4
M6	21	4	8	9	3	3	12	1	4
p Value[a]	0.120			0.273			0.368		

Abbreviations: CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 = Hammersmith Infant Neurologic Examination Part 2 motor milestones score; IV = invasive ventilation or noninvasive ventilation ≥16 h/d; MFM = Motor Function Measure; M0 = before treatment; M2 = 2 months of treatment; M6 = 6 months of treatment; NG = nasogastric tube; NIV = noninvasive ventilation <16 h/d; PEG = percutaneous endoscopic gastrostomy; SMN = survival motor neuron.
SMN2 copy number effect was not seen in any category. It was calculated by Mann-Whitney *U* test apart from sex distribution, which was calculated by the Pearson χ^2 test, and respiratory and nutritional support, which also was calculated by the Pearson χ^2 test, not validated because the sample size was too small, and not significant. Additional parametric statistical tests did not show a significant effect of *SMN2* copy number in any category.
[a] Friedman test.
[b] Wilcoxon test.

Figure 1 Longitudinal motor function data: modified HINE-2, CHOP INTEND, and MFM
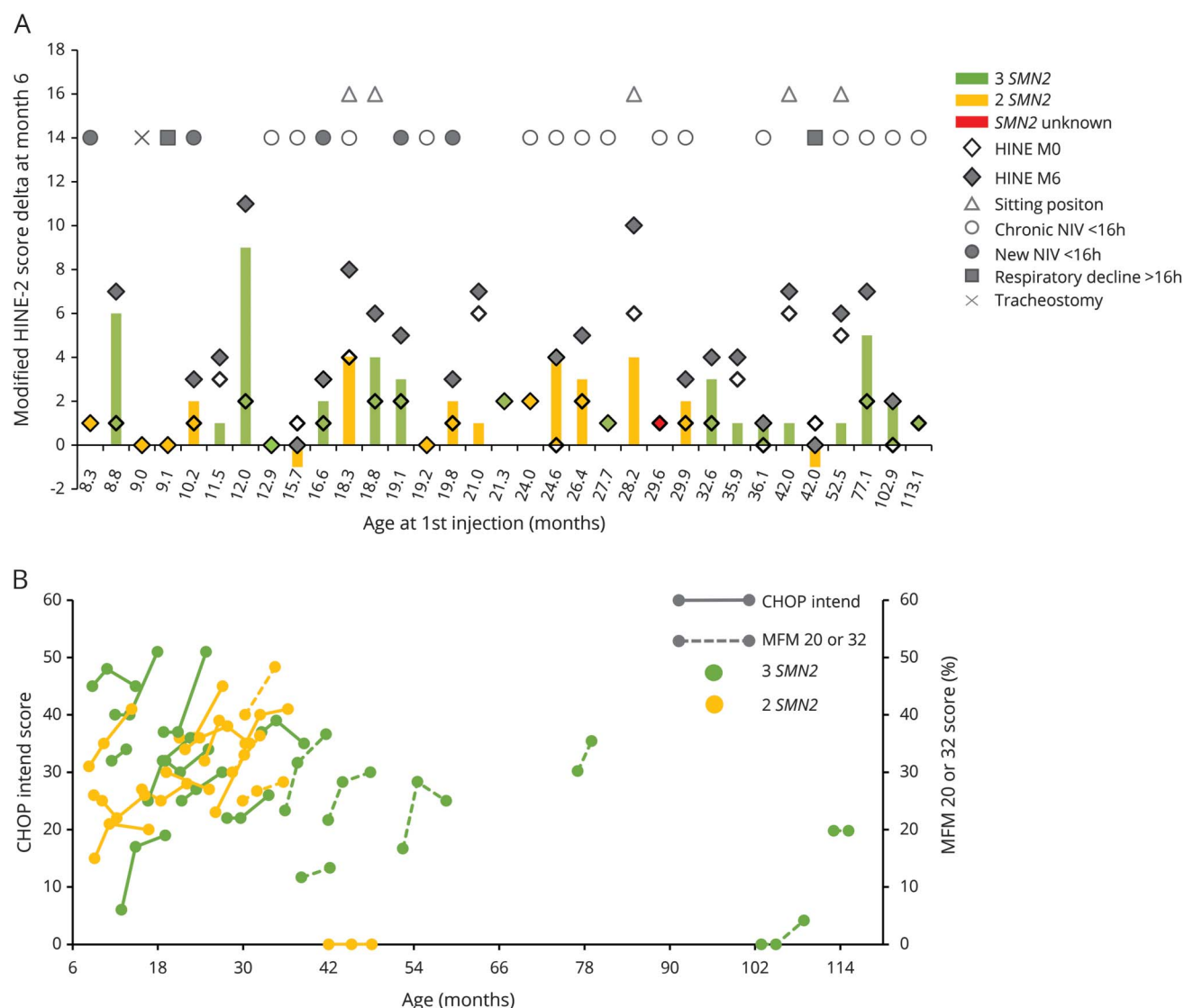
(A) Longitudinal motor function data for patients classified by age at first injection from the youngest to the oldest. Bars represent change in modified Hammersmith Infant Neurologic Examination Part 2 (HINE-2) scores at 6 months of treatment (M6); contoured diamonds represent score at baseline; and filled diamonds represent score at M6. Data points are color-coded for the survival motor neuron 2 (SMN2) copy number. Triangles indicate patients who acquired stable sitting position. Contoured circles are for patients who were on ventilator support at both the beginning of treatment (M0) and M6; full circles indicate patients who started ventilator support during treatment. Squares are for patients who degraded from ventilator support of <16 h/d at M0 to full-time ventilation at M6, and "X" is for a patient who had no support at M0 and because of respiratory failure was started on full-time invasive ventilation and tracheotomized. (B) Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores (full lines, left vertical axis) and Motor Function Measure (MFM) scores (dashed lines, right vertical axis) color-coded for the SMN2 copy number. The patient whose number of SMN2 copies was unknown was not evaluated because of poor cooperation. Nine patients had <3 evaluations due to center change or poor cooperation. NIV = noninvasive ventilation.

