Long-term Safety and Efficacy of Ozanimod in RMS: Interim Analysis of DAYBREAK

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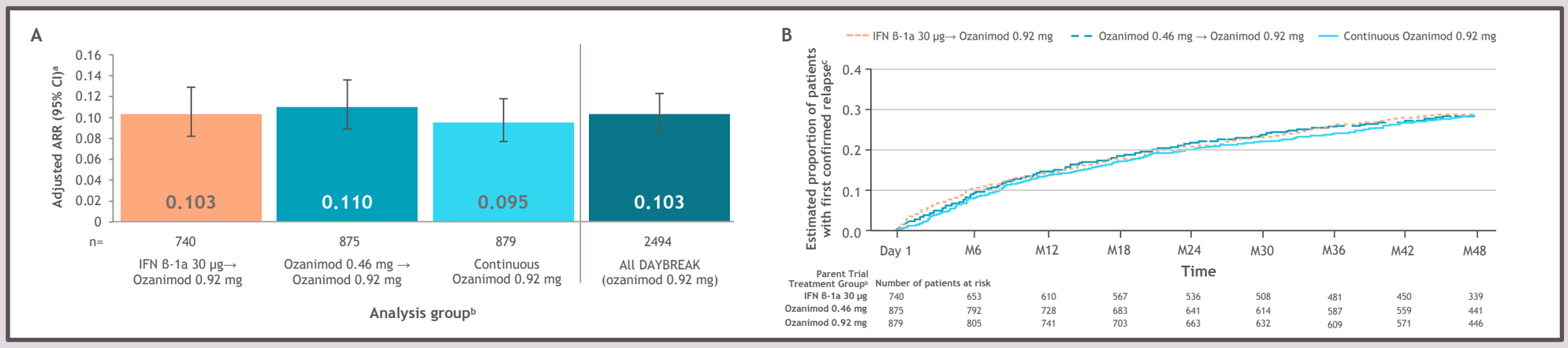
Ozanimod treatment demonstrated sustained efficacy with a low annualised relapse rate (ARR) (Figure 1A) and most participants remaining relapse free during DAYBREAK (Figure 1B)

- The greatest numerical reduction in ARR from phase 3 parent trial to DAYBREAK occurred among those who switched from IFN ß-1a to ozanimod 0.92 mg
- At months 36 and 48, 75% and 71% of participants, respectively, were relapse free in DAYBREAK
  - Among those who continuously received ozanimod 0.92 mg in both a parent trial and DAYBREAK, 64% remained relapse free throughout 60 cumulative months of treatment (the last time point for which more than half of the analysis group had assessments; n = 493)

Figure 1. ARR in DAYBREAK, ITT population (A). Kaplan-Meier curve for time to first confirmed relapse during DAYBREAK, ITT population (B)



[a]Based on the negative binomial regression model, adjusted for region (Eastern Europe vs rest of world), age at parent baseline, and the parent baseline number of GdE lesions. The natural log transformation of time on treatment is used as an offset term to adjust for persons having different exposure times. [b]All participants received ozanimod 0.92 mg during DAYBREAK. [c]Analysed using Kaplan-Meier analysis, with censoring of participants for whom follow-up ended before a relapse occurred. ARR, annualised relapse rate; GdE, gadolinium-enhancing; IFN, interferon.

