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Original article

Ozanimod in relapsing multiple sclerosis: Pooled safety results from the clinical development program

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ABSTRACT

Background: Ozanimod, an oral sphingosine 1-phosphate receptor 1 and 5 modulator, is approved in multiple countries for the treatment of relapsing multiple sclerosis (RMS). In phase 3 trials, ozanimod was well tolerated and superior to interferon beta-1a 30 μg once-weekly in reducing clinical and radiologic disease activity. The objective of this integrated safety analysis was to evaluate the safety of extended ozanimod exposure in participants with RMS from all clinical trials and compare it with phase 3 trial data.

Methods: We report pooled incidence and study duration–adjusted incidence rates (IR) of treatment-emergent adverse events (TEAEs) from an interim data cut (January 31, 2019) of RMS participants treated with ozanimod. Data were pooled from a phase 1 pharmacokinetic/pharmacodynamic trial, a placebo-controlled phase 2 trial with dose-blinded extension, 2 large active-controlled phase 3 trials, and an open-label extension (OLE). Results were compared with pooled phase 3 trial data.

Results: At the data cutoff, 2631 RMS participants had exposure to ozanimod 0.92 mg (mean 32.0 months) and 2787 had exposure to either ozanimod 0.46 or 0.92 mg (mean 37.1 months). The IRs per 1000 person-years (PY) for any TEAE (772.2) and serious TEAEs (33.2) in the overall population were similar to those in the phase 3

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSR, central serous choroidopathy; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IFN, interferon; IR, incidence rates; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; ME, macular edema; MERP, Macular Edema Review Panel; OCT, optical coherence tomography; OLE, open-label extension; PFT, pulmonary function test; PML, progressive multifocal leukoencephalopathy; PY, person-years; S1P, sphingosine 1-phosphate; ULN, upper limit of normal.

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population (896.1 and 31.2, respectively). There were no serious opportunistic infections. There were no second-degree or higher atrioventricular blocks on electrocardiogram. Hepatic enzyme elevations declined over time. Malignancy rates remained low with longer exposure. Pulmonary function tests showed minimal reductions in lung function. Seven ozanimod-treated participants with comorbid risk factors had confirmed macular edema, including 3 in the ongoing OLE.

Conclusions: Safety results in this larger RMS population with greater ozanimod exposure demonstrated no new safety concerns and were consistent with phase 3 trial results.

1. Introduction

Ozanimod is a sphingosine 1-phosphate (S1P) receptor 1 and 5 modulator (Scott et al., 2016) approved in multiple countries for the treatment of relapsing multiple sclerosis (RMS) (Zeposia package insert, 2020; Zeposia summary of product characteristics 2020). Ozanimod blocks the capacity of lymphocytes to egress from lymphoid tissue, reducing the number of lymphocytes in peripheral blood (Scott et al., 2016). While the exact mechanism of ozanimod in RMS is unknown, it may involve reduced migration of lymphocytes into the central nervous system.

In the phase 3 RADIANCE (Cohen et al., 2019b) and SUNBEAM (Comi et al., 2019) trials, oral ozanimod 0.92 mg (equivalent to ozanimod HCl 1 mg) or 0.46 mg (equivalent to ozanimod HCl 0.5 mg) once daily was superior to intramuscular interferon (IFN) beta-1a 30 μg once weekly on measures of disease activity and in slowing brain volume loss. Ozanimod was generally well tolerated, with completion rates of approximately 90% in the pivotal phase 3 trials. Both doses of ozanimod demonstrated a favorable safety profile compared with IFN beta-1a, a well-established treatment for RMS.

This integrated safety analysis of participants who received ozanimod in all RMS studies was undertaken to provide a comprehensive perspective of the safety of ozanimod 0.92 mg and to characterize its safety profile in a large RMS population with a longer duration of exposure than in the phase 3 trials.

2. Methods

2.1. Ozanimod clinical trial study designs and RMS populations

The ozanimod clinical development program in RMS included 4 randomized trials: an unpublished phase 1 pharmacokinetic/pharmacodynamic study, a phase 2 study (Cohen et al., 2016) that included a dose-blinded extension (Cohen et al., 2019a), and 2 similarly designed phase 3 trials of differing durations (Cohen et al., 2019b; Comi et al., 2019) (Fig. 1). Upon completion of any of those trials, participants were eligible to enroll in DAYBREAK, an ongoing open-label extension (OLE) study. Institutional review boards approved the use of human subjects in each study included in this analysis, and all participants provided written informed consent.

All parent trials enrolled men and women 18 to 55 years of age with MS diagnosed by 2010 McDonald criteria who exhibited a relapsing clinical course, had a history of brain magnetic resonance imaging (MRI) lesions consistent with MS, and an Expanded Disability Status Scale score of 0 to 5.0 (phase 2 and 3) or 0 to 6.0 (phase 1) (Cohen et al., 2016; Cohen et al., 2019b; Comi et al., 2019). This analysis pools ozanimod-treated participants from all RMS trials, including the extensions, with a data cutoff of January 31, 2019. At data cutoff, only DAYBREAK was ongoing.

2.2. Safety assessments and outcomes

The safety assessment schedule is available in Table A.1. Treatment-emergent adverse events (TEAEs) were coded using MedDRA version 18.1.

External experts in liver dysfunction examined overall hepatic safety and conducted in-depth reviews of specific cases of potential clinical significance (eg, concurrent elevations of aminotransferases and bilirubin). An independent expert Macular Edema Review Panel (MERP) reviewed TEAEs related to macular edema (ME), cases of central foveal thickness >20% of baseline, and any relevant optical coherence tomography (OCT) abnormalities.