regardless of the *SMN2* copies number (table and figure 2A). Five patients (16.6%, 5 of 30) acquired a stable (>30 seconds), support-free sitting position (figure 1A). Median progress on the CHOP INTEND scale (n = 17) was 4 points at M6 (figure 1B and table). Although patients who scored ≥2 points on the modified HINE-2 at baseline presented with an improvement 2 times higher than patients scoring <2, the difference did not reach statistical significance (figure 2A).
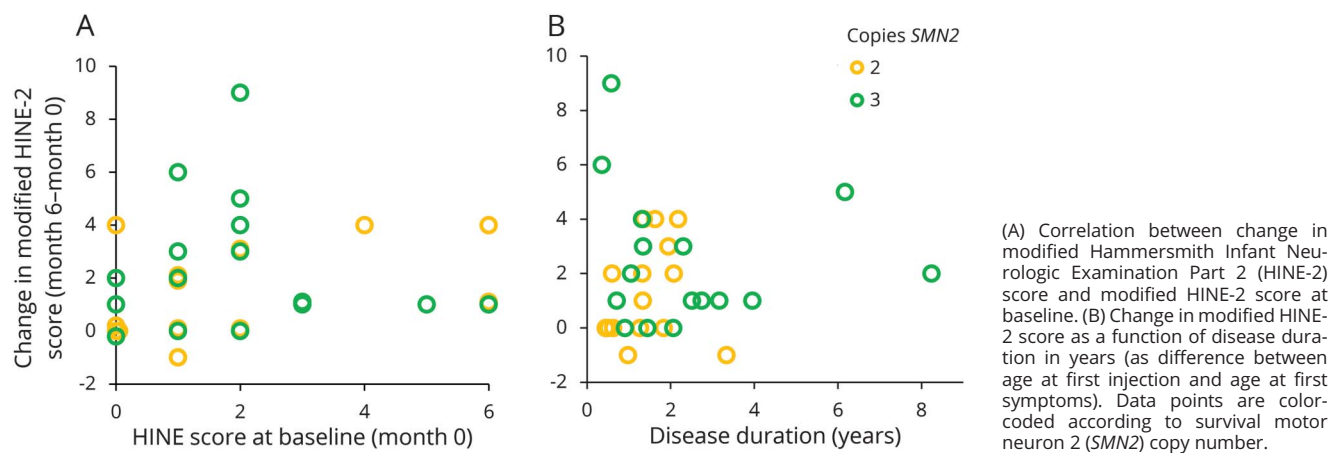
Seventeen hospitalizations concerning 9 patients were recorded. Thirteen were due to respiratory events, and 3

resulted in respiratory failure. The remaining were caused by fever, vomiting, gastroenteritis, and gastrostomy insertion. No other major events or laboratory abnormalities were reported.

Discussion

In this cohort, we found significant motor function improvement after 6 months of treatment and no safety concerns. The response to treatment was highly variable, but new motor acquisitions were attained even in 8-year-old patients. The overall response was comparable to that in the previously

Figure 2 Change in HINE-2 scores

(A) Correlation between change in modified Hammersmith Infant Neurologic Examination Part 2 (HINE-2) score and modified HINE-2 score at baseline. (B) Change in modified HINE-2 score as a function of disease duration in years (as difference between age at first injection and age at first symptoms). Data points are color-coded according to survival motor neuron 2 (*SMN2*) copy number.

studied younger population.[8] In our cohort, the increase in respiratory support was in some cases a result of a more proactive approach motivated by participation in the EAP. In some patients, respiratory worsening was observed despite motor improvement, suggesting a slower action of nusinersen on the respiratory symptoms and the possible intercurrent infections that might destabilize these weak patients.