Introduction

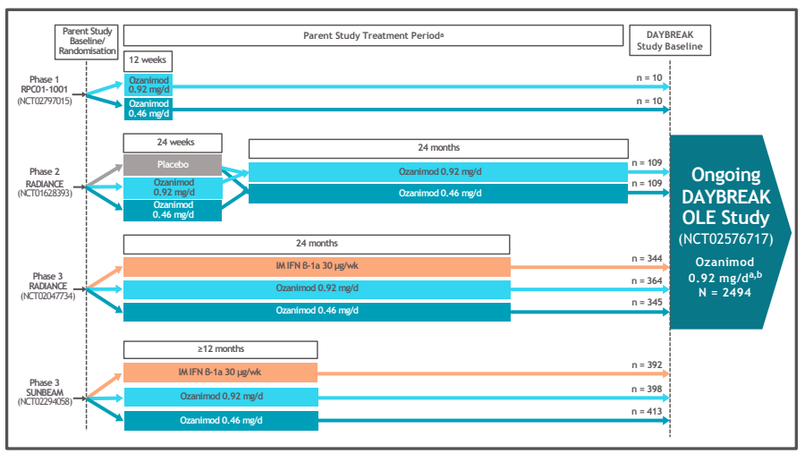
- Ozanimod is a sphingosine 1-phosphate receptor 1 and 5 modulator approved in multiple countries for the treatment of adults with relapsing forms of multiple sclerosis (RMS) and is approved for the treatment of moderately to severely active ulcerative colitis in the United States[1,2]
- Four clinical trials of ozanimod in RMS were completed, including a phase 1 pharmacokinetic/pharmacodynamic study, a phase 2 study with an extension period,[3,4] and 2 active-controlled phase 3 trials[5,6]
- In the phase 3 trials, ozanimod 0.92 mg/d for up to 24 months was associated with significantly fewer relapses and smaller lesion counts on brain MRI and slowed brain volume loss relative to intramuscular interferon (IFN) ß-1a 30 µg/wk[5,6]
  - Ozanimod was well tolerated, with fewer treatment-emergent adverse events (TEAEs) leading to discontinuation than IFN ß-1a
- Participants who completed any of the RMS trials were eligible to enrol in DAYBREAK, an open-label extension (OLE) trial of ozanimod 0.92 mg/d
- Objective: To report the efficacy and safety of extended exposure to ozanimod from the ongoing DAYBREAK trial (data cutoff 2 February 2021)

Methods

Study design and participants

- Participants received ozanimod 0.92 mg/d (equivalent to ozanimod HCl 1 mg) in DAYBREAK (NCT02576717) (**Figure 2**)

Figure 2. Parent studies and DAYBREAK study design



[a]Parent trial participants were aged 18–55 years with MS diagnosed by the revised 2010 McDonald criteria,[7] had brain MRI lesions consistent with multiple sclerosis, and an Expanded Disability Status Scale score of 0–5.0 (phase 2 and 3) or 0–6.0 (phase 1)[3,5,6] In all trials, upon initiation of ozanimod, participants received 0.23 mg (equivalent to ozanimod HCl 0.25 mg) on days 1–4, 0.46 mg (equivalent to ozanimod HCl 0.5 mg) on days 5–7, and then their assigned dose of 0.46 mg or 0.92 mg (equivalent to ozanimod HCl 1 mg) on day 8 and thereafter. All participants entering the phase 2 dose-blinded extension period underwent dose escalation, even if treated with ozanimod in the parent trial, to maintain the blind. [b]In DAYBREAK, dose escalation was performed for all participants entering from one of the active-controlled phase 3 trials, irrespective of prior treatment assignment (to maintain the blinding in the parent trials); dose escalation was not performed for those entering from the phase 1 or 2 trials, unless the last dose of ozanimod was >14 days before entering DAYBREAK. HCl, hydrochloride; IFN, interferon; IM, intramuscular; MS, multiple sclerosis; OLE, open-label extension.

Results

Baseline demographics and participant characteristics

- Of 2639 participants potentially eligible for DAYBREAK, 2494 enroled and received at least one dose of ozanimod 0.92 mg; 2055 (82.4%) were continuing in DAYBREAK at the data cutoff
- **Exposure:** At data cutoff, mean (range) ozanimod exposure in DAYBREAK was 46.8 (0.03–62.7) months (9725.6 person-years [PY]); mean duration of any ozanimod exposure during the parent trials and DAYBREAK was 60.7 months (12617.1 PY) with a maximum of 98.8 months
- Baseline demographics and disease characteristics were generally consistent across parent trial treatment groups (**Table 1**)