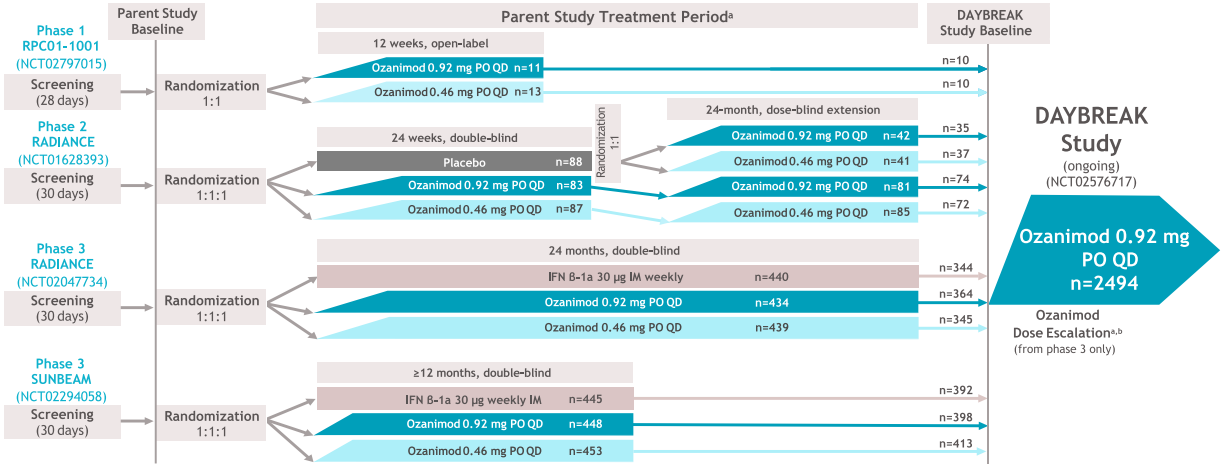

Fig. 1. RMS clinical development program for ozanimod: studies included in this analysis
HCl: hydrochloride; IFN: interferon; IM: intramuscular; OLE: open-label extension; PO: per os (oral); QD: once daily.
[a]In all trials, upon initiation of ozanimod, participants received 0.23 mg (equivalent to ozanimod HCl 0.25 mg) on days 1 to 4, 0.46 mg (equivalent to ozanimod HCl 0.5 mg) on days 5 to 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.

Outcomes included incidence and study duration–adjusted incidence rates (IR) per 1000 person-years (PY) (100,000 PY for malignancies) of TEAEs, severe TEAEs, serious TEAEs, and TEAEs leading to discontinuation of study drug. We also report the incidence and study duration–adjusted IR of TEAEs of special interest, which include events potentially associated with S1P receptor modulation as well as events potentially related to immune modulation. As first-dose cardiac effects are reported in the primary study publications, this analysis focused on longer-term cardiac safety outcomes only. Concurrent absolute lymphocyte count (ALC) $<0.2 \times 10^9$/L and infection was evaluated. Monoamine oxidase B (MAO-B) metabolizes one of the minor active metabolites of ozanimod, RP101075, to form CC112273, the major active metabolite; furthermore, active metabolites of ozanimod (CC112273 and CC1084037) inhibit MAO-B with more than 1000-fold selectivity over MAO-A in vitro (Zeposia package insert, 2020; Zeposia summary of product characteristics, 2020). Therefore, we assessed the potential for drug interactions in patients concurrently taking ozanimod and either serotonergic medications (which are metabolized primarily by MAO-A) or MAO inhibitors. We also report deaths and pregnancy outcomes among all ozanimod-treated participants.

2.3. Statistical analyses

Safety results among those exposed to at least one dose of ozanimod 0.92 mg (the approved dose) are presented in the pooled population from all RMS trials as well as in the phase 3 trials as a point of reference. Compared with the phase 3 trials, the pooled population had a longer mean duration of exposure to ozanimod due to continued treatment in DAYBREAK. For safety outcomes with low event rates and/or longer time to onset (malignancies, ME, drug interactions, and pregnancies), calculated incidences and IRs for all participants exposed to either dose of ozanimod (0.46 or 0.92 mg) are presented. TEAE rates are reported throughout the duration of ozanimod exposure, through the cutoff date; ALC and blood pressure (BP) over time are presented through month 42, the last time point for which about 40% or more of participants have data available. All outcomes were analyzed descriptively.

2.4. Data availability statement

Celgene, a Bristol Myers Squibb company, is committed to responsible and transparent sharing of clinical trial data with patients, healthcare practitioners, and independent researchers for the purpose of improving scientific and medical knowledge as well as fostering innovative treatment approaches. Data requests may be submitted to Celgene, a Bristol Myers Squibb company, at https://vivli.org/ourmember/celgene/ and must include a description of the research proposal.

3. Results

3.1. Study population

Overall, 2631 participants with RMS received ozanimod 0.92 mg (Fig. 1). As of the data cutoff, mean (SD [standard deviation]) exposure to ozanimod 0.92 mg was 32.0 months (12.8) with 7058.5 PY on study, maximum exposure was about 75 months, and approximately 90% (2256/2494) of DAYBREAK participants were still receiving ozanimod 0.92 mg. For comparison, in the phase 3 trials, exposure to ozanimod 0.92 mg (n=882) was 18.1 months (6.0) with 1345.4 PY on study.

In addition, 1033 participants had exposure to ozanimod 0.46 mg in one of the parent trials, 877 of whom subsequently received ozanimod 0.92 mg in DAYBREAK. Participants who were exposed to any ozanimod dose were included in select analyses (Section 2.3). At data cutoff, mean (SD) overall exposure to any ozanimod dose (n=2787) was 37.1 months (14.7) with 8688.3 PY in any RMS study. In the phase 3 trials, mean (SD) combined exposure to either ozanimod dose (n=1774) was 17.9 months (5.97) with 2686.8 PY on study. Demographics and baseline disease characteristics are provided in Table 1.

3.2. TEAEs

The study duration–adjusted IR of any TEAE was 772.2/1000 PY among participants exposed to ozanimod 0.92 mg in RMS trials; for comparison, the IR in the ozanimod 0.92 mg groups from the phase 3

Table 1
Demographic and baseline disease characteristics: safety population.

	Phase 3 Study Population	Overall RMS Population	
	Ozanimod 0.92 mg (N=882)	Ozanimod 0.92 mg (N=2631)	Any Ozanimod (N=2787)[a]
Age, mean (SD) years	35.4 (9.1)	36.0 (9.2)	35.9 (9.1)
Sex, n (%)			
Female	576 (65.3)	1765 (67.1)	1868 (67.0)
Male	306 (34.7)	866 (32.9)	919 (33.0)
Race, n (%)			
White	876 (99.3)	2608 (99.1)	2758 (99.0)
Black	5 (0.6)	16 (0.6)	21 (0.8)
Asian	1 (0.1)	4 (0.2)	4 (0.1)
Other	0	3 (0.1)	4 (0.1)
Hispanic ethnicity, n (%)	16 (1.8)	29 (1.1)	32 (1.1)
Region, n (%)			
Eastern Europe	790 (89.6)	2365 (89.9)	2490 (89.3)
Rest of world	92 (10.4)	266 (10.1)	297 (10.7)
BMI, mean (SD), kg/m^2	24.3 (4.8)	24.3 (4.8)	24.3 (4.8)
Time since MS symptom onset, mean (SD), years	6.9 (6.3)	6.8 (6.2)	6.8 (6.1)
Time since MS diagnosis, mean (SD), years	3.8 (4.7)	3.7 (4.6)	3.7 (4.6)
EDSS score, mean (SD)	2.6 (1.2)	2.6 (1.2)	2.6 (1.2)
Number of GdE lesions, mean (SD)	1.7 (3.6)	1.6 (3.3)	1.7 (3.3)
Number of T2 lesions, mean (SD)	51.3 (36.3)	51.4 (36.2)	51.2 (36.1)
Prior exposure to any MS disease-modifying therapy, n (%)	252 (28.6)	753 (28.6)	801 (28.7)[b]

Abbreviations: BMI, body mass index; EDSS, Expanded Disability Status Scale; GdE, gadolinium-enhancing; MS, multiple sclerosis; OLE, open-label extension; RMS, relapsing multiple sclerosis; SD, standard deviation.

