Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial

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Summary

Background Ozanimod is a sphingosine 1-phosphate receptor modulator, which selectively binds to sphingosine 1-phosphate receptor subtypes 1 and 5 with high affinity. In the RADIANCE phase 2 study in participants with relapsing multiple sclerosis, ozanimod was associated with better efficacy than placebo on MRI measures and was well tolerated. The RADIANCE phase 3 study aimed to confirm the safety and efficacy of ozanimod versus interferon beta-1a in individuals with relapsing multiple sclerosis.

Methods We did a 24-month, multicentre, double-blind, double-dummy phase 3 trial in participants with relapsing multiple sclerosis at 147 medical centres and clinical practices in 21 countries. Participants were aged 18–55 years, had multiple sclerosis according to 2010 McDonald criteria, a relapsing clinical course, brain MRI lesions consistent with multiple sclerosis, an expanded disability status scale score of 0·0–5·0, and either at least one relapse within 12 months before screening or at least one relapse within 24 months before screening plus at least one gadolinium-enhancing lesion within the 12 months before randomisation. Participants were randomly assigned (1:1:1) via an interactive voice response system to daily oral ozanimod 1·0 mg or 0·5 mg or weekly intramuscular interferon beta-1a 30 μg. Participants, investigators, and study staff were masked to treatment allocation. The primary endpoint was annualised relapse rate (ARR) over 24 months. The primary analysis was done in the intention-to-treat population of all participants who received study drug and safety was assessed in all randomly assigned participants who received study drug, grouped by highest dose of ozanimod received. This trial is registered at ClinicalTrials.gov, NCT02047734, and EudraCT, 2012-002714-40.

Findings Between Dec 27, 2013, and March 31, 2015, we screened 1695 participants, of which 375 did not meet inclusion criteria. 1320 participants were enrolled and randomly assigned to a group, of whom 1313 received study drug (433 assigned to ozanimod 1·0 mg, 439 assigned to ozanimod 0·5 mg, and 441 assigned to interferon beta-1a) and 1138 (86·7%) completed 24 months of treatment. Adjusted ARRs were 0·17 (95% CI 0·14–0·21) with ozanimod 1·0 mg, 0·22 (0·18–0·26) with ozanimod 0·5 mg, and 0·28 (0·23–0·32) with interferon beta-1a, with rate ratios versus interferon beta-1a of 0·62 (95% CI 0·51–0·77; p<0·0001) for ozanimod 1·0 mg and 0·79 (0·65 to 0·96; p=0·0167) for ozanimod 0·5 mg. The incidence of treatment-emergent adverse events was higher in the interferon beta-1a group (365 [83·0%] of 440 participants) than in the ozanimod 1·0 mg group (324 [74·7%] of 434) or the ozanimod 0·5 mg group (326 [74·3%] of 439). More participants in the interferon beta-1a group had treatment-emergent adverse events leading to treatment discontinuation than in the ozanimod groups. Incidences of infections and serious treatment-emergent adverse events were similar across treatment groups. No cases of ozanimod-related symptomatic reduction in heart rate and no second-degree or third-degree cases of atrioventricular block were reported.

Interpretation In this 24-month phase 3 study in participants with relapsing multiple sclerosis, ozanimod was well tolerated and associated with a significantly lower rate of clinical relapses than intramuscular interferon beta-1a. These findings show the potential of ozanimod as an effective oral therapy for individuals with relapsing multiple sclerosis.

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Introduction

Sphingosine 1-phosphate receptor modulation is an effective treatment for multiple sclerosis.[1] Antagonism of sphingosine 1-phosphate receptor subtype 1 inhibits egress of lymphocytes from lymph nodes, thereby decreasing circulating lymphocytes.[2,3] Preclinical evidence suggests that the modulation of sphingosine 1-phosphate receptor subtype 1 and subtype 5 might have direct CNS effects

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See **Online** for appendix

Research in context

Evidence before this study

We did a PubMed search on Dec 2, 2018 using the search string "(ozanimod OR RPC1063) AND multiple sclerosis," without restrictions on language or publication date. Two clinical trial publications were identified, the RADIANCE phase 2 trial in participants with relapsing multiple sclerosis and a separately published 2-year dose-blinded extension of RADIANCE phase 2. In the randomised, placebo-controlled, 24-week RADIANCE phase 2 study (NCT01628393, EudraCT 2012–002714–40) of 258 participants with relapsing multiple sclerosis, ozanimod 1·0 mg or 0·5 mg was associated with lower mean cumulative numbers of gadolinium-enhancing lesions and new or enlarging T2 lesions over weeks 12–24 (primary endpoint) compared with placebo, without notable cardiovascular, pulmonary, ophthalmic, or infectious adverse events. In the 2-year dose-blinded extension of RADIANCE phase 2, participants with relapsing multiple sclerosis who continued ozanimod showed sustained efficacy based on MRI and clinical outcomes, whereas the efficacy of ozanimod among participants who received placebo in the main trial and switched to ozanimod in the extension period was similar to that observed in participants who received continuous ozanimod. Ozanimod remained well tolerated and no new safety concerns emerged during the extension period.

Added value of this study

The RADIANCE phase 3 trial (NCT02047734; EudraCT 2012–002714–40) builds on the findings of RADIANCE phase 2 with a larger population of participants with relapsing multiple sclerosis (n=1313), a longer duration (24 months), and an active comparator (intramuscular interferon beta-1a 30 µg). Both doses of ozanimod (1·0 mg and 0·5 mg) were associated with significantly lower adjusted annualised relapse rate and mean numbers of new or enlarging T2 lesions and gadolinium-enhancing lesions relative to interferon beta-1a, and slowed brain volume loss, including whole brain volume, cortical grey matter volume, and thalamic volume. In a prespecified pooled analysis of data from RADIANCE phase 3 and SUNBEAM (NCT02294058; EudraCT 2014–002320–27), the proportion of participants with confirmed disability progression was low, with no differences between treatment groups. Ozanimod was well tolerated, consistent with RADIANCE phase 2 and its extension.

Implications of all the available evidence

Along with the preceding RADIANCE phase 2 study and its extension, and the second phase 3 study of ozanimod (SUNBEAM), which is reported separately, this study contributes to the evidence supporting the efficacy and tolerability of ozanimod in relapsing multiple sclerosis.

resulting in the reduction of inflammatory cytokines, demyelination, and axonal loss, and the preservation of GABAergic transmission.[4–6]

Ozanimod, a sphingosine 1-phosphate receptor modulator that selectively binds to sphingosine 1-phosphate receptor subtypes 1 and 5 with high affinity,[2] is in clinical development for treatment of relapsing multiple sclerosis and inflammatory bowel disease. In the 24-week, randomised, phase 2 RADIANCE trial of 258 participants with relapsing multiple sclerosis, gadolinium-enhancing and new or enlarging T2 lesions on brain MRI were fewer in those treated with ozanimod 1·0 mg or 0·5 mg than placebo.[7] During the 2-year, dose-blinded extension study, participants who continued ozanimod showed sustained efficacy on the basis of MRI and clinical outcomes; ozanimod efficacy in those who switched from placebo was similar to that in participants who received continuous ozanimod.[8] No serious cardiac events, serious opportunistic infections, or macular oedema were reported in the 2·5-year period of the study or its extension.[7,8] RADIANCE phase 3 was initiated on the basis of interim results from the RADIANCE phase 2 trial. We present the safety and efficacy analyses of once-daily oral ozanimod 1·0 mg or 0·5 mg versus weekly intramuscular interferon beta-1a 30 µg over 24 months in participants with relapsing multiple sclerosis in RADIANCE phase 3. Another phase 3 trial of at least 12 months of treatment with ozanimod in patients with relapsing multiple sclerosis, the SUNBEAM trial[9] (NCT02294058; EudraCT 2014–002320–27), was

conducted concurrently with RADIANCE phase 3 and is reported separately.

Methods

Study design

RADIANCE was a 24-month, multicentre, randomised, double-blind, double-dummy, active-controlled, parallel-group, phase 3 trial (appendix p 6) done at 147 academic medical centres and clinical practices in 21 countries (appendix p 7). As part of an accelerated approach to clinical development, the RADIANCE phase 2 and phase 3 trial dates overlapped, such that RADIANCE phase 3 commenced after a planned interim analysis, including thorough safety review by the data monitoring committee, of RADIANCE phase 2. The institutional review board or ethics committee at each site approved the protocol, which conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles.