Table 1. Demographics and disease characteristics at DAYBREAK baseline

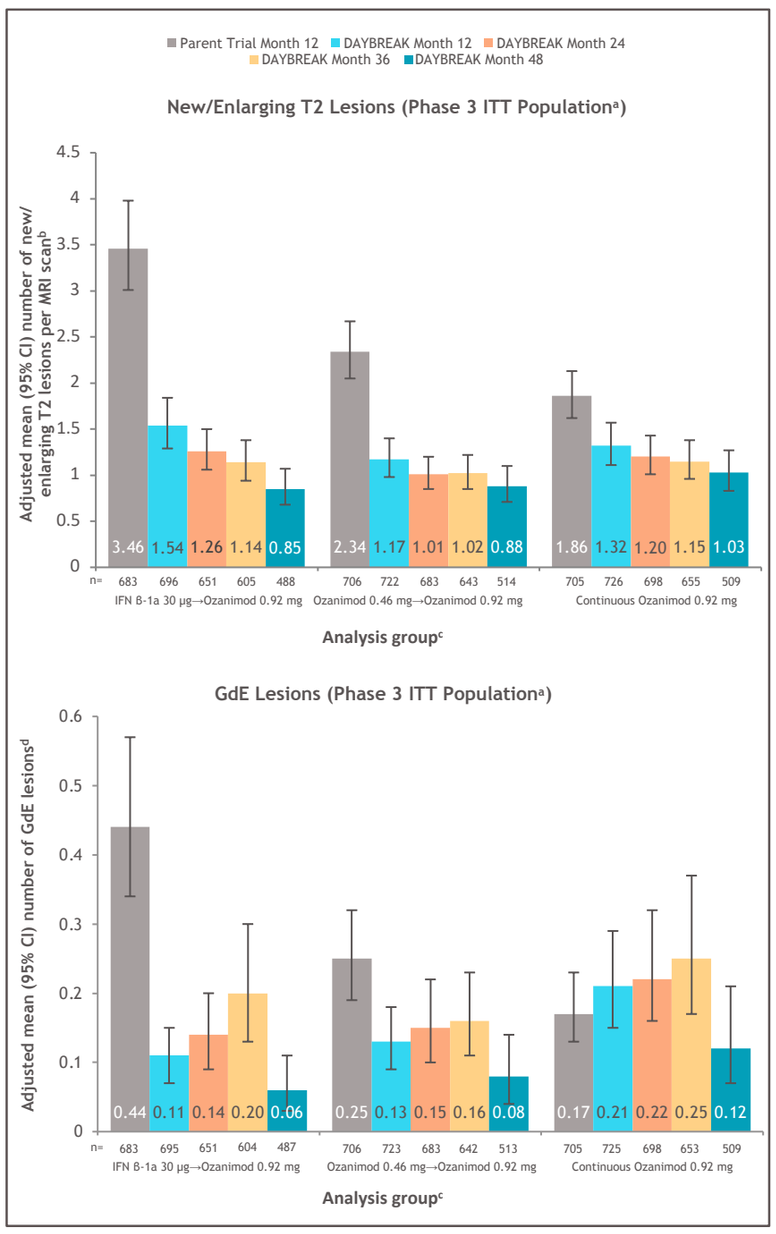
	IFN ß-1a 30 µg→ Ozanimod 0.92 mg (n = 736)	Ozanimod 0.46 mg→ Ozanimod 0.92 mg (n = 877)	Continuous Ozanimod 0.92 mg (n = 881)	All DAYBREAK Ozanimod 0.92 mg (N = 2494)
Age, mean (SD), y	37.4 (9.1)	38.0 (9.3)	37.6 (9.3)	37.7 (9.2)
Gender, n (%)				
Female	498 (67.7)	595 (67.8)	575 (65.3)	1668 (66.9)
Male	238 (32.3)	282 (32.2)	306 (34.7)	826 (33.1)
Race, n (%)				
White	734 (99.7)	865 (98.6)	875 (99.3)	2474 (99.2)
Black	1 (0.1)	7 (0.8)	6 (0.7)	14 (0.6)
Asian	0	3 (0.3)	0	3 (0.1)
Other	1 (0.1)	2 (0.2)	0	3 (0.1)
Region, n (%)				
Eastern Europe	672 (91.3)	791 (90.2)	783 (88.9)	2246 (90.1)
Western Europe	44 (6.0)	46 (5.2)	54 (6.1)	144 (5.8)
North America	13 (1.8)	33 (3.8)	35 (4.0)	81 (3.2)
Rest of world[a]	7 (1.0)	7 (0.8)	9 (1.0)	23 (0.9)
Age at symptom onset, mean (SD), y	29.5 (8.8)	29.7 (9.1)[b]	29.2 (8.8)[c]	29.5 (8.9)[d]
EDSS, mean (SD)	2.5 (1.3)	2.6 (1.3)	2.6 (1.3)	2.6 (1.3)

[a]Rest of world includes New Zealand and South Africa. [b]n = 867. [c]n = 871. [d]n = 2474. EDSS, Expanded Disability Status Scale; IFN, interferon; SD, standard deviation.