[a] Includes participants who received only ozanimod 0.92 mg as well as those who received ozanimod 0.46 mg alone (if they did not enroll in the OLE study) or followed by ozanimod 0.92 mg in the OLE study.

[b] Previous disease-modifying therapies used by the "any ozanimod" group included glatiramer acetate (n=317 [11.4%]), interferon beta-1a (n=288 [10.3%]), interferon beta-1b (n=229 [8.2%]), peginterferon beta-1a (n=35 [1.3%]), teriflunomide (n=33 [1.2%]), daclizumab (n=12 [0.4%]), dimethyl fumarate (n=9 [0.3%]), interferon (unspecified, n=8 [0.3%]), and mitoxantrone (n=2 [0.07%]).

Table 2
TEAEs in participants with RMS who were treated with ozanimod 0.92 mg.

	Phase 3 Study Population (N=882)		Overall RMS Population (N=2631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Any TEAE	592 (67.1)	896.1 (825.4–971.3)	2106 (80.0)	772.2 (739.5–805.9)
Severe TEAEs	22 (2.5)	16.5 (10.4–25.0)	129 (4.9)	18.7 (15.6–22.2)
Serious TEAEs	41 (4.6)	31.2 (22.4–42.4)	224 (8.5)	33.2 (29.0–37.9)
Permanent discontinuation for TEAEs	26 (2.9)	19.4 (12.7–28.5)	66 (2.5)	9.4 (7.3–11.9)
TEAEs in ≥5% of participants				
Nasopharyngitis	98 (11.1)	78.8 (64.0–96.1)	457 (17.4)	72.9 (66.3–79.9)
Headache	78 (8.8)	61.7 (48.8–77.0)	339 (12.9)	52.5 (47.0–58.4)
URTI	52 (5.9)	40.3 (30.1–52.8)	249 (9.5)	37.6 (33.1–42.6)
Lymphopenia	NA[b]	NA[b]	222 (8.4)	33.1 (28.9–37.8)
ALC decreased	NA[b]	NA[b]	181 (6.9)	26.6 (22.9–30.8)
GGT increased	40 (4.5)	30.5 (21.8–41.6)	174 (6.6)	25.8 (22.1–30.0)
Back pain	35 (4.0)	26.6 (18.5–37.0)	162 (6.2)	23.9 (20.3–27.8)
Hypertension	30 (3.4)	22.8 (15.4–32.5)	141 (5.4)	20.7 (17.4–24.4)
UTI	36 (4.1)	27.4 (19.2–37.9)	138 (5.2)	20.2 (17.0–23.9)
ALT increased	47 (5.3)	36.2 (26.6–48.1)	129 (4.9)	19.0 (15.8–22.5)
Influenza-like illness	44 (5.0)	34.4 (25.0–46.2)	65 (2.5)	9.4 (7.3–12.0)
Serious TEAEs in ≥2 participants				
Appendicitis	3 (0.3)	2.2 (0.5–6.5)	8 (0.3)	1.1 (0.5–2.2)
Uterine leiomyoma	1 (0.1)	0.7 (0.0–4.1)	8 (0.3)	1.1 (0.5–2.2)
Pyelonephritis acute	1 (0.1)	0.7 (0.0–4.1)	7 (0.3)	1.0 (0.4–2.0)
Intervertebral disc disorder	2 (0.2)	1.5 (0.2–5.4)	6 (0.2)	0.9 (0.3–1.9)
Depression	0	0 (0.0–2.7)	4 (0.2)	0.6 (0.2–1.5)
Intervertebral disc protrusion	1 (0.1)	0.7 (0.0–4.1)	4 (0.2)	0.6 (0.2–1.5)
Pneumonia	0	0 (0.0–2.7)	4 (0.2)	0.6 (0.2–1.5)
Uterine hemorrhage	0	0.0 (0.0–2.7)	4 (0.2)	0.6 (0.2–1.5)
Abortion spontaneous	1 (0.1)	0.7 (0.0–4.1)	3 (0.1)	0.4 (0.1–1.2)
Craniocerebral injury	1 (0.1)	0.7 (0.0–4.1)	3 (0.1)	0.4 (0.1–1.2)
Epilepsy	1 (0.1)	0.7 (0.0–4.1)	3 (0.1)	0.4 (0.1–1.2)
Headache	0	0 (0.0–2.7)	3 (0.1)	0.4 (0.1–1.2)

ALC: absolute lymphocyte count; ALT: alanine aminotransferase; CI: confidence interval; GGT: gamma-glutamyl transferase; IR: incidence rate; NA: not applicable; PY: person-years; RMS: relapsing multiple sclerosis; TEAEs: treatment-emergent adverse events; URTI: upper respiratory tract infection; UTI: urinary tract infection.

[a] IR/1000 PY, study duration–adjusted incidence rate per 1000 person-years, calculated as number of participants with a TEAE of interest/PY x 1000, where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

[b] Investigators in the phase 3 RMS studies were blinded to lymphocyte count data (a key pharmacodynamic effect of ozanimod); therefore, TEAEs related to lymphocyte counts were not reported.

trials was 896.1/1000 PY (Table 2). The most common TEAEs were nasopharyngitis, headache, upper respiratory tract infection, and lymphopenia. The study duration–adjusted IR for serious TEAEs was 33.2/1000 PY among ozanimod 0.92 mg recipients across all RMS trials and 31.2/1000 PY in the phase 3 trials (Table 2).