Participants

Participants were aged 18–55 years with multiple sclerosis according to 2010 McDonald criteria,[10] a relapsing clinical course (relapsing–remitting, progressive–relapsing, or secondary progressive), brain MRI lesions consistent with multiple sclerosis, an expanded disability status scale (EDSS) score of 0·0–5·0, either at least one relapse within 12 months before screening or at least one relapse within 24 months before screening plus at least one gadolinium-enhancing lesion within the 12 months

before randomisation, no history of relapse or systemic corticosteroid or adrenocorticotrophic hormone use from 30 days before screening through randomisation, and positive varicella zoster virus immunoglobulin G antibody status or varicella zoster virus vaccination at least 30 days before randomisation.

Exclusion criteria included primary progressive multiple sclerosis; disease duration greater than 15 years and an EDSS of 2·0 or less; previous inability to tolerate interferon beta; specific cardiovascular conditions (eg, recent myocardial infarction, stroke, or prolonged Fridericia-corrected QT interval [QTcF]); resting heart rate less than 55 beats per min (bpm) at screening; previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers; and any active infection. Individuals with a history of macular oedema were eligible. Complete inclusion and exclusion criteria are in the appendix (pp 7–9). Participants provided written informed consent.

Randomisation and masking

Participants were randomised (1:1:1) via an interactive voice response system to ozanimod 1·0 mg, ozanimod 0·5 mg, or interferon beta-1a. The randomisation sequence was generated by the contract research organisation and based on a blocked algorithm stratified by baseline EDSS score (≤3·5 vs >3·5) and country. Study personnel used electronic case report forms to store and transmit participant information. Participants were assigned unique identifier numbers; access to the electronic case report forms were password protected and limited to study personnel.

Placebos consisting of daily oral capsules identical in appearance to ozanimod were given to participants in the interferon beta-1a group and weekly intramuscular injections identical to interferon beta-1a were given to participants in the ozanimod group. Prophylactic treatment with acetaminophen or ibuprofen was recommended 1 h before and every 6 h for 24 h after interferon beta-1a or placebo injection. An assessor masked to treatment and previous EDSS results investigated participants using the EDSS (Neurostatus method) at all visits. The assessor was not involved in treatment and participants were instructed to not discuss clinical symptoms or adverse effects with them. A treating neurologist, the investigator, handled all other assessments and supervised medical management. Participants, investigators, EDSS assessors, study personnel, MRI reviewers (NeuroRx, Montreal, QC, Canada), and the funder were masked to treatment and total and differential white blood cell counts.

Study monitors did regular site visits to monitor study conduct, including masking requirements and the potential for unmasking.

Procedures

Participants in the ozanimod groups were given daily oral ozanimod HCl 1·0 mg (equivalent to ozanimod 0·92 mg) or 0·5 mg (equivalent to 0·46 mg; manufactured for Celgene by Norwich Pharmaceuticals, Norwich, NY, USA), or weekly intramuscular interferon beta-1a 30 µg (manufactured by Biogen, Cambridge, MA, USA) for 24 months. An initial 7-day dose escalation[3] was used for ozanimod and oral placebo. Participants in the ozanimod groups received ozanimod HCl 0·25 mg (equivalent to ozanimod 0·23 mg) on days 1–4, 0·5 mg on days 5–7, and then their assigned dose starting on day 8. Vital signs were measured predose and hourly for 6 h after the initial dose; electrocardiograms (ECGs) were done predose and at 6 h. If heart rate was less than 45 bpm or at its lowest postdose value at 6 h or if 6-h ECG showed second-degree or third-degree atrioventricular block or prolonged QTcF interval, monitoring was extended until event resolution. Monitoring was repeated on days 5 and 8 at the investigator's discretion for participants with a cardiac safety issue on the previous day of dose escalation.

Study visits occurred at screening, baseline, and months 1, 3, 6, 9, 12, 15, 18, 21, and 24. Neurological and EDSS assessments were performed at screening, each visit from months 3 to 24, and at the time of suspected relapse. Brain MRI was performed at screening, month 12, and month 24. Adverse events were assessed at each visit.

Liver function tests were done at screening, month 1, and at 3-month intervals through month 24. Optical coherence tomography was done at screening and months 6, 12, and 24. Ophthalmology assessments, including eye history, visual acuity, and dilated ophthalmoscopy were obtained if macular oedema was suspected. An expert macular oedema review panel masked to treatment assessed all optical coherence tomography images from participants with reported adverse events of macular oedema and related terms, cases of increased central foveal thickness more than 20% from baseline, or any relevant optical coherence tomography abnormality. Pulmonary function tests (forced expiratory volume in 1 s [FEV_1] and forced vital capacity [FVC]) were performed at screening and months 3, 6, 12, and 24, and diffusing capacity of the lungs for carbon monoxide (if available locally) was assessed at screening and months 12 and 24. Macular oedema or pulmonary function test abnormalities were followed until resolution or no further improvement was expected by the investigator (with ≥3 months follow-up). Skin examinations were performed at screening and months 12 and 24. Study treatment was discontinued for participants with alanine aminotransferase or aspartate aminotransferase concentrations more than five times the upper limit of normal (ULN) after confirmation on retest within 14 days, new or worsening macular oedema, FEV_1 or FVC less than 50% of predicted, or pregnancy.

Whole brain volume and cortical grey matter volume were measured using SienaX, and thalamic volume was measured using ThalamicVolume software (appendix p 9). Percentage change in brain volume was established using SIENA for whole brain volume and Jacobian atrophy software using longitudinal Jacobian integration[11] for cortical grey matter and thalamic volumes.

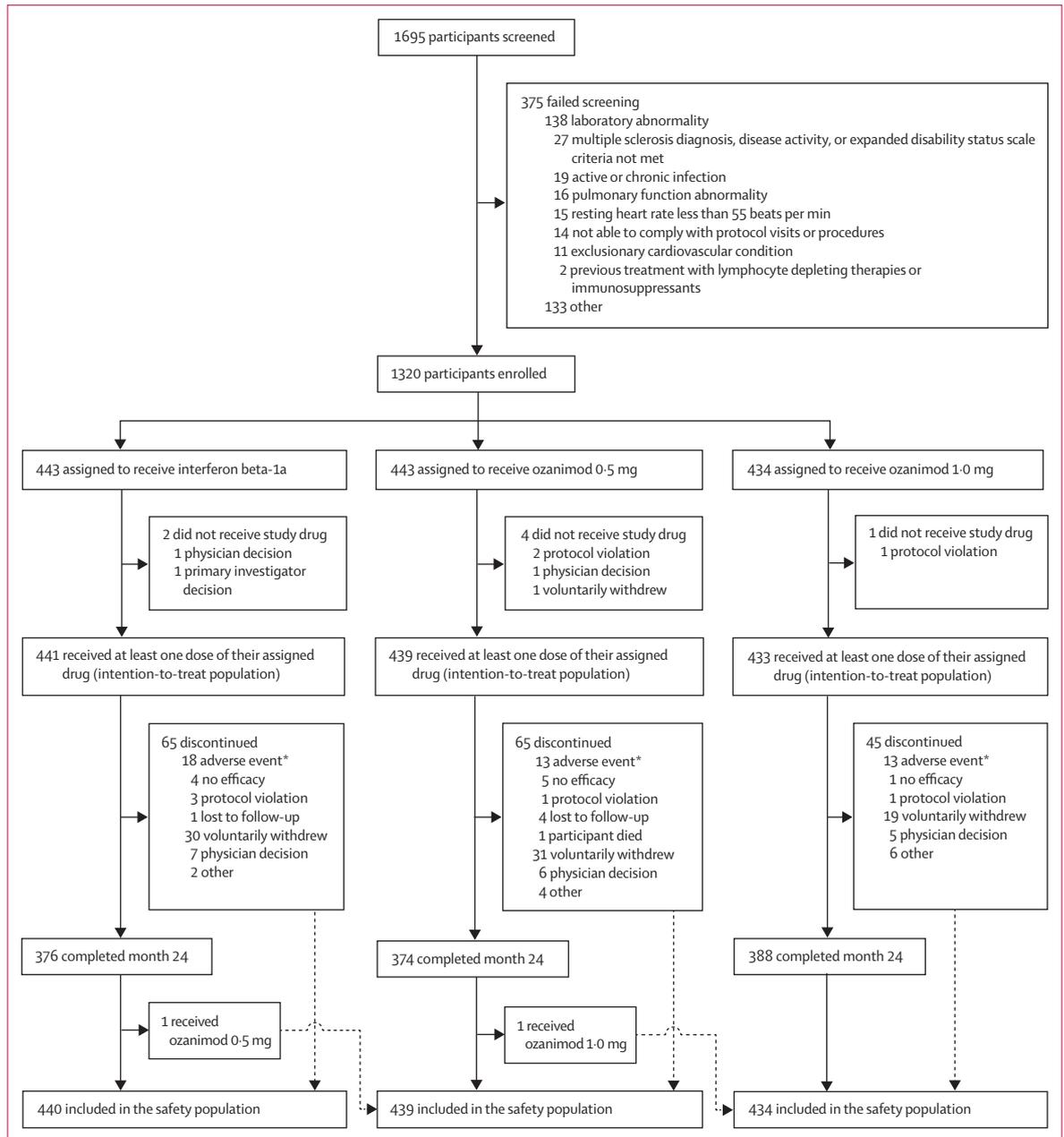For the **Neurostatus method** see www.neurostatus.net