Only patients with 2 *SMN2* copies were included in the previous phase 3 study.[8] In our cohort, about half of patients had 3 *SMN2* copies, which could explain the magnitude of response despite the older age at inclusion in comparison with A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (ENDEAR) study. Patients with 3 *SMN2* copies were older and had a longer disease duration than patients with 2 *SMN2* copies, which may partially explain the absence of copy number effect. The lack of copy number effect could be also related to the small number of patients, the limited follow-up period, the heterogeneity of the population, or the existence of other, not-yet-identified disease modifiers. However, the absence of *SMN2* copy number effect was also found by others.[7] We did not observe a significant effect of age or HINE-2 scale score at baseline, but here also our sample size and heterogeneity could play a role.

The distribution of age in our cohort is unequal in that most of our patients (30 of 33, 90%) were younger than 53 months, which is a limitation for the extrapolation of the results. Another limitation of our study is the single-point baseline assessment, related to technical and ethics reasons, and the lack of control group, although this is compensated for by recent natural history studies.[3–5] More patients and longer follow-up will be necessary to identify prognostic factors and to determine when a child should be considered a nonresponder. It is likely that there are still unidentified genetic factors that contribute to the large heterogeneity in clinical response in our patients, as well as in patients from the phase 3 studies.[8,10]

It should be noted that many parents reported improvements during treatment with nusinersen that were not captured by the measures used and that were not predefined in data collection such as louder voice, better endurance, and more efficient coughing. Better definition of these outcomes might be useful for long-term follow-up of these patients.

Despite its limitations, this study provides Class IV evidence that nusinersen is beneficial for patients with SMA1 between 7 and 113 months of age.

Author contributions

Dr. K. Aragon-Gawinska's contribution includes drafting/revising the manuscript for content, analysis and interpretation of data, acquisition of data, study coordination. Dr. A.M. Seferian's contribution includes revising the manuscript for content, analysis and interpretation of data, acquisition of data. Dr. A. Daron's contribution includes revising the manuscript for content, analysis and interpretation of data, acquisition of data, study supervision or coordination. Dr. E. Gargaun's contribution includes study concept and design, revising the manuscript for content, acquisition of data. Dr. C. Vuillerot's and Dr. C. Cances' contribution includes revising the manuscript for content, analysis and interpretation of data, acquisition of data. Dr. J. Ropars', Dr. M. Chouchane's, Dr. I. Cuppen's, Dr. I. Hughes', Dr. M. Illingworth's, Dr. C. Marini-Bettolo's, Dr. J. Rambaud's, and Dr. J. Taytard's contribution includes revising the manuscript for content and acquisition of data. Mrs. M. Annoussamy's contribution includes study concept and design, revising the manuscript for content and analysis, and interpretation of data, including statistical analysis. Dr. M. Scoto's contribution includes revising the manuscript for content, analysis and interpretation of data, acquisition of data and study coordination. Dr. T. Gidaro's contribution includes study concept and design, revising the manuscript for content, analysis and interpretation of data, acquisition of data and study supervision or coordination. Dr. L. Servais' contribution includes study concept and design,

Disclosure

K. Aragon-Gawinska received congress funding from SMA Poland Foundation. A. Seferian reports no disclosures relevant to the manuscript. A. Daron is principal investigator in a Roche- and Avexis-sponsored trial. E. Gargaun received travelling and congress funding from Biogen. C. Vuillerot is principal investigator in a Roche-sponsored trial and received consultancy fees from Roche and Biogen. C. Cances, J. Ropars, M. Chouchane, and I. Cuppen report no disclosures relevant to the manuscript. I. Hughes received consultancy fees and traveling and congress funding from Biogen. M. Illingworth received traveling and congress funding from Santhera. C. Marini-Bettolo, received consultancy fees and travelling and congress funding from Biogen. J. Rambaud, J. Taytard, and M. Annoussamy report no disclosures relevant to the manuscript. M. Scoto is coprincipal investigator in the SMA Reach UK study and Roche-sponsored SMA trial and is peer reviewer for SMA Support UK. T. Gidaro reports no disclosures relevant to the manuscript. L. Servais is principal investigator in Biogen-, Roche-, and Avexis-sponsored studies; serves on scientific advisory boards of Biogen, Roche, Avexis, and the SMA foundation; and received honorarium for lectures and consultancies from Roche and Biogen. Go to Neurology.org/N for full disclosures.

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