3.3. Cardiovascular effects

Modest gradual increases in mean sitting/supine systolic and diastolic BP continued over time during treatment with ozanimod 0.92 mg (Table A.2). Blood pressure increases were detectable approximately 3 months after treatment initiation. After 42 months of ozanimod 0.92 mg, systolic BP had increased from a mean (SD) of 116.5 (12.23) at baseline to 122.1 (12.49) mm Hg and diastolic BP increased from a mean (SD) of 74.3 (9.17) to 77.4 (9.14) mm Hg. In the phase 3 trials, the increase from baseline in systolic BP was about 1 to 2 mm Hg greater with ozanimod than IFN beta-1a, whereas impact on diastolic BP was similar between the two treatment groups. There was no increase in exposure-adjusted IRs of hypertension-related TEAEs (22.8/1000 PY in phase 3 vs 20.7/1000 PY in the overall RMS population) and no increase in the IRs of bradycardias, cardiac conduction abnormalities, and ischemic heart conditions with longer exposure (Table A.3). Two patients were hospitalized for hypertension, which resolved without ozanimod interruption. There were no cases of second-degree Mobitz type 1 or higher atrioventricular block observed on electrocardiogram (ECG). Eleven participants (0.4%) exposed to ozanimod 0.92 mg experienced ischemic heart conditions (Table A.3).

3.4. Hepatic effects

Among participants treated with ozanimod 0.92 mg across the RMS trials, 3.9% had a maximum alanine aminotransferase (ALT) level ≥3 x the upper limit of normal (ULN), 1.2% had a maximum aspartate aminotransferase (AST) level ≥3 x ULN, and 2.4% experienced maximum bilirubin >2 x ULN (Table 3); there was no clear temporal pattern to these abnormalities relative to start of treatment. Consecutive ALT ≥3 x ULN occurred in 1.1% and consecutive AST ≥3 x ULN occurred in 0.2%. The majority of participants with ≥1 assessment after an abnormality was detected recovered to ≤1 x ULN while still on treatment (ALT: 84/110 [76.4%]; AST: 24/25 [96.0%]; bilirubin: 27/52 [51.9%]). Except for bilirubin, the same was true for recovery in the phase 3 trials (ALT: 25/41 [61.0%]; AST: 5/5 [100%]; bilirubin: 4/14 [28.6%]). Mean (SD) maximum change from baseline was 27.0 IU/L (66.3) for ALT, 12.8 IU/L (44.0) for AST, and 6.05 μmol/L (5.4) for bilirubin. There were no cases of severe drug-induced liver injury.

The most common hepatobiliary TEAE was hyperbilirubinemia (n=24 [0.9%]; Table 3); six of these participants had bilirubin >1 × ULN and one had bilirubin >2 × ULN at baseline. There were six serious hepatobiliary TEAEs among all RMS participants treated with ozanimod 0.92 mg: one case each of cholelithiasis, biliary polyp, acute cholecystitis, chronic cholecystitis, cholestasis, and chronic hepatitis.

3.5. Macular edema

In the phase 3 trials, TEAEs of ME or cystoid ME were reported in 2/

Table 3
Hepatic laboratory abnormalities and TEAEs in participants with RMS treated with ozanimod 0.92 mg.

	Phase 3 Study Population (N=882)		Overall RMS Population (N=2631)	
Based on laboratory testing	n=878		n=2623	
Maximum ALT				
≥3 x ULN, n (%)	48 (5.5)		102 (3.9)	
≥5 x ULN, n (%)	14 (1.6)		25 (1.0)	
≥10 x ULN, n (%)	4 (0.5)		9 (0.3)	
Mean (SD) maximum change from baseline, IU/L	28.4 (61.0)		27.0 (66.3)	
Maximum AST				
≥3 x ULN, n (%)	9 (1.0)		31 (1.2)	
≥5 x ULN, n (%)	5 (0.6)		13 (0.5)	
≥10 x ULN, n (%)	4 (0.5)		6 (0.2)	
Mean (SD) maximum change from baseline, IU/L	13.7 (34.4)		12.8 (44.0)	
Maximum Bilirubin				
>2 x ULN, n (%)	14 (1.6)		64 (2.4)	
>3 x ULN, n (%)	3 (0.3)		9 (0.3)	
Mean (SD) maximum change from baseline, μmol/L	4.6 (4.9)		6.1 (5.4)	
Hy's Law cases[a], n	0		0	
	N (%)	IR/1000 PY[b] (95% CI)	N (%)	IR/1000 PY[b] (95% CI)
Any Hepatobiliary TEAEs, n (%)	15 (1.7)	11.2 (6.3–18.5)	73 (2.8)	10.5 (8.3–13.2)
Hepatobiliary TEAEs in ≥3 participants, n (%)				
Hyperbilirubinemia	3 (0.3)	2.2 (0.5–6.5)	24 (0.9)	3.4 (2.2–5.1)
Cholecystitis chronic	1 (0.1)	0.7 (0.0–4.1)	7 (0.3)	1.0 (0.4–2.0)
Biliary dyskinesia	0	0 (0.0–2.7)	5 (0.2)	0.7 (0.2–1.7)
Hepatic cyst	0	0 (0.0–2.7)	5 (0.2)	0.7 (0.2–1.7)
Cholelithiasis	1 (0.1)	0.7 (0.0–4.1)	4 (0.2)	0.6 (0.2–1.5)
Chronic hepatitis	0	0 (0.0–2.7)	3 (0.1)	0.4 (0.1–1.2)
Hepatitis	0	0 (0.0–2.7)	3 (0.1)	0.4 (0.1–1.2)
Hepatitis toxic	2 (0.2)	1.5 (0.2–5.4)	3 (0.1)	0.4 (0.1–1.2)
Hypertransaminasemia	1 (0.1)	0.7 (0.0–4.1)	3 (0.1)	0.4 (0.1–1.2)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; IR: incidence rate; PY: person-years; RMS: relapsing multiple sclerosis; SD: standard deviation; TEAEs: treatment-emergent adverse events; ULN: upper limit of normal.

[a] Hy's Law, defined as ALT or AST ≥3 x ULN plus total bilirubin >2 x ULN without cholestasis and without alternative explanation, is used by the US Food and Drug Administration to identify drugs likely to cause severe drug-induced liver injury (Food and Drug Administration, 2009). An unblinded external panel of expert hepatologists reviewed all cases of concurrent ALT/AST elevations ≥3 x ULN and bilirubin >2 x ULN and concluded that none met Hy's Law criteria due to alternate explanations and based on the pattern of abnormalities.