Figure 1: Trial profile
*Adverse events leading to discontinuation are in the appendix (pp 24–25).

Participants who completed the 24-month study were eligible to enrol in a long-term, open-label extension study (RPC01-3001; NCT02576717, EudraCT 2015-002500-91).

Outcomes

The primary endpoint was annualised relapse rate (ARR) over 24 months based on confirmed, protocol-defined relapses. Relapses were defined as new or worsening neurological symptoms persisting for more than 24 h, not attributable to confounding factors, and preceded by stable or improving neurological status for at least 30 days. Relapses were confirmed when accompanied by objective neurological worsening (EDSS increase ≥0·5 on overall score, 2 points on one functional system scale score, or 1 point on two or more functional system scale scores).

Key secondary endpoints were number of new or enlarging T2 brain MRI lesions over 24 months; number of gadolinium-enhancing brain MRI lesions at month 24; and time to onset of disability progression (EDSS worsening of ≥1-point increase, confirmed after 3 and 6 months).

Disability progression was assessed as a prespecified pooled analysis with data from the phase 3 SUNBEAM trial[9] (NCT02294058; EudraCT 2014–002320–27; treatment duration, ≥12 months), which was conducted concurrently with RADIANCE phase 3 and reported separately. Other secondary endpoints were proportions of participants free of gadolinium-enhancing and new or enlarging T2 lesions at month 24; changes in multiple sclerosis functional composite (MSFC) score and the physical and mental health composite scores of the multiple sclerosis quality of life-54 (MSQOL-54) measurement from baseline to month 24; and percentage change in whole brain atrophy from baseline to 24 months. Changes in cortical grey matter and thalamic volume were prespecified exploratory endpoints.

Safety analyses included the incidence and type of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to discontinuation of study treatment. TEAEs are adverse events that started on or after the date of the first dose of study drug, or preceded study day 1 but worsened in severity on or after day 1. TEAEs were assessed by system organ class (using MedDRA, version 18.1), severity, and causality.

Participants were monitored for the following adverse events of special interest: cardiac abnormalities (bradycardia, conduction abnormalities, and new ischaemic changes on ECG); serious or opportunistic infections; hepatotoxicity (confirmed alanine aminotransferase or aspartate aminotransferase at least three times the ULN, with or without raised bilirubin); ophthalmic abnormalities; pulmonary function test abnormalities; and cutaneous and other malignancies. Suicidality, which is common among those with multiple sclerosis, was assessed at each visit.

Statistical analysis

A sample size of about 400 participants per treatment group was estimated using a Poisson regression model and the method of Nicholas and colleagues.[12] This sample size was predicted to provide about 90% power at a two-sided significance level of 0·025 to detect a 37% lower 24-month ARR (ARR 0·19) for each ozanimod dose group, assuming an ARR of 0·3 in the interferon beta-1a group,[13] extra-Poisson variation ($\sigma^2 = 1\cdot3$), and a 17% dropout rate.

The primary endpoint was analysed using a prespecified Poisson regression model adjusted for region (eastern Europe vs rest of world), baseline age, and baseline number of gadolinium-enhancing lesions and included the natural log transformation of time on study as an offset term. Statistical testing was performed between each ozanimod dose and interferon beta-1a at a two-sided significance level of 0·025 to account for multiple comparisons. Additional sensitivity analyses were performed to assess assumptions regarding the Poisson model (appendix p 12).

To control for type 1 error, a hierarchical testing procedure was used to assess key secondary endpoints (appendix p 10). If both ozanimod doses reached statistical

significance on the primary endpoint, then ozanimod 1·0 mg would be compared with interferon beta-1a for number of new or enlarging T2 lesions over 24 months at a two-sided α of 0·05. If that comparison was statistically significant, then this endpoint would be tested for ozanimod 0·5 mg versus interferon beta-1a at a two-sided α of 0·05. The same procedure was then followed for number of gadolinium-enhancing lesions at month 24, followed by time to onset of confirmed disability progression (pooled with SUNBEAM), until a comparison did not reach statistical significance, after which all subsequent comparisons would be considered exploratory. If only one of the ozanimod doses was statistically significant on the primary endpoint, then the hierarchical testing procedure would be executed on the surviving dose at a two-sided α of 0·025. The number of new or

	Interferon beta-1a group (n=441)	Ozanimod 0·5 mg group (n=439)	Ozanimod 1·0 mg group (n=433)
Age, years	35·1 (9·1)	35·4 (8·8)	36·0 (8·9)
Sex			
Female	304 (68·9%)	287 (65·4%)	291 (67·2%)
Male	137 (31·1%)	152 (34·6%)	142 (32·8%)
Race			
White	432 (98·0%)	431 (98·2%)	428 (98·8%)
Black	7 (1·6%)	6 (1·4%)	5 (1·2%)
Asian	1 (0·2%)	0	0
Other	1 (0·2%)	2 (0·5%)	0
Bodyweight, kg	70·1 (16·4)	69·5 (14·7)	70·9 (17·0)
Region			
Eastern Europe	379 (85·9%)	378 (86·1%)	374 (86·4%)
Western Europe	40 (9·1%)	40 (9·1%)	36 (8·3%)
North America	16 (3·6%)	16 (3·6%)	16 (3·7%)
Southern Africa	6 (1·4%)	5 (1·1%)	7 (1·6%)
Time since multiple sclerosis symptom onset, years	6·4 (6·07)	6·2 (5·55)	6·9 (6·20)
Time since multiple sclerosis diagnosis, years	3·6 (4·61)	3·5 (4·21)	4·0 (5·17)
Type of multiple sclerosis			
Relapsing-remitting multiple sclerosis	432 (98·0%)	432 (98·4%)	425 (98·2%)
Progressive-relapsing multiple sclerosis	8 (1·8%)	7 (1·6%)	8 (1·8%)
Secondary progressive multiple sclerosis	1 (0·2%)	0	0
Expanded disability status scale score	2·5 (1·16)	2·5 (1·17)	2·6 (1·15)
Number of relapses in previous 12 months	1·3 (0·58)	1·4 (0·64)	1·3 (0·56)
Number of relapses in previous 24 months	1·8 (0·86)	1·8 (0·90)	1·7 (0·82)
Previous disease-modifying therapy*	126 (28·6%)	131 (29·8%)	123 (28·4%)
Number of gadolinium-enhancing lesions	1·8 (3·54)	1·8 (3·62)	1·6 (3·78)
Gadolinium-enhancing lesion volume, cm³	0·25 (0·62)	0·23 (0·53)	0·21 (0·53)
Number of T2 lesions	48·7 (32·62)	48·7 (36·27)	47·9 (32·37)
T2 lesion volume, cm³	11·50 (13·29)	11·18 (13·64)	11·64 (13·40)
Normalised brain volume, cm³†	1449·58 (77·16)	1452·85 (71·98)	1441·95 (79·23)

Data are n (%) or mean (SD). *Previous disease-modifying therapies include interferon beta-1a, pegylated interferon beta-1a, interferon beta-1b, glatiramer acetate, daclizumab, dimethyl fumarate, and teriflunomide. †Data available for 432 participants in the ozanimod 1·0 mg group, 437 in the ozanimod 0·5 mg group, and 439 in the interferon beta-1a group.