Additional efficacy outcomes

- Adjusted mean number of new/enlarging T2 lesions per scan at month 48 of DAYBREAK was low and similar, regardless of parent trial treatment group **(Figure 3A)**, as were adjusted mean number of GdE lesions at month 48 (**Figure 3B**)
- The decrease in new/enlarging T2 lesion count per scan from phase 3 parent trial to DAYBREAK was greatest for participants switching from IFN ß-1a to ozanimod 0.92 mg (**Figure 3A**)
- Upon switching to ozanimod, participants initially treated with IFN ß-1a experienced a decline in number of gadolinium-enhancing (GdE) lesions to similar numbers for continuously treated ozanimod 0.92 mg participants (**Figure 3B**)

Figure 3. Number of new/enlarging T2 lesions per scan (A) and number of GdE lesions at month 12 of the active-controlled phase 3 parent trials and months 12, 24, 36, and 48 of DAYBREAK (B), by parent trial treatment group



[a]New/enlarging T2 lesions and GdE lesions were analysed only in the subset of participants who entered DAYBREAK from an active-controlled phase 3 trial. [b]Relative to parent trial baseline in the parent trial, and DAYBREAK baseline in DAYBREAK; based on negative binomial regression model, adjusted for study, region (Eastern Europe vs rest of world), age at baseline, and baseline number of GdE lesions, with the log of the number of postbaseline scans as an offset term in the model. [c]All participants received ozanimod 0.92 mg during DAYBREAK. [d]Based on negative binomial regression model, adjusted for study, region (Eastern Europe vs rest of world), age at baseline, and the baseline number of GdE lesions. GdE, gadolinium-enhancing; IFN, interferon.

- During DAYBREAK, 346/2494 (13.9%) participants had confirmed disability progression at 3 months (CDP-3) and 285/2494 (11.4%) had confirmed disability progression at 6 months (CDP-6) by the data cutoff
  - Rates were similar across parent trial treatment groups

Safety

- In DAYBREAK, 2143 (85.9%) participants had any TEAE, 298 (11.9%) had a serious TEAE (SAE), and 75 (3.0%) discontinued due to a TEAE (**Table 2**)
  - The low discontinuation rate due to TEAEs suggests that ozanimod was well tolerated
- Similar rates of TEAEs and SAEs occurred when assessed by parent trial treatment group (**Table 2**)
- Prior to the 2 February 2021 data cutoff, 3 participants died from malignancies, 2 from accidents, and 1 each from pulmonary embolism following leg fracture surgery, community-acquired pneumonia, cerebral hemorrhage probably due to rupture of a preexisting occult aneurysm, and sudden death due to unknown cause
  - One additional participant died from active COVID-19 infection/pulmonary embolism and 2 additional deaths occurred due to complications following COVID-19 infection (acute respiratory failure, lung abscess following pneumonia)
    - These deaths occurred among 190 participants who had confirmed (n = 160) or suspected (n = 30) COVID-19 prior to 10 May 2021 (the data cutoff for a separate COVID-19 analysis). Most cases (n=176/190 [92.6%]) were nonserious

Table 2. Safety during DAYBREAK by parent trial treatment group and overall DAYBREAK population[a]

	IFN ß-1a 30 µg→ Ozanimod 0.92 mg (n = 736)	Ozanimod 0.46 mg→ Ozanimod 0.92 mg (n = 877)	Continuous Ozanimod 0.92 mg (n = 881)	All DAYBREAK Ozanimod 0.92 mg (N = 2494)	
				n (%)	IR/1000 PY[b] (95% CI)
Any TEAE	647 (87.9)	750 (85.5)	746 (84.7)	2143 (85.9)	693.4 (664.6-723.4)
Severe TEAEs	68 (9.2)	69 (7.9)	53 (6.0)	190 (7.6)	20.7 (18.0-23.9)
Serious TEAEs	84 (11.4)	111 (12.7)	103 (11.7)	298 (11.9)	33.3 (29.8-37.4)
TEAEs leading to permanent treatment discontinuation	27 (3.7)	24 (2.7)	24 (2.7)	75 (3.0)	7.9 (6.3-9.9)
Individual TEAEs in ≥5% of overall DAYBREAK population					
Nasopharyngitis	150 (20.4)	169 (19.3)	170 (19.3)	489 (19.6)	59.3 (54.2-64.8)
Headache	124 (16.8)	132 (15.1)	137 (15.6)	393 (15.8)	46.1 (41.8-50.9)
Upper RTI	88 (12.0)	94 (10.7)	96 (10.9)	278 (11.1)	31.5 (28.0-35.5)
Lymphopenia[c]	84 (11.4)	96 (10.9)	77 (8.7)	257 (10.3)	29.4 (26.0-33.3)
ALC decreased[c]	62 (8.4)	78 (8.9)	78 (8.9)	218 (8.7)	24.5 (21.5-28.0)
Back pain	60 (8.2)	74 (8.4)	71 (8.1)	205 (8.2)	22.7 (19.8-26.0)
Hypertension[d]	65 (8.8)	74 (8.4)	48 (5.4)	187 (7.5)	20.7 (17.9-23.9)
GGT increased	65 (8.8)	54 (6.2)	52 (5.9)	171 (6.9)	18.9 (16.2-21.9)
Bronchitis	35 (4.8)	59 (6.7)	51 (5.8)	145 (5.8)	15.8 (13.4-18.6)
RTI	44 (6.0)	53 (6.0)	48 (5.4)	145 (5.8)	15.9 (13.5-18.7)
UTI	38 (5.2)	54 (6.2)	51 (5.8)	143 (5.7)	15.6 (13.3-18.4)
Viral RTI	39 (5.3)	49 (5.6)	44 (5.0)	132 (5.3)	14.4 (12.1-17.0)
Depression-related TEAEs[e]	38 (5.2)	48 (5.5)	43 (4.9)	129 (5.2)	14.0 (11.8-16.6)