[b] IR/1000 PY, study duration–adjusted incidence rate per 1000 person-years, calculated as number of participants with a TEAE of interest/PY x 1000, where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

882 (0.2%) participants treated with ozanimod 0.92 mg, 3/892 (0.3%) treated with ozanimod 0.46 mg, and 3/885 (0.3%) treated with IFN beta-1a. Across the ozanimod clinical development program, there were 10 (0.4%) reported TEAEs of ME or cystoid ME among 2787 RMS participants treated with either ozanimod dose.

The MERP confirmed seven cases (0.3%) of ME (IR 0.8/1000 PY; 95% confidence interval [CI] 0.3–1.7), four in participants treated with ozanimod 0.92 mg and three in participants treated with ozanimod 0.46 mg. This included four cases (ozanimod 0.92 mg: n=1; 0.46 mg: n=3) that occurred during the phase 3 trials, affecting 0.2% of 1774 ozanimod-treated participants (IR 1.5/1000 PY; 95% CI 0.4–3.8); the other three cases occurred in DAYBREAK, in participants who had switched to ozanimod from IFN beta-1a. Across all seven MERP-confirmed cases, onset of ME occurred 15 to 366 days after ozanimod was first initiated (Table A.4). There were no MERP-confirmed cases of ME in the phase 3 IFN beta-1a groups.

All cases of confirmed ME had pre-existing risk factors or confounding conditions consisting of a history of ME, ME secondary to ocular trauma, central serous choroidopathy (CSR), uveitis, prior unreported uveitis (intraocular inflammation), pigment epithelial detachment with possible choroidal neovascularization, and a history of retinopathy and optic neuritis (Table A.4). Ozanimod was permanently withdrawn in all but one person with trace ME due to CSR who was allowed to continue treatment because the choroidal process associated with CSR-related ME differs from intraretinal ME associated with S1P-related cases. As of the data cutoff, ME had resolved in all patients who discontinued ozanimod. As of March 2020, ME was ongoing in the patient who continued on ozanimod.

3.6. ALC reductions

Among participants treated with ozanimod 0.92 mg, mean ALC was reduced to 51% of baseline at the first assessment and 44% of baseline at month 3, after which mean ALC was maintained at approximately 40% of baseline (Fig. 2). Among the 2631 participants exposed to ozanimod 0.92 mg, ALC was less than the lower limit of normal, $<0.8 \times 10^9$/L, $<0.5 \times 10^9$/L, or $<0.2 \times 10^9$/L on at least one measurement in 2488 (94.9%), 2345 (89.5%), 1669 (63.4%), and 182 (6.9%) participants, respectively.

3.7. Infections

Across all RMS studies, the overall incidence of infection among participants treated with ozanimod 0.92 mg was 48.6% (IR 270.1/1000 PY) (Table 4), which was similar to the incidence in the phase 3 trials (35.1%; IR 300.5/1000 PY). The most common infections were nasopharyngitis, upper respiratory tract infection, and urinary tract infection (Table 4).

The incidence of serious infections was 1.7% in the overall RMS population treated with ozanimod 0.92 mg (IR 6.3/1000 PY) and 1.0% in phase 3 trial participants treated with the same dose (IR 6.7/1000 PY). Serious infections occurring in more than two participants are

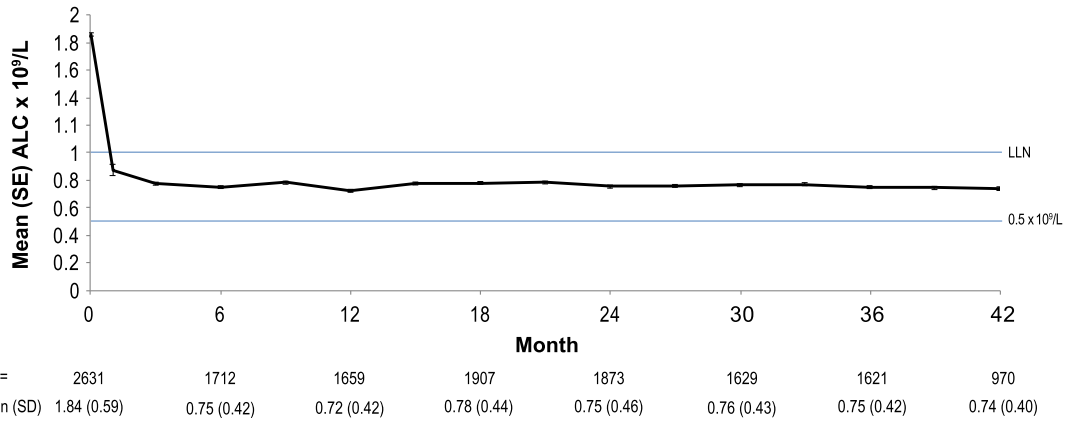

Fig. 2. Mean (SE) ALC by visit during treatment with ozanimod 0.92 mg: overall RMS population
ALC: absolute lymphocyte count; LLN: lower limit of normal; RMS: relapsing multiple sclerosis; SE: standard error.

shown in Table 2, and a complete list is provided in Table A.5. There was one infection-related death: a bed-ridden participant was hospitalized and discontinued ozanimod due to community-acquired pneumonia after >5.2 years of ozanimod treatment, and died of respiratory failure 11 days later.

Opportunistic infections occurred in 113/2631 (4.3%) participants treated with ozanimod 0.92 mg (IR 16.4/1000 PY) across all trials, including 16/882 (1.8%) cases during phase 3 (IR 12.0/1000 PY). Herpes virus infections were the most frequent opportunistic infection and included oral herpes and herpes zoster/varicella zoster virus infection (Table 4). None of the herpes zoster infections were serious, and the affected participants continued treatment with ozanimod without adverse clinical consequences. There were no serious opportunistic infections, including progressive multifocal leukoencephalopathy (PML).

One participant (0.5%) had an ALC $<0.2 \times 10^9$/L around the time of onset of a serious infection (pyelonephritis) and one (0.5%) had an ALC $<0.2 \times 10^9$/L around the onset of a nonserious opportunistic infection (oral herpes) (Table 4). Both infections occurred during DAYBREAK. Thus, there was no apparent association between ALC $<0.2 \times 10^9$/L and serious or opportunistic infections.