Table 1: Baseline demographic and clinical characteristics (intention-to-treat population)

	Interferon beta-1a group (n=441)	Ozanimod 0·5 mg group (n=439)			Ozanimod 1·0 mg group (n=433)		
		Absolute value	Difference vs interferon beta-1a*	p value	Absolute value	Difference vs interferon beta-1a*	p value
Primary endpoint							
Adjusted ARR through month 24	0·28 (0·23 to 0·32)	0·22 (0·18 to 0·26)	RR 0·79 (0·65 to 0·96)	0·0167	0·17 (0·14 to 0·21)	RR 0·62 (0·51 to 0·77)	<0·0001
Secondary endpoints							
Adjusted mean number of new or enlarging T2 lesions per scan over 24 months	3·18 (2·64 to 3·84)	2·09 (1·74 to 2·51)	RR 0·66 (0·53 to 0·81)	0·0001	1·84 (1·52 to 2·21)	RR 0·58 (0·47 to 0·71)	<0·0001
Adjusted mean number of gadolinium-enhancing lesions at month 24	0·37 (0·26 to 0·54)	0·20 (0·13 to 0·30)	RR 0·53 (0·35 to 0·81)	0·0030	0·18 (0·12 to 0·27)	RR 0·47 (0·31 to 0·73)	0·0006
Pooled disability progression†							
Participants with confirmed disability progression at 3 months	69/889 (7·8%)	58/890 (6·5%)	HR 0·82 (0·58 to 1·17)	0·2698‡	67/880 (7·6%)	HR 0·95 (0·68 to 1·33)	0·7651
Participants with confirmed disability progression at 6 months	36/889 (4·0%)	43/890 (4·8%)	HR 1·19 (0·76 to 1·85)	0·4447‡	51/880 (5·8%)	HR 1·41 (0·92 to 2·17)	0·1126‡
RADIANCE phase 3 only disability progression§							
Participants with confirmed disability progression at 3 months	50/441 (11·3%)	41/439 (9·3%)	HR 0·80 (0·53 to 1·21)	0·2849§	54/433 (12·5%)	HR 1·05 (0·71 to 1·54)	0·8224§
Participants with confirmed disability progression at 6 months	29/441 (6·6%)	32/439 (7·3%)	HR 1·10 (0·66 to 1·82)	0·7154§	42/433 (9·7%)	HR 1·44 (0·89 to 2·31)	0·1353§

Data are n/N (%) unless otherwise stated and ranges in parentheses are 95% CIs. ARR=annualised relapse rate. HR=hazard ratio. RR=rate ratio. *Rate for ozanimod divided by rate for interferon beta-1a. †Pooled analysis of RADIANCE phase 3 and SUNBEAM (duration ≥12 months) was the prespecified analysis for disability progression. ‡Nominal p value because of the hierarchical testing results. §Excluded from the hierarchical testing, so all p values are nominal.

Table 2: Primary and secondary efficacy endpoints in rank order according to hierarchical testing (intention-to-treat population)

enlarging T2 lesions over 24 months and number of gadolinium-enhancing lesions at month 24 were analysed using a negative binomial regression model adjusted for region, baseline age, and baseline number of gadolinium-enhancing lesions and included the natural log transformation of the number of available MRI scans as an offset term.

Prespecified analyses were performed for ARR and the MRI lesion count endpoints for the following subgroups: baseline EDSS (≤3·5 vs >3·5); baseline gadolinium-enhancing lesions (present vs absent); treatment-naive versus previous disease-modifying therapy; baseline age (≤40 years vs >40 years); sex (female vs male); race (white vs non-white); bodyweight (less than median vs median or greater); relapses in previous 12 months (less than two vs two or more; ARR endpoint only); and region (eastern Europe vs rest of world). Analyses were not performed for any subgroup comprising less than 5% of the overall population.

Analysis of time to onset of 3-month and 6-month confirmed disability progression was pooled with SUNBEAM[9] because neither RADIANCE phase 3 nor SUNBEAM was powered to detect a treatment difference with a two-sided α of 0·05. For both the pooled analysis and the analysis of RADIANCE phase 3 only, time to onset of disability progression was analysed using a Cox proportional hazards model adjusted for study, region,

baseline age, and baseline EDSS score. A Kaplan-Meier analysis of the difference in time to onset of disability progression curves was done.

For brain volume loss, change from baseline was calculated using descriptive statistics. Comparisons of percentage change from baseline in brain volume loss between interferon beta-1a and ozanimod 1·0 mg or 0·5 mg used an analysis of covariance (ANCOVA) model adjusted for region, baseline EDSS category, and baseline brain volume, with missing data imputed via the last-observation-carried-forward method.

Using the study population as the reference population, Z scores were calculated for each MSFC component (timed 25-foot walk test, nine-hole peg test, and paced auditory serial addition test [PASAT]) and averaged to derive an overall composite score. Ozanimod was compared with interferon beta-1a for change from baseline in MSFC scores and MSQOL-54 physical and mental health composite scores using ANCOVA, with models adjusted for region, EDSS score, and baseline value of interest. Safety outcomes were reported as incidence of TEAEs in each treatment group, with inclusion limited to one occurrence of a preferred term per participant. Statistical hypothesis testing was not performed on any safety results.

The primary analysis was done in the intention-to-treat population of all randomly assigned participants who received study drug, grouped by assigned treatment.

The safety population included all randomly assigned participants who received study drug, grouped by highest dose of ozanimod received.

All statistical analyses were done using SAS, version 9.1 or higher. No interim analyses were planned or done. The RADIANCE trial steering committee participated in study design and data review. An independent data monitoring committee monitored enrolment, treatment compliance, adherence to the follow-up schedule, and safety data, but not efficacy data; they monitored accumulating data on a quarterly basis and had the ability to modify or stop the trial because of safety concerns.

This study is registered with ClinicalTrials.gov, NCT02047734, and EudraCT, 2012-002714-40.
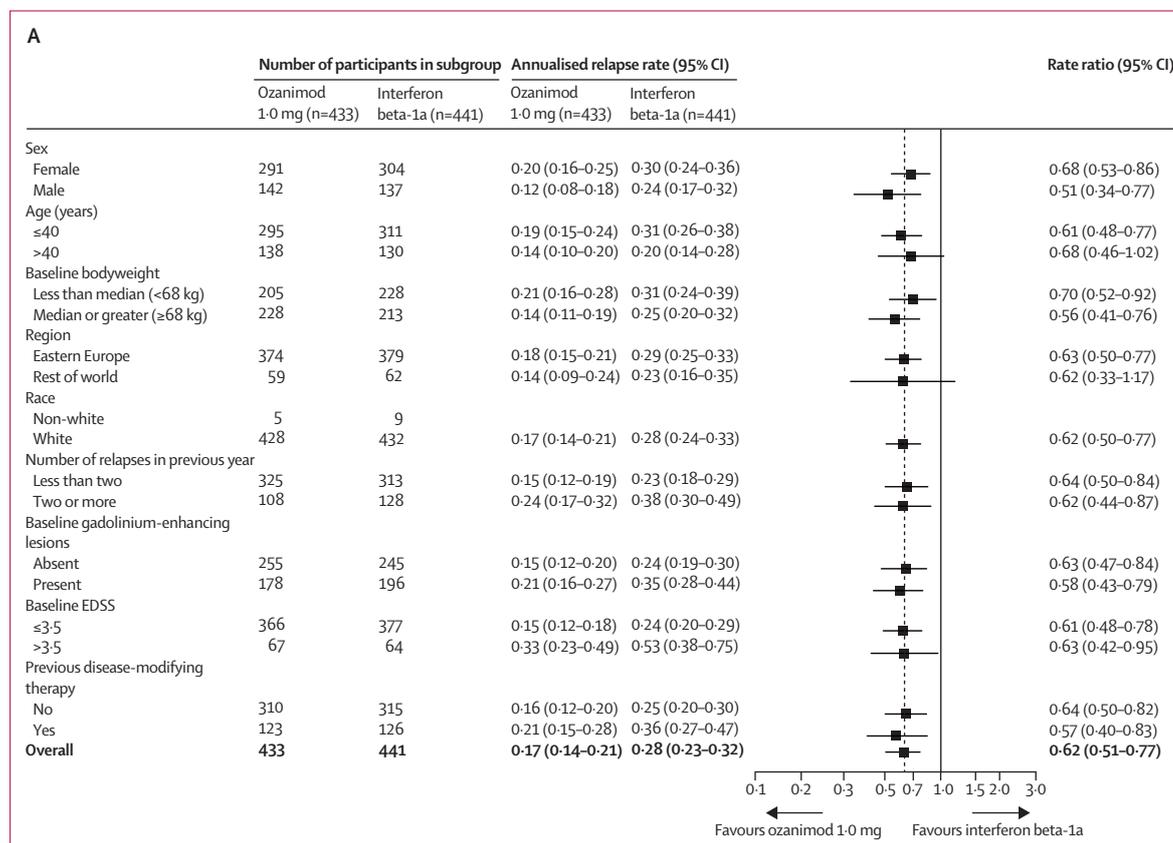
Role of the funding source