[a]TEAE incidence was summarized by Medical Dictionary for Regulatory Activities version 22.1 preferred term. [b]IRs per 1000 PY were calculated as follows to adjust for time on study: number of persons/person-years × 1000 for specific system organ class category or preferred term subcategory. Person-years for each category/subcategory: for a person in a particular category/subcategory, the time on study is calculated based on the date the person first has a TEAE within the category/subcategory (date of first TEAE - first dose date of study drug + 1)/365.25; for persons who do not have a TEAE in the category/subcategory, the time on study is the study duration (last date on study- first dose date of study drug +1)/365.25. [c]ALC reductions are an expected pharmacodynamic effect related to the mechanism of ozanimod; although investigators were not required to report ALC reductions as TEAEs, lymphopenia and ALC decreases were reported as TEAEs according to investigator determination. [d]Includes preferred terms of hypertension, essential hypertension, labile hypertension, systolic hypertension, and hypertensive crisis. [e]Includes preferred terms of depression, depressed mood, and depressive symptoms. ALC, absolute lymphocyte count; GGT, gamma-glutamyl transferase; IFN, interferon; IR, incidence rate; PY, person-years; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

- 56.7% of DAYBREAK participants experienced an infection (incidence rate [IR], 243.5/1000 PY [95% CI 231.1-256.5]) most commonly respiratory and urinary tract infections; 2.8% experienced a serious infection (IR 7.4/1000 PY [95% CI 5.8-9.3])
  - <6% of participants experienced opportunistic infections (IR 15.2/1000 PY [95% CI 12.9-18.0]), most commonly oral herpes (2.0%) and herpes zoster infections (1.7%); none of the herpes infections were serious or disseminated
  - There were no serious opportunistic infections at the time of the data cut; however, a case of progressive multifocal leukoencephalopathy was reported in March 2021 in a 46-year-old woman who had received ozanimod 0.92 mg for about 4 years. The patient remains under the investigator's care
- During the parent trials and DAYBREAK, 38 (1.4%; IR 358.7/100,000 PY [95% CI 253.9-492.4]) of 2786 participants exposed to either dose of ozanimod developed treatment-emergent malignancies
  - This included 1 malignant melanoma (0.04%; IR 9.4/100,000 PY [95% CI 0.2-52.4]), 13 nonmelanoma skin cancers (0.5%, IR 122.6/100,000 PY [95% CI 65.3-209.6]), and 24 (0.9%; IR 226.0/100,000 PY [95% CI 144.8-336.2]) noncutaneous malignancies
- During DAYBREAK, there were 9 (0.4%; IR 0.9/1000 PY [95% CI 0.5–1.8]) TEAEs of macular oedema
  - The Macular Edema Review Panel confirmed 4 macular oedema cases (0.2%; IR 0.4/1000 PY [95% CI 0.2–1.1]) during DAYBREAK; 3 cases were resolved and 1 was ongoing at data cutoff
- Cardiac TEAEs occurred in 69 (2.8%; IR 7.4/1000 PY [95% CI 5.8-9.3]) DAYBREAK participants, 7 of whom had serious events (3 myocardial infarctions, and 1 each of myocardial ischemia, unstable angina, bradycardia, and coronary artery stenosis)
- In the overall DAYBREAK population, absolute lymphocyte count (based on single assessments) was <0.2 × 10^9/L in 244 (9.8%) of 2488 participants
  - 30/187 participants (16.0% or 1.2% of the overall safety population [30/2488]) who had a repeat ALC assessment within 30 days had a consecutive ALC <0.2 × 10^9/L on retest, suggesting most instances were transient