3.8. Malignancies

Among 2787 participants with any ozanimod exposure in any RMS study, there have been 11 nonmelanoma skin cancers, 1 melanoma, and 13 noncutaneous malignancies that were treatment emergent (Table 5). The overall IR of malignancy (289.3/100,000 PY; 95% CI 187.2–427.1) was similar to the rate in participants with ≤24 months' ozanimod exposure in phase 3 trials (298.2/100,000 PY; 95% CI 128.7–587.6) (Table 5). For comparison, in the phase 3 trials, there were two treatment-emergent malignancies (basal cell carcinoma and chronic lymphocytic leukemia) reported in 885 participants treated with IFN beta-1a (IR 150.8/100,000 PY; 95% CI 18.3–544.8). Prior to data cutoff, three deaths occurred in patients with malignancies, including metastatic malignant neoplasm of unknown primary, metastatic pancreatic cancer, and glioblastoma.

3.9. Pulmonary function

Pulmonary function test (PFT) abnormalities (forced expiratory volume in 1 second [FEV_1] or forced vital capacity [FVC] decrease to <80% of baseline) occurred in 311/2631 (11.8%) RMS participants treated with ozanimod 0.92 mg across all RMS clinical trials, which included 90/882 (10.2%) participants treated with ozanimod 0.92 mg in the phase 3 studies. FEV_1 was <80% of baseline at any visit in 242/2568 (9.4%) and for two consecutive postbaseline visits or on the last postbaseline visit in 171/2568 (6.7%) participants treated with ozanimod 0.92 mg across all RMS trials; the corresponding incidence for reductions in FVC was 204/2568 (7.9%) at any visit and 146/2568 (5.7%) for two consecutive visits or on the last postbaseline visit.

Pulmonary adverse events occurred in 39/2631 (1.5%) participants with RMS who received ozanimod 0.92 mg, including one report (<0.1%) of serious chronic obstructive pulmonary disease. Dyspnea occurred in 10/2631 (0.4%) participants exposed to ozanimod 0.92 mg across all RMS trials; one participant discontinued ozanimod because of dyspnea.

3.10. Potential drug interactions

During the RMS trials, 573/2787 (20.6%) participants concurrently received ozanimod 0.92 or 0.46 mg and serotonergic medications, including psychoanaleptic or psycholeptic drugs (12.2%), analgesics (7.8%), nasal preparations (2.0%), cough/cold preparations (1.5%), and anesthetics (0.7%). No participants developed serotonin syndrome (preferred terms serotonin syndrome, neuroleptic malignant syndrome, hyperthermia malignant). Three (0.1%) participants in the RMS trials concurrently took ozanimod 0.92 or 0.46 mg and an MAO inhibitor (moclobemide in all three cases); none experienced hypertensive crisis.

3.11. Pregnancy outcomes

Participants with reproductive potential were required to use effective contraception during ozanimod trials. Nonetheless, 36 of 1868 female participants became pregnant while taking either dose of ozanimod as of the data cutoff; one was initially carrying twins. Outcomes include 24 live births: 18 normal and 3 premature but normal infants (12.5% of live births), and 1 report each of neonatal icterus, late intrauterine growth retardation with subsequent normal progress over the first year, and duplex kidney. There were five early spontaneous abortions (13.5%) (of which one was loss of a twin) and seven elective terminations. One participant refused consent to follow-up.

3.12. Mortality

There were eight deaths, of which three were from malignancies and one from pneumonia, as described above. Two were accidents: a drowning reported in phase 3 RADIANCE (Cohen et al., 2019b) and a pedestrian-train accident. One participant died from a pulmonary embolism after a 38-day hospitalization for surgical repair of a lower limb fracture. Another died as a result of chronic kidney failure approximately 10 months after prematurely discontinuing ozanimod 0.92 mg during phase 3 RADIANCE due to Guillain-Barré syndrome and posterior reversible encephalopathy syndrome.

Table 4
Infections in participants with RMS who were treated with ozanimod 0.92 mg.

	Phase 3 Study Population (N=882)		Overall RMS Population (N=2631)	
	Incidence, n (%)	IR/1000 PY[a] (95% CI)	Incidence, n (%)	IR/1000 PY[a] (95% CI)
Any infection	310 (35.1)	300.5 (268.0–335.9)	1278 (48.6)	270.1 (255.5–285.3)
Any serious infection[b]	9 (1.0)	6.7 (3.1–12.8)	44 (1.7)	6.3 (4.6–8.4)
Any opportunistic infection	16 (1.8)	12.0 (6.9–19.5)	113 (4.3)	16.4 (13.5–19.7)
Infections in ≥2% of participants				
Nasopharyngitis	98 (11.1)	78.8 (64.0–96.1)	457 (17.4)	72.9 (66.3–79.9)
URTI	52 (5.9)	40.3 (30.1–52.8)	249 (9.5)	37.6 (33.1–42.6)
UTI	36 (4.1)	27.4 (19.2–37.9)	138 (5.2)	20.2 (17.0–23.9)
Bronchitis	23 (2.6)	17.3 (11.0–26.0)	118 (4.5)	17.2 (14.2–20.6)
Pharyngitis	28 (3.2)	21.2 (14.1–30.6)	91 (3.5)	13.2 (10.6–16.2)
Respiratory tract infection	18 (2.0)	13.5 (8.0–21.4)	110 (4.2)	16.0 (13.1–19.2)
Respiratory tract infection viral	21 (2.4)	15.8 (9.8–24.2)	99 (3.8)	14.3 (11.7–17.5)
Influenza	9 (1.0)	6.7 (3.1–12.8)	73 (2.8)	10.5 (8.2–13.2)
Rhinitis	19 (2.2)	14.3 (8.6–22.4)	77 (2.9)	11.1 (8.8–13.9)
Sinusitis	13 (1.5)	9.8 (5.2–16.7)	76 (2.9)	10.9 (8.6–13.7)
Opportunistic infection in ≥2 participants[c]				
Oral herpes	6 (0.7)	4.5 (1.6–9.7)	40 (1.5)	5.7 (4.1–7.8)
Herpes zoster (including VZV)	5 (0.6)	3.7 (1.2–8.7)	37 (1.4)	5.3 (3.7–7.3)
Herpes simplex	1 (0.1)	0.7 (0.0–4.1)	12 (0.5)	1.7 (0.9–3.0)
Genital herpes	0	0 (0.0–2.7)	5 (0.2)	0.7 (0.2–1.7)
Fungal infection	0	0 (0.0–2.7)	4 (0.2)	0.6 (0.2–1.5)
Candida infection	0	0 (0.0–2.7)	3 (0.1)	0.4 (0.1–1.2)
Oral fungal infection	0	0 (0.0–2.7)	3 (0.1)	0.4 (0.1–1.2)
Herpes dermatitis	0	0 (0.0–2.7)	2 (0.07)	0.3 (0.0–1.0)
Genital fungal infection	1 (0.1)	0.7 (0.0–4.1)	2 (0.07)	0.3 (0.0–1.0)
Minimal postbaseline ALC $<0.5 \times 10^9$/L	480 (54.4)	542.5 (495.1–593.3)	1669 (63.4)	450.6 (429.3–472.8)
Minimal postbaseline ALC $<0.2 \times 10^9$/L	29 (3.3)	21.9 (14.7–31.4)	182 (6.9)	26.7 (23.0–30.9)
ALC $<0.2 \times 10^9$/L around onset of any infection	2 (6.9)	1.5 (0.2–5.4)	18 (9.9)	2.6 (1.5–4.0)
ALC $<0.2 \times 10^9$/L around onset of serious infection[d]	0	0 (0.0–2.7)	1/182 (0.5) (pyelonephritis)	0.1 (0.0–0.8)
ALC $<0.2 \times 10^9$/L around onset of opportunistic infection[d]	0	0 (0.0–2.7)	1/182 (0.5) (oral herpes)	0.1 (0.0–0.8)