The funder of this study was involved in study design, data analysis, data interpretation, and writing of the report, but not data collection. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 27, 2013, and March 31, 2015, 1695 participants were screened, of which 375 did not meet inclusion criteria (figure 1). 1320 participants were enrolled and randomly assigned to either ozanimod 0·5 mg (n=443), ozanimod 1·0 mg (n=434), or interferon beta-1a (n=443). Seven participants did not receive any study drug and were excluded from analyses and 175 participants discontinued before month 24 (65 [14·8%] in the ozanimod 0·5 mg group, 45 [10·4%] in the ozanimod 1·0 mg group, and 65 [14·7%] in the interferon beta-1a group). The two most common reasons for discontinuation of study drug were voluntary withdrawal and TEAEs. No notable differences were reported among treatment groups in baseline demographics or disease characteristics (table 1). Mean age was 35·5 years (SD 8·9), 882 (67·2%) of 1313 participants were women and 431 (32·8%) were men, mean time since multiple sclerosis symptom onset was 6·5 years (5·9), and mean time since multiple sclerosis diagnosis was 3·7 years (4·7). Changes to the original protocol and statistical analysis plan implemented after the first participant was enrolled are summarised in the appendix (pp 10–11).

Adjusted ARRs were 0·17 (95% CI 0·14–0·21) with ozanimod 1·0 mg, 0·22 (0·18–0·26) with ozanimod 0·5 mg, and 0·28 (0·23–0·32) with interferon beta-1a (table 2; appendix p 11). Versus interferon beta-1a, the rate ratio (RR) was 0·62 (95% CI 0·51–0·77; p<0·0001) for ozanimod 1·0 mg and 0·79 (0·65 to 0·96; p=0·0167) for ozanimod 0·5 mg. The adjusted mean number

	Number of participants in subgroup		Annualised relapse rate (95% CI)			Rate ratio (95% CI)
	Ozanimod 1·0 mg (n=433)	Interferon beta-1a (n=441)	Ozanimod 1·0 mg (n=433)	Interferon beta-1a (n=441)		
Sex						
Female	291	304	0·20 (0·16–0·25)	0·30 (0·24–0·36)		0·68 (0·53–0·86)
Male	142	137	0·12 (0·08–0·18)	0·24 (0·17–0·32)		0·51 (0·34–0·77)
Age (years)						
≤40	295	311	0·19 (0·15–0·24)	0·31 (0·26–0·38)		0·61 (0·48–0·77)
>40	138	130	0·14 (0·10–0·20)	0·20 (0·14–0·28)		0·68 (0·46–1·02)
Baseline bodyweight						
Less than median (<68 kg)	205	228	0·21 (0·16–0·28)	0·31 (0·24–0·39)		0·70 (0·52–0·92)
Median or greater (≥68 kg)	228	213	0·14 (0·11–0·19)	0·25 (0·20–0·32)		0·56 (0·41–0·76)
Region						
Eastern Europe	374	379	0·18 (0·15–0·21)	0·29 (0·25–0·33)		0·63 (0·50–0·77)
Rest of world	59	62	0·14 (0·09–0·24)	0·23 (0·16–0·35)		0·62 (0·33–1·17)
Race						
Non-white	5	9				
White	428	432	0·17 (0·14–0·21)	0·28 (0·24–0·33)		0·62 (0·50–0·77)
Number of relapses in previous year						
Less than two	325	313	0·15 (0·12–0·19)	0·23 (0·18–0·29)		0·64 (0·50–0·84)
Two or more	108	128	0·24 (0·17–0·32)	0·38 (0·30–0·49)		0·62 (0·44–0·87)
Baseline gadolinium-enhancing lesions						
Absent	255	245	0·15 (0·12–0·20)	0·24 (0·19–0·30)		0·63 (0·47–0·84)
Present	178	196	0·21 (0·16–0·27)	0·35 (0·28–0·44)		0·58 (0·43–0·79)
Baseline EDSS						
≤3·5	366	377	0·15 (0·12–0·18)	0·24 (0·20–0·29)		0·61 (0·48–0·78)
>3·5	67	64	0·33 (0·23–0·49)	0·53 (0·38–0·75)		0·63 (0·42–0·95)
Previous disease-modifying therapy						
No	310	315	0·16 (0·12–0·20)	0·25 (0·20–0·30)		0·64 (0·50–0·82)
Yes	123	126	0·21 (0·15–0·28)	0·36 (0·27–0·47)		0·57 (0·40–0·83)
Overall	**433**	**441**	**0·17 (0·14–0·21)**	**0·28 (0·23–0·32)**		**0·62 (0·51–0·77)**

(Figure 2 continues on next page)

B

	Number of participants in subgroup		Annualised relapse rate (95% CI)			Rate ratio (95% CI)
	Ozanimod 0·5 mg (n=439)	Interferon beta-1a (n=441)	Ozanimod 0·5 mg (n=439)	Interferon beta-1a (n=441)		
Sex						
Female	287	304	0·20 (0·16–0·25)	0·30 (0·24–0·36)		0·68 (0·53–0·86)
Male	152	137	0·25 (0·18–0·33)	0·24 (0·17–0·32)		1·04 (0·74–1·46)
Age (years)						
≤40	320	311	0·25 (0·20–0·30)	0·31 (0·26–0·38)		0·78 (0·63–0·98)
>40	119	130	0·16 (0·11–0·23)	0·20 (0·14–0·28)		0·79 (0·53–1·18)
Baseline bodyweight						
Less than median (<68 kg)	214	228	0·22 (0·17–0·29)	0·31 (0·24–0·39)		0·73 (0·52–0·96)
Median or greater (≥68 kg)	225	213	0·21 (0·17–0·27)	0·25 (0·20–0·32)		0·84 (0·64–1·10)
Region						
Eastern Europe	378	379	0·22 (0·19–0·26)	0·29 (0·25–0·33)		0·76 (0·62–0·93)
Rest of world	61	62	0·25 (0·17–0·37)	0·23 (0·16–0·35)		1·07 (0·62–1·86)
Race						
Non-white	8	9				
White	431	432	0·22 (0·18–0·26)	0·28 (0·24–0·33)		0·78 (0·65–0·95)
Number of relapses in previous year						
Less than two	291	313	0·17 (0·14–0·22)	0·23 (0·18–0·29)		0·75 (0·58–0·97)
Two or more	148	128	0·30 (0·23–0·39)	0·38 (0·30–0·49)		0·79 (0·59–1·06)
Baseline gadolinium-enhancing lesions						
Absent	249	245	0·15 (0·12–0·20)	0·24 (0·19–0·30)		0·63 (0·48–0·84)
Present	190	196	0·34 (0·27–0·44)	0·35 (0·28–0·44)		0·98 (0·75–1·27)
Baseline EDSS						
≤3·5	368	377	0·18 (0·15–0·23)	0·24 (0·20–0·29)		0·77 (0·61–0·97)
>3·5	71	64	0·41 (0·30–0·57)	0·53 (0·38–0·75)		0·78 (0·54–1·14)
Previous disease-modifying therapy						
No	308	315	0·23 (0·18–0·28)	0·25 (0·20–0·30)		0·92 (0·74–1·16)
Yes	131	126	0·19 (0·14–0·26)	0·36 (0·27–0·47)		0·54 (0·37–0·77)
Overall	**439**	**441**	**0·22 (0·18–0·26)**	**0·28 (0·23–0·32)**		**0·79 (0·65–0·96)**