Conclusions

- In this interim analysis of DAYBREAK, the OLE of all completed phase 1-3 trials of ozanimod in RMS, ozanimod treatment demonstrated sustained efficacy with low ARR, new/enlarging T2 and GdE lesion counts on brain MRI, and disability progression over 48 months
- Clinical and radiologic disease activity remained low in participants who received continuous ozanimod 0.92 mg, and participants who switched to ozanimod 0.92 mg from either IFN ß-1a or ozanimod 0.46 mg had numerically lower ARR and decreases in brain MRI lesion counts after the switch
- This analysis characterises safety of ozanimod over a longer period than previously reported (mean 46.8 months; max 62.7 months in DAYBREAK alone); ozanimod was generally well tolerated
- Overall safety and tolerability of ozanimod was consistent with the phase 3 trials,[5,6] with 82.4% retention at data cutoff
- Data from this long-term observational study of patients treated for up to 62.7 months are consistent with the established safety profile of ozanimod and with sustained control of disease activity and disability progression

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Acknowledgements

- The patients and families who made these studies possible
- The clinical study teams who participated
- The DAYBREAK study was supported by Celgene International II
- All authors contributed to and approved the presentation; writing and editorial assistance was provided by Jessica D. Herr, PharmD of Peloton Advantage, LLC, an OPEN Health company, and funded by Bristol Myers Squibb

Disclosures

KWS: consulting for Biogen, Celgene, Genzyme, Merck, Novartis, Ono Pharma, Roche, Synthon, and Teva. **LS**: consulting for AbbVie, Atreca, Celgene, Novartis, Teva, Tolerion, and EMD Serono, and research support from Atara, Biogen, and Celgene. **GC**: compensation for consulting and/or speaking activities from Almirall, Biogen, Celgene, EXCEMED, Forward Pharma, Genzyme, Merck, Novartis, Roche, Sanofi, and Teva. **ABO**: participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from Atara Biotherapeutics, Biogen, BMS-Celgene, EMD Serono, Sanofi Genzyme, Novartis, and Roche-Genentech. **DLA**: personal fees for consulting and/or grants from Albert Charitable Trust, Alexion Pharma, Biogen, Celgene, Frequency Therapeutics, Genentech, Med-Ex Learning, Merck Serono, Novartis, Population Council, Roche, and Sanofi-Aventis; grants from Biogen, Immunotec, and Novartis; and an equity interest in NeuroRx. **HPH**: personal fees for consulting, serving on steering committees, and speaking from Bayer Healthcare, Biogen, Celgene, GeNeuro, Genzyme, Merck, MedImmune, Novartis, Octapharma, Roche, Sanofi, and Teva. **XM**: received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past 3 years with Actelion, Alexion, Bayer, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, EXCEMED, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, Merck, Mylan, MSIF, Nervgen, NMSS, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceuticals, and TG Therapeutics. **EKH**: personal compensation for consulting and speaking for Actelion, Biogen, Celgene Corporation, Merck, Novartis, Roche, Sanofi, and Teva, and is supported by Czech Ministry of Education, project PROGRES Q27/LF1. **JH, SA, JKS, FS, NM, and DS**: employees and shareholders of Bristol Myers Squibb. **LK**: institutional research support: steering committee, advisory board, and consultancy fees: Actelion, Bayer HealthCare, Biogen, Bristol Myers Squibb, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, Shionogi, and TG Therapeutics; speaker fees: Bayer HealthCare, Biogen, Merck, Novartis, Roche, and Sanofi; support of educational activities: Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva; license fees for Neurostatus products; and grants: Bayer HealthCare, Biogen, European Union, Innosuisse, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation. **JAC**: personal compensation for consulting for Adamas, Atara, Bristol Myers Squibb, Convelo, MedDay, and Mylan; and serving as an Editor of *Multiple Sclerosis Journal*. **BACC**: personal compensation for consulting for Alexion, Atara, Autobahn, Avotres, EMD Serono, Novartis, Sanofi, TG Therapeutics, and Therini, and received grant support from Genentech.

Presented at the 29th Annual Meeting of the European Charcot Foundation; 14-18 November 2021; Baveno, Italy
Previously presented at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 13-15 October 2021; The Digital Experience

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