ALC: absolute lymphocyte count; CI: confidence interval; IR: incidence rate; PY: person-years. RMS, relapsing multiple sclerosis; TEAEs, treatment-emergent adverse events; VZV, varicella-zoster virus.

[a] IR/1000 PY, study duration–adjusted incidence rate per 1000 person-years, calculated as number of participants with a TEAE of interest/PY x 1000, where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

[b] Serious infections occurring in >2 participants can be found in Table 2; a complete list of serious infections in participants with RMS who were treated with ozanimod 0.92 mg is available in table A-5.

[c] Additional opportunistic infections that occurred in a single participant each (IR <0.1/1000 PY) across all participants exposed to ozanimod 0.92 mg in any of the RMS trials included anal fungal infection, gastrointestinal candidiasis, esophageal candidiasis, oral candidiasis, ophthalmic herpes simplex, herpes virus infection, nasal herpes, and varicella; 4 of these 8 infections occurred during the phase 3 trials.

[d] Participants who experienced an initial serious infection or opportunistic infection and had an ALC $<0.2 \times 10^9$/L at the laboratory visit prior to the event to either the time of the event or the assessment just after onset of the event.

3.13. Clinical rebound

The number of participants with posttreatment follow-up data is limited, as most were continuing in DAYBREAK at data cutoff. However, as of this analysis, there have been no posttreatment AEs indicative of rebound (MS flare).

4. Discussion

This analysis provides a comprehensive perspective of the safety of ozanimod 0.92 mg. The 2631 participants from all ozanimod RMS clinical trials had a mean duration of exposure to ozanimod 0.92 mg that was approximately 14 months longer than ozanimod exposure in the 12- to 24-month phase 3 studies (Cohen et al., 2019b; Comi et al., 2019). The safety profile in this population was generally consistent with that reported in the phase 3 trials (Cohen et al., 2019b; Comi et al., 2019) and does not point to any new safety concerns with continued ozanimod use.

Long-term cardiovascular safety was evaluated because S1P receptors are expressed by cardiomyocytes (Li and Zhang, 2016), and cardiovascular abnormalities have been reported with other S1P modulators (Kappos et al., 2018; Kappos et al., 2014; Olsson et al., 2014). Mean systolic and diastolic BP increased with continued use of ozanimod 0.92 mg; however, there was no increase in the IR of hypertension-related TEAEs in the overall RMS population compared with the phase 3 population. Slowing of heart rate can occur after first-dose exposure to S1P modulators; however, as reported previously (Cohen et al., 2016; Cohen et al., 2019b; Comi et al., 2019; Tran et al., 2017), effects on heart rate and atrioventricular conduction are attenuated by dose escalation when initiating ozanimod and such effects are uncommon with continued use. There were no second-degree Mobitz type 1 or higher atrioventricular blocks based on ECG, and few (0.4%) participants exposed to ozanimod 0.92 mg in any of the RMS trials experienced ischemic heart conditions.

Hepatic enzyme elevations and hepatic-related TEAEs did not increase with continued ozanimod exposure. Hepatic enzyme elevations were generally asymptomatic, transient, and did not lead to severe drug-induced liver injury.

ME cases independent of coexisting risk factors have been reported in studies of fingolimod (0.4% with 0.5 mg/d), siponimod (2% with 2 mg/d), and ponesimod (0.9% with 10, 20, or 40 mg/d) (Kappos et al., 2018; Kappos et al., 2014; Olsson et al., 2014). ME rates with ozanimod were 0.3% to 0.4%, and all confirmed cases had predisposing comorbid conditions.

ALC reductions are an expected part of the mechanism of action of S1P modulators. Ozanimod 0.92 mg reduced ALC to approximately 40% of baseline, and about 7% of participants who received ozanimod 0.92 mg developed ALC counts $<0.2 \times 10^9$/L on at least one laboratory assessment. For comparison, ALC counts $<0.2 \times 10^9$/L were reported in

Table 5
Treatment-emergent malignancies by preferred term in participants with RMS who were exposed to any dose of ozanimod (0.46 and/or 0.92 mg).

	Phase 3 Study Population (N=1774)		Overall RMS Population (N=2787)	
	Incidence, n (%)	IR/100,000 PY[a] (95% CI)	Incidence, n (%)	IR/100,000 PY[a] (95% CI)
Treatment-emergent malignancies	8 (0.5)	298.2 (128.7–587.6)	25 (0.9)	289.3 (187.2–427.1)
Cutaneous	4 (0.2)	149.0 (40.6–381.6)	12 (0.4)	138.8 (71.7– 242.4)
Basal cell carcinoma	3 (0.2)	111.8 (23.0–326.6)	9 (0.3)	104.0 (47.6–197.5)
Keratoacanthoma	1 (0.06)	37.2 (0.9–207.4)	1 (0.04)	11.5 (0.3–64.3)
Squamous cell carcinoma	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Malignant melanoma	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Nonmelanoma skin cancer	4 (0.2)	149.0 (40.6–381.6)	11 (0.4)	127.2 (63.5–227.6)
Noncutaneous	4 (0.2)	148.9 (40.6–381.4)	13 (0.5)	150.1 (79.9–256.7)
Breast cancer (women only)[b]	3/1174 (0.3)	168.7 (34.8–493.0)	5/1868 (0.3)	86.4 (28.0–201.5)
Cervix carcinoma	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3-64.3)
Testicular seminoma (pure) stage I[c]	1 (0.06)	37.2 (0.9–207.4)	1 (0.04)	11.5 (0.3–64.3)
Bile duct cancer[d]	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Clear cell renal carcinoma	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Glioblastoma	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Malignant neoplasm	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Pancreatic carcinoma metastatic	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Papillary thyroid cancer	0	0 (0.0–2.7)	1 (0.04)	11.5 (0.3–64.3)
Treatment-emergent malignancies, excluding NMSC	4 (0.2)	148.9 (40.6–381.4)	14 (0.5)	161.7 (88.4–271.2)