0·1 0·2 0·3 0·5 0·7 1·0 1·5 2·0 3·0

← Favours ozanimod 0·5 mg   Favours interferon beta-1a →

Figure 2: **Annualised relapse rates during the treatment period by ozanimod dose and subgroups (intention-to-treat population)**
(A) Ozanimod 1·0 mg versus interferon beta-1a 30 µg. (B) Ozanimod 0·5 mg versus interferon beta-1a 30 µg. Covariates in the models for region, age at baseline, and baseline number of gadolinium-enhancing lesions were not included for the respective subgroups. Any subgroup that did not have at least 5% of the overall sample size was not included in subgroup analyses. The vertical dotted lines mark the rate ratios for the overall study population. EDSS=expanded disability status scale.

of new or enlarging T2 lesions per scan over 24 months was 1·84 (95% CI 1·52–2·21) with ozanimod 1·0 mg, 2·09 (1·74–2·51) with ozanimod 0·5 mg, and 3·18 (2·64–3·84) with interferon beta-1a, with an RR versus interferon beta-1a of 0·58 (95% CI 0·47–0·71; p<0·0001) for ozanimod 1·0 mg and 0·66 (0·53–0·81; p=0·0001) for ozanimod 0·5 mg (table 2; appendix p 13). The adjusted mean number of gadolinium-enhancing lesions at 24 months was 0·18 (95% CI 0·12–0·27) with ozanimod 1·0 mg, 0·20 (0·13–0·30) with ozanimod 0·5 mg, and 0·37 (0·26–0·54) with interferon beta-1a, with an RR versus interferon beta-1a of 0·47 (0·31–0·73; p=0·0006) for ozanimod 1·0 mg and 0·53 (0·35–0·81; p=0·0030) for ozanimod 0·5 mg (table 2; appendix p 13).

RRs and 95% CIs of ARRs, new or enlarging T2 lesion count over 24 months, and gadolinium-enhancing lesion count at month 24 indicated that both doses of ozanimod were at least as effective as interferon beta-1a across all subgroups studied, and ozanimod was favoured over interferon beta-1a in most subgroups (figure 2; appendix pp 14–17). The small sample size resulted in particularly wide CIs for subanalyses of non-eastern European region and baseline EDSS greater than 3·5, and no RRs

could be calculated for the non-white subgroup because of the very small sample size.

In the pooled analysis of RADIANCE phase 3 and SUNBEAM,[9] the proportions of participants with confirmed disability progression at 3 months and at 6 months were not significantly different between treatment groups (table 2; appendix p 18). Similar results were observed for confirmed disability progression in the RADIANCE phase 3 cohort alone.

Both ozanimod doses reduced brain volume loss, including whole brain volume, cortical grey matter, and thalamic volume loss, over 24 months compared with interferon beta-1a (table 3; appendix pp 19–21). Brain volume data were not normally distributed; consequently, median percentage change in brain volume from baseline to month 24 was also compared between each ozanimod dose and interferon beta-1a using ranked ANCOVA (observed data; appendix pp 22–24).

TEAEs were reported in 324 (74·7%) of 434 participants who received ozanimod 1·0 mg, 326 (74·3%) of 439 participants who received ozanimod 0·5 mg, and 365 (83·0%) of 440 participants who received interferon beta-1a (table 4). Most events were mild or moderate.

	Interferon beta-1a group (n=441)	Ozanimod 0·5 mg group (n=439)			Ozanimod 1·0 mg group (n=433)		
		Absolute value	Difference vs interferon beta-1a	Nominal p value	Absolute value	Difference vs interferon beta-1a	Nominal p value
Whole brain volume							
Participants with data available	397	398	..	..	390	..	..
Mean percentage change from baseline to month 24*	−0·937 (0·944)	−0·707 (0·746)	0·224 (0·106 to 0·342)†	0·0002	−0·707 (0·878)	0·244 (0·125 to 0·363)†	<0·0001
Cortical grey matter volume‡							
Participants with data available	390	388	..	..	382	..	..
Mean percentage change from baseline to month 24*	−1·11 (0·957)	−0·50 (0·798)	0·61 (0·49 to 0·73)†	<0·0001	−0·44 (0·859)	0·67 (0·55 to 0·79)†	<0·0001
Thalamic volume‡							
Participants with data available	391	389	..	..	385	..	..
Mean percentage change from baseline to month 24*	−1·85 (1·966)	−1·50 (1·791)	0·34 (0·07 to 0·61)†	0·0133	−1·40 (2·055)	0·49 (0·22 to 0·75)†	0·0004
Proportion of participants who were gadolinium-enhancing lesion-free at month 24§	56·2 (51·6 to 60·9)	63·3 (58·8 to 67·8)	7·1 (0·6 to 13·6)¶	0·0320	65·6 (61·1 to 70·1)	9·4 (2·9 to 15·8)¶	0·0047
Proportion of participants who were new or enlarging T2 lesion-free at month 24§	18·4 (14·8 to 22·0)	23·5 (19·5 to 27·4)	5·1 (−0·3 to 10·5)¶	0·0581	23·8 (19·8 to 27·8)	5·4 (0·0 to 10·8)¶	0·0466
MSFC score‖							
Participants with data available	441	439	..	..	432	..	..
Mean change from baseline to month 24	−0·067 (0·745)	0·032 (0·475)	0·101 (0·013 to 0·190)†	0·0246	−0·006 (0·779)	0·060 (−0·029 to 0·148)†	0·1874
MSFC score with LCLA measurement of visual function as a component‖							
Participants with data available	437	435	..	..	428	..	..
Mean change from baseline to month 24	−0·052 (0·601)	0·036 (0·440)	0·093 (0·020 to 0·165)†	0·0123	−0·010 (0·622)	0·043 (−0·030 to 0·116)†	0·2480
MSQOL-54							
Participants with data available	441	439	..	..	433	..	..
Mean change from baseline to month 24 in physical health composite summary**	−1·526 (12·319)	0·609 (12·315)	1·849 (0·258 to 3·440)†	0·0228	0·209 (12·321)	1·345 (−0·252 to 2·943)†	0·0988
Mean change from baseline to month 24 in mental health composite summary**	−1·831 (16·422)	−1·182 (14·379)	0·587 (−1·339 to 2·513)†	0·5501	−1·517 (15·544)	0·380 (−1·553 to 2·313)†	0·6997

Data are n, mean (SD), or % (95% CI). LCLA=low-contrast letter acuity. MSFC=multiple sclerosis functional composite. MSQOL-54=54-item multiple sclerosis quality of life. *Missing data imputed using last observation carried forward. †Difference in means and p values for comparison between ozanimod and interferon beta-1a are based on the analysis of covariance model, adjusted for region (eastern Europe vs rest of world), expanded disability status scale category at baseline, and baseline value of interest. ‡Exploratory endpoint. §Calculated using non-responder imputation to account for missing data. ¶Difference in proportions between ozanimod and interferon beta-1a are based on Wald 95% CI; p value based on the Cochran-Mantel-Haenszel test stratified by region (eastern Europe vs rest of world) and expanded disability status scale category at baseline. ‖MSFC score was calculated by creating Z scores for each MSFC component and averaging them to create an overall composite score. If a score from one trial was missing for the timed 25-foot walk test or nine-hole peg test, the Z score was calculated from the non-missing score. If both scores were missing, or if the paced auditory serial addition test score was missing, because of multiple sclerosis-related or other physical limitation, the participant received a Z score of −13·7 for the timed 25-foot walk test, 777 s for the nine-hole peg test, and 0 for the paced auditory serial addition test; if the scores were missing for some other reason, then last observation carried forward was used to impute the Z score for that visit. **Missing data imputed using a mixed-effects regression model (random slope and intercept).

Table 3: **Additional secondary and exploratory endpoints not included in hierarchical testing (intention-to-treat population)**

TEAEs occurring in at least 5% of participants treated with ozanimod and with a numerical difference of at least 1% versus interferon beta-1a were nasopharyngitis, alanine aminotransferase increase, hypertension, γ-glutamyltransferase increase, pharyngitis, and urinary tract infection. The most frequent TEAEs (≥5%) in the interferon beta-1a group were influenza-like illness, headache, nasopharyngitis, upper respiratory tract infection, pyrexia, and orthostatic hypotension. TEAEs with a numerical difference of at least 1% between the interferon beta-1a group and either ozanimod group are in the appendix (p 25). The incidence of serious TEAEs was similar across treatment groups, and no pattern of serious

TEAEs was identified (table 4; appendix pp 26–27). Serious TEAEs occurring in more than one participant in any treatment group were appendicitis (two [0·5%] with ozanimod 1·0 mg, one [0·2%] with ozanimod 0·5 mg, and two [0·5%] with interferon beta-1a), ovarian cyst (two [0·5%] with ozanimod 1·0 mg), and sinus tachycardia (two [0·5%] ozanimod 0·5 mg). More participants in the interferon beta-1a group had TEAEs leading to treatment discontinuation than in the ozanimod groups (appendix p 28). The most frequent TEAEs leading to discontinuation (at least two participants in any group) were influenza-like illness, alanine aminotransferase increase, aspartate aminotransferase increase, and macular

	Interferon beta-1a (n=440)	Ozanimod 0·5 mg (n=439)	Ozanimod 1·0 mg (n=434)
Adverse events	365 (83·0%)	326 (74·3%)	324 (74·7%)
Severe adverse events	19 (4·3%)	19 (4·3%)	15 (3·5%)
Serious adverse events	28 (6·4%)	31 (7·1%)	28 (6·5%)
Adverse events leading to discontinuation of study drug	18 (4·1%)	14 (3·2%)	13 (3·0%)
Death	0	1 (0·2%)	0
Adverse events occurring in at least 2% of ozanimod-treated participants and with an incidence of at least 1% higher than in the interferon beta-1a group			
Nasopharyngitis	48 (10·9%)	59 (13·4%)	68 (15·7%)
Alanine aminotransferase increased	20 (4·5%)	29 (6·6%)	26 (6·0%)
Hypertension	14 (3·2%)	20 (4·6%)	24 (5·5%)
γ-glutamyltransferase increased	9 (2·0%)	16 (3·6%)	25 (5·8%)
Pharyngitis	15 (3·4%)	24 (5·5%)	17 (3·9%)
Urinary tract infection	17 (3·9%)	22 (5·0%)	19 (4·4%)
Back pain	14 (3·2%)	21 (4·8%)	18 (4·1%)
Fatigue	12 (2·7%)	17 (3·9%)	16 (3·7%)
Arthralgia	6 (1·4%)	17 (3·9%)	15 (3·5%)
Upper abdominal pain	6 (1·4%)	8 (1·8%)	14 (3·2%)
Diarrhoea	8 (1·8%)	14 (3·2%)	8 (1·8%)
Dizziness	5 (1·1%)	10 (2·3%)	8 (1·8%)

Data are n (%). Recurrent events in the same participant were counted only once. Only treatment-emergent adverse events are reported.

Table 4: **Participants who had treatment-emergent adverse events (safety population)**

oedema in participants who received interferon beta-1a and alanine aminotransferase increase, urticaria, and γ-glutamyltransferase increase in the combined ozanimod groups. One case of posterior reversible encephalopathy syndrome was reported about 10 months after treatment initiation in a participant in the ozanimod 1·0 mg group with Guillain-Barré syndrome. One participant in the ozanimod 0·5 mg group died on study day 637 because of accidental drowning, which was considered unrelated to the study drug.

The maximum mean reduction in supine heart rate on day 1 over hours 1–6 after administration of ozanimod 0·25 mg was 0·6 bpm at 5 h (mean heart rate 68 bpm [SD 9]; appendix p 30). Four ozanimod-treated participants had a minimum supine heart rate less than 45 bpm over hours 1–6 on day 1 (appendix p 29) which all resolved spontaneously by hour 7 or 8. All of these participants had low predose heart rate (55–64 bpm) and remained asymptomatic. Symptomatic bradycardia was reported as a TEAE after the initial ozanimod 0·25 mg dose in one participant with a history of dysautonomia and low predose blood pressure (90/60 mm Hg) and heart rate (60 bpm by pulse and 48 bpm by ECG). At 6 h postdose, dizziness, supine heart rate of 47 bpm, and blood pressure of 80/55 mm Hg were reported. The participant was treated with subcutaneous atropine 0·5 mg; the dizziness resolved within 20 min and the participant continued in the study. No clinically meaningful cardiac TEAEs considered related to study drug were reported during dose escalation. No ECG findings or TEAEs of second-degree or third-degree atrioventricular block were reported on day 1 or thereafter. Serious cardiac TEAEs were infrequent and similar across treatment groups, with none reported in the ozanimod 1·0 mg group (appendix p 26).

The incidence of infection-related TEAEs was similar across treatment groups. Serious infections were infrequent, and no serious opportunistic infections occurred (appendix p 26). Among the participants who received ozanimod, mean absolute lymphocyte count (ALC) decreased from baseline to month 3 and remained stable through month 24 (appendix p 31). Mean ALC at month 24 was 0·753 (SD 0·454)×10^9 cells per L (43·2% of baseline) in the ozanimod 1·0 mg group, 1·012 (0·536)×10^9 cells per L (54·2% of baseline) in the ozanimod 0·5 mg group, and 1·833 (1·138)×10^9 cells per L (98·9% of baseline) in the interferon beta-1a group. Mean minimum ALC at any time point during the study was 0·525 (SD 0·295)×10^9 cells per L in the ozanimod 1·0 mg group, 0·750 (0·387)×10^9 cells per L in the ozanimod 0·5 mg group, and 1·284 (0·503)×10^9 cells per L in the interferon beta-1a group. At least one postbaseline ALC less than 0·2×10^9 cells per L was recorded in 18 (4·2%) participants in the ozanimod 1·0 mg group, four (0·9%) in the ozanimod 0·5 mg group, and none in the interferon beta-1a group. 249 (57·8%) participants in the ozanimod 1·0 mg group, 108 (24·7%) in the ozanimod 0·5 mg group, and six (1·4%) in the interferon beta-1a group had at least one ALC less than 0·5×10^9 cells per L (appendix p 31). No participant had serious infections when lymphocyte counts were less than 0·2×10^9 cells per L. Herpes zoster cases were few in number (four [0·9%] with ozanimod 1·0 mg; two [0·5%] with ozanimod 0·5 mg; and one [0·2%] with interferon beta-1a), affected a single dermatome, were non-serious, not associated with ALC less than 0·2×10^9 cells per L, and resolved with oral acyclovir.

Alanine aminotransferase increases of at least three times the ULN occurred in 29 (6·7%) of 431 participants in the ozanimod 1·0 mg group, 26 (5·9%) of 438 in the ozanimod 0·5 mg group, and 17 (3·9%) of 434 participants in the interferon beta-1a group (appendix p 29). Most were transient and resolved without study drug discontinuation. Seven (1·6%) participants treated with ozanimod 1·0 mg, three (0·7%) treated with ozanimod 0·5 mg, and six (1·4%) treated with interferon beta-1a had TEAEs of hepatobiliary dysfunction or related investigations that led to treatment discontinuation.