CI: confidence interval (based on the Poisson distribution); IR: incidence rate; NMSC: nonmelanoma skin cancer; PY: person-years; RMS: relapsing multiple sclerosis.
[a] IR/100,000 PY, study duration–adjusted incidence rate per 100,000 person-years, calculated as number of persons having the malignancy of interest/person-years x 100,000, where person-years = (date first malignancy of interest was documented – date of first dose of study drug + 1)/365.25; for participants not having the malignancy of interest, the time on study is the study duration (last date on study – first dose date of study drug +1)/365.25.
[b] Breast cancer includes cases using preferred terms of invasive breast cancer, breast cancer, and breast neoplasm.
[c] Diagnosed on study day 51.
[d] Diagnosis changed and confirmed after the data cutoff to hydatid cysts.

18% of FREEDOMS participants treated with fingolimod 0.5 mg/d (Kappos et al., 2014).

In the overall RMS population that had longer ozanimod 0.92 mg exposure, overall rates of infections and serious infections were similar to those with ≤24 months' exposure in phase 3 trials. The incidence and IR for opportunistic infections, particularly herpes infections, were higher in the overall RMS population than in the phase 3 subgroup; however, the 95% CIs for the IRs in the overall population overlapped completely with the wide 95% CIs from the phase 3 trials. As of the data cutoff, no serious opportunistic infections, including PML, have occurred in ozanimod-treated participants. An association between ALC $<0.2 \times 10^9$/L and serious or opportunistic infections was not detected.

The overall malignancy rate observed among all ozanimod-treated RMS study participants (289.3/100,000 PY) was similar to those with less exposure in phase 3 trials (298.2/100,000 PY). It was also consistent with reported malignancy rates among MS patients treated with other disease-modifying therapies (IR 290 to 1190/100,000 PY) (Cook et al., 2019) and the rate of invasive cancers in a general Swedish age-matched non-MS population (310/100,000 PY) (Alping et al., 2020). Although there were more malignancies reported with ozanimod than with IFN beta-1a in the phase 3 trials, (Cohen et al., 2019b; Comi et al., 2019) the low number of malignancies, relatively short duration of follow-up, and IRs with wide, overlapping CIs do not suggest an increase in the overall risk of malignancies with ozanimod. There were no lymphomas or other lymphoproliferative diseases. Five cases of breast cancer have been reported in ozanimod-treated women with RMS (IR 86.4/100,000 PY); this rate remains within the expected incidence of breast cancer of 5.35 events over the treatment period, derived by applying the breast cancer IR (92.4/100,000 PY) in an age-matched female population from the Surveillance, Epidemiology, and End Results to the female RMS participants with exposure to ozanimod (5789.5 PY). The IR (95% CI) per 100,000 PY for nonmelanoma skin cancers was comparable in the overall RMS population (127.2 [63.5–227.6]) and the phase 3 study population (149.0 [40.6–381.6]), suggesting that with longer exposure, the incidence did not increase. Furthermore, the IR (95% CI) in the overall RMS population was not markedly different from the IR (95% CI) of nonmelanoma skin cancer in a UK population of MS patients aged ≤59 years (101.8 [69.66–143.78]/100,000 PY) (adapted from Persson et al., 2020).

Mild but persistent declines in FEV_1 and FVC were noted in ozanimod-treated RMS patients beginning as early as 3 months of treatment. These changes were generally not symptomatic or associated with reported TEAEs and were not progressive. Dose-dependent reductions in FEV_1 have been reported with other S1P modulators (Mayzent package insert 2020; Calabresi et al., 2014; Olsson et al., 2014).

About 21% of ozanimod-treated participants were concurrently using serotonergic drugs, and 0.1% were using MAO inhibitors. To date, there have been no cases suggestive of serotonin toxicity or serotonin syndrome among concurrent users of serotonergic medications, and no cases of hypertensive crisis among the three participants who concomitantly used ozanimod and an MAO inhibitor during the RMS trials.

Although the mean effective half-life of ozanimod active metabolites is approximately 11 days, elimination may take up to 3 months (Zeposia package insert, 2020; Zeposia summary of product characteristics, 2020); therefore, the 36 women who became pregnant during ozanimod treatment and continued their pregnancies after stopping ozanimod likely had some level of drug exposure during the majority of their first trimester. The rate of spontaneous abortion (13.5%) was within the expected rate (about 20%) in the general population (Rossen et al., 2018), and the rate of preterm birth (8.3% of pregnancies; 12.5% of live births) was similar to the European estimate of 8.7% (Chawanpaiboon et al., 2019). The only congenital abnormality, duplex kidney, occurs in the general population at a frequency of about 1.8% (Privett et al., 1976). Nonclinical data indicate potential teratogenic effects; it is recommended that women use effective contraception during ozanimod treatment and for at least 3 months thereafter (Zeposia package insert 2020; Zeposia summary of product characteristics 2020). Labels for other S1P receptor modulators contain similar statements regarding fetal risk (Gilenya package insert 2019; Mayzent package insert 2020).

This analysis included a large pooled RMS population comprising participants with varying durations of disease, baseline levels of clinical and MRI disease activity, disability, and history of disease-modifying therapy use. These data allow a comparison between the phase 3 experience and longer-term exposure in a larger number of patients due to inclusion of the OLE. One limitation is the lack of a control group in the OLE, preventing direct comparisons to other disease-modifying therapies. Given that >99% of the participants were white, and nearly

90% hailed from Eastern Europe, generalizability of the findings to other populations is unknown. This is the longest duration of ozanimod exposure reported to date (mean 32 months); however, since disease-modifying therapy for RMS in clinical practice is of indefinite duration, it is important to continue to collect safety data from longer term follow-up, which is ongoing in DAYBREAK.

5. Conclusions

Safety results in this larger RMS population were generally consistent with those of the phase 3 trials, providing reassurance of the safety of continued use of ozanimod relative to previous shorter periods of observation. Planned future analyses from DAYBREAK, the ongoing OLE study, will provide further information about longer-term safety and tolerability of ozanimod.

CRediT authorship contribution statement

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