TEAEs of macular oedema were scarce: two (0·5%) were reported with interferon beta-1a, one (0·2%) with ozanimod 0·5 mg, and one (0·2%) with ozanimod

1·0 mg; cystoid macular oedema was reported in one additional participant (0·2%) in the ozanimod 0·5 mg group. The expert review panel confirmed two cases of macular oedema, both in the ozanimod 0·5 mg group; one had a pre-existing risk factor (history of macular oedema) and the other had a confounding factor (central serous choroidopathy).

A low incidence of pulmonary TEAEs was observed across treatment groups without association to pulmonary function test findings; no participants discontinued study drug because of these events. Malignancies were reported for four (0·9%) of 434 participants in the ozanimod 1·0 mg group (breast cancer, invasive breast carcinoma, keratoacanthoma, and basal cell carcinoma); three (0·7%) of 439 in the ozanimod 0·5 mg group (malignant melanoma in situ [pre-existing], medulloblastoma [pre-existing], and basal cell carcinoma), and two (0·5%) of 440 in the interferon beta-1a group (chronic lymphocytic leukaemia and basal cell carcinoma). The incidence of TEAEs of depression was low and similar across groups. One participant in the ozanimod 0·5 mg group attempted suicide on day 334 of the study (deemed unlikely to be related to study medication), and one participant on ozanimod 0·5 mg had suicidal ideation on day 35 (deemed possibly related to study medication) but completed the study. Additional TEAEs of interest are presented in the appendix (p 30).

Discussion

In this 24-month phase 3 study, ozanimod was associated with significantly lower adjusted ARR, number of new or enlarging T2 lesions, and number of gadolinium-enhancing lesions compared with intramuscular interferon beta-1a in participants with relapsing multiple sclerosis. The ARR with interferon beta-1a and difference in ARR between ozanimod and interferon beta-1a are consistent with assumptions made in the sample size calculations and with other studies of oral and infusion therapies using interferon beta-1a as an active comparator.[14–19] Although the study was not designed to show a difference between doses, ozanimod 1·0 mg consistently showed numerically greater efficacy than ozanimod 0·5 mg.

The time to confirmed disability progression in the pooled analysis of the RADIANCE phase 3 and SUNBEAM[9] studies was similar for both ozanimod doses and interferon beta-1a, without evidence of risk reduction. Neither individual study was powered to detect a significant difference in this endpoint, and the shorter duration of observation for SUNBEAM (≥12 months) might have contributed to the low rates of disability progression in the pooled dataset.

Treatment with ozanimod resulted in less brain volume loss, including whole brain volume, cortical grey matter volume, and thalamic volume loss, than interferon beta-1a, suggesting that ozanimod might protect against structural changes associated with disease progression.

Ozanimod was well tolerated, with a lower incidence of TEAEs leading to discontinuation than interferon beta-1a. During dose escalation, no clinically meaningful cardiac findings were reported including second-degree or third-degree atrioventricular block or symptomatic bradycardia considered related to study drug. Although a reduction in heart rate has been observed with initiation of sphingosine 1-phosphate receptor modulation, gradual dose escalation of ozanimod can mitigate this effect.[3]

The incidence of infections was similar across treatment groups and no serious opportunistic infections occurred. Ozanimod led to a dose-related decrease in mean ALC, which is an expected pharmacodynamic effect of sphingosine 1-phosphate receptor modulators. ALC less than 0.2×10^9 cells per L was uncommon and was not associated with serious or opportunistic infections.

No specific risk of malignancy was identified; however, this conclusion should be treated with caution given the small size of the study and its short duration.

RADIANCE phase 3 assessed clinically meaningful measures of disease activity in a typical population with active relapsing multiple sclerosis. With a 24-month duration, RADIANCE phase 3 is the longest randomised controlled trial supporting the safety, efficacy, and tolerability of ozanimod in participants with relapsing multiple sclerosis. Demographics and baseline characteristics of the overall study population were consistent with those in phase 3 studies in relapsing multiple sclerosis,[14,17,18,20–24] except that participants from eastern Europe were over-represented. The fact that most participants were white and eastern European might limit generalisability; however, region was adjusted for in the statistical analyses of efficacy. Small sample sizes led to wide CIs in the subgroups of non-eastern Europeans and baseline EDSS greater than 3·5, limiting interpretation of findings in these subgroups. The study duration was insufficient to assess long-term safety and treatment effects on disability progression. Longer-term safety and efficacy data will be assessed in the ongoing open-label extension study. Finally, although the MSFC was originally designed to use the PASAT as a measure of cognitive processing speed, the symbol digit modalities test (SDMT) is gaining favour as an alternative that is at least as sensitive as, and possibly more sensitive than, the PASAT in patients with multiple sclerosis.[25,26] Although RADIANCE phase 3 used the PASAT, the SDMT was used as a component of the MSFC in SUNBEAM.[9]

In RADIANCE phase 3, treatment with ozanimod for 24 months resulted in greater efficacy on clinically meaningful measures of disease activity (relapses and MRI lesions) than treatment with interferon beta-1a in a cohort with active relapsing multiple sclerosis, with 1·0 mg providing numerically greater efficacy than 0·5 mg. These findings, coupled with the observed tolerability profile, support the potential of ozanimod as an effective oral therapy for individuals with relapsing multiple sclerosis.

For more on the **clinical trials data sharing policy of Celgene** see https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/

References

1   Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov* 2010; **9:** 883–97.

2   Scott FL, Clemons B, Brooks J, et al. Ozanimod (RPC1063) is a potent sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist with autoimmune disease-modifying activity. *Br J Pharmacol* 2016; **173:** 1778–92.

3   Tran JQ, Hartung JP, Peach RJ, et al. Results from the first-in-human study with ozanimod, a novel, selective sphingosine-1-phosphate receptor modulator. *J Clin Pharmacol* 2017; **57:** 988–96.

4   Gentile A, Musella A, Bullitta S, et al. Siponimod (BAF312) prevents synaptic neurodegeneration in experimental multiple sclerosis. *J Neuroinflammation* 2016; **13:** 207.

5   Groves A, Kihara Y, Chun J. Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. *J Neurol Sci* 2013; **328:** 9–18.

6   Slowik A, Schmidt T, Beyer C, Amor S, Clarner T, Kipp M. The sphingosine 1-phosphate receptor agonist FTY720 is neuroprotective after cuprizone-induced CNS demyelination. *Br J Pharmacol* 2015; **172:** 80–92.

7   Cohen JA, Arnold DL, Comi G, et al. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2016; **15:** 373–81.

8   Cohen JA, Comi G, Arnold DL, et al. Efficacy and safety of ozanimod in multiple sclerosis: dose-blinded extension of a randomized phase II study. *Mult Scler* 2019; **25:** 1255–62.

9   Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol* 2019; published online Sept 3. http://dx.doi.org/10.1016/S1474-4422(19)30239-X.

10 Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; **69:** 292–302.

11 Nakamura K, Guizard N, Fonov VS, Narayanan S, Collins DL, Arnold DL. Jacobian integration method increases the statistical power to measure gray matter atrophy in multiple sclerosis. *Neuroimage Clin* 2013; **4:** 10–17.

12 Nicholas R, Straube S, Schmidli H, Schneider S, Friede T. Trends in annualized relapse rates in relapsing-remitting multiple sclerosis and consequences for clinical trial design. *Mult Scler* 2011; **17:** 1211–17.

13 Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol* 2008; **7:** 903–14.

14 Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 402–15.

15 Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; **380:** 1819–28.

16 Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; **380:** 1829–39.

17 Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017; **376:** 221–34.

18 Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2015; **373:** 1418–28.

19 Vollmer TL, Sorensen PS, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *J Neurol* 2014; **261:** 773–83.

20 Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; **13:** 545–56.

21 Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; **367:** 1087–97.

22 Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; **367:** 1098–107.

23 Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; **13:** 247–56.

24 Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 387–401.

25 Drake AS, Weinstock-Guttman B, Morrow SA, Hojnacki D, Munschauer FE, Benedict RH. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the symbol digit modalities test. *Mult Scler* 2010; **16:** 228–37.

26 Strober L, DeLuca J, Benedict RH, et al. Symbol digit modalities test: a valid clinical trial endpoint for measuring cognition in multiple sclerosis. *Mult Scler* 2018; published online Oct 18. DOI:10.1177/1352458518808204.