Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial

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Summary

Background Ozanimod, a sphingosine 1-phosphate receptor modulator, selectively binds to receptor subtypes 1 and 5 with high affinity. The RADIANCE phase 2 study showed that ozanimod had better efficacy than placebo on MRI measures, with a favourable safety profile, in participants with relapsing multiple sclerosis. The SUNBEAM study aimed to assess the safety and efficacy of ozanimod versus intramuscular interferon beta-1a in participants with relapsing multiple sclerosis.

Methods SUNBEAM was a randomised, double-blind, double-dummy, active-controlled phase 3 trial done at 152 academic medical centres and clinical practices in 20 countries. We enrolled participants aged 18–55 years with relapsing multiple sclerosis, baseline expanded disability status scale (EDSS) score of 0·0–5·0, and either at least one relapse within the 12 months before screening or at least one relapse within 24 months plus at least one gadolinium-enhancing lesion within 12 months before screening. Participants were randomly assigned 1:1:1 by a blocked algorithm stratified by country and baseline EDSS score to at least 12 months treatment of either once-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 assignment. The primary endpoint was annualised relapse rate (ARR) during the treatment period and was assessed in the intention-to-treat population. Safety was assessed in all participants according to the highest dose of ozanimod received. This trial is registered at ClinicalTrials.gov, number NCT02294058 and EudraCT, number 2014–002320–27.

Findings Between Dec 18, 2014, and Nov 12, 2015, 1346 participants were enrolled and randomly assigned to ozanimod 1·0 mg (n=447), ozanimod 0·5 mg (n=451), or interferon beta-1a (n=448). 91 (6·8%) participants discontinued the study drug (29 in the ozanimod 1·0 mg group; 26 in the ozanimod 0·5 mg group; and 36 in the interferon beta-1a group). Adjusted ARRs were 0·35 (0·28–0·44) for interferon beta-1a, 0·18 (95% CI 0·14–0·24) for ozanimod 1·0 mg (rate ratio [RR] of 0·52 [0·41–0·66] *vs* interferon beta-1a; p<0·0001), and 0·24 (0·19–0·31) for ozanimod 0·5 mg (RR 0·69 [0·55–0·86] *vs* interferon beta-1a; p=0·0013). Few ozanimod-treated participants discontinued treatment because of adverse events (13 [2·9%] who received ozanimod 1·0 mg; seven [1·5%] who received ozanimod 0·5 mg; and 16 [3·6%] who received interferon beta-1a). No first-dose, clinically significant bradycardia or second-degree or third-degree atrioventricular block was reported. The incidence of serious adverse events was low and similar across treatment groups (13 [2·9%] participants who received ozanimod 1·0 mg; 16 [3·5%] who received ozanimod 0·5 mg; and 11 [2·5%] who received interferon beta-1a). No serious opportunistic infections occurred in ozanimod-treated participants.

Interpretation In participants with relapsing multiple sclerosis treated for at least 12 months, ozanimod was well tolerated and demonstrated a significantly lower relapse rate than interferon beta-1a. These findings provide support for ozanimod as an oral therapy for individuals with relapsing multiple sclerosis.

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Introduction

Injectable, oral, and infused treatments across various drug classes are available for patients with relapsing multiple sclerosis.[1] Oral therapies differ in tolerability, efficacy, safety, and mechanism of action.[1]

One approach to treatment of relapsing multiple sclerosis targets the sphingosine 1-phosphate ligand–receptor system to modulate the autoimmune response.[2] Five G-protein-coupled sphingosine 1-phosphate receptors, designated sphingosine 1-phosphate receptor subtypes 1–5, interact with sphingosine 1-phosphate; each receptor has a unique distribution and, when coupled with a sphingosine 1-phosphate ligand, triggers different physiological effects.[3] Sphingosine 1-phosphate is an important

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Research in context

Evidence before this study

We did a PubMed search with the search terms "(ozanimod OR RPC1063) AND multiple sclerosis", with no language or time period restrictions, on Dec 2, 2018, which yielded two clinical studies, a phase 2, randomised, placebo-controlled trial of ozanimod in 258 participants with relapsing multiple sclerosis (RADIANCE phase 2; NCT01628393; EudraCT 2012–002714–40), and its separately published 2-year dose-blinded extension study. In RADIANCE phase 2, ozanimod 1·0 mg or 0·5 mg was well tolerated and resulted in significantly fewer mean cumulative numbers of gadolinium-enhancing lesions and new or enlarging T2 lesions over weeks 12–24 (primary endpoint) than placebo. Participants who continued their previously assigned dose of ozanimod during the 2-year, dose-blinded extension period had sustained efficacy based on low MRI disease activity and clinical relapses. Those who switched from placebo in RADIANCE phase 2 to ozanimod during the extension period had efficacy similar to that observed in participants who received ozanimod during both study periods. Ozanimod was well tolerated during the 2-year extension study and adverse events were consistent with those seen during the placebo-controlled period.

Added value of this study

Compared with the phase 2 RADIANCE study, the phase 3 SUNBEAM study included a larger patient cohort, longer duration of treatment, and an active comparator already in use for relapsing multiple sclerosis. The SUNBEAM study also assessed the effect of ozanimod on disability progression, brain volume loss, cognitive measures, and quality of life.

Implications of all the available evidence

The SUNBEAM trial reinforces and expands the results from the RADIANCE phase 2 trial and supports ozanimod as a potential oral treatment for patients with relapsing multiple sclerosis. Additional clinical studies will assess the long-term effects of ozanimod on safety and disease outcomes.

signal for egress of lymphocytes from lymphoid organs to the circulation through engagement of sphingosine 1-phosphate subtype 1 receptors on lymphocytes.[4,5] Sphingosine 1-phosphate receptor modulators downregulate expression of sphingosine 1-phosphate subtype 1 receptors on lymphocytes, resulting in lymphocyte accumulation in lymph nodes and a decrease in circulating lymphocytes.[6,7] Activation of sphingosine 1-phosphate subtype 1 receptors in atrial myocytes can lead to bradycardia.[8] Dose escalation of sphingosine 1-phosphate subtype 1 receptor modulators might attenuate the initial heart rate-reducing effects of sphingosine 1-phosphate subtype 1 activation.[9–11] Preclinical evidence suggests that sphingosine 1-phosphate receptor subtype 5, which is expressed primarily in the brain,[3] might mediate survival of oligodendrocytes, which are important for neuronal remyelination.[12]

Ozanimod, an oral, once-daily sphingosine 1-phosphate receptor modulator, which binds with high affinity selectively to sphingosine 1-phosphate receptor subtypes 1 and 5,[13] is in clinical development for treatment of relapsing multiple sclerosis and inflammatory bowel disease. In the RADIANCE phase 2 trial[14] and its extension trial,[11] ozanimod treatment for up to 2·5 years in participants with relapsing multiple sclerosis was associated with low mean numbers of new or enlarging T2 and gadolinium-enhancing MRI lesions, with no serious opportunistic infections, malignancies, cardiac events, or macular oedema. We report results from one of two phase 3 studies (SUNBEAM) comparing the safety and efficacy of once-daily, oral ozanimod with weekly intramuscular interferon beta-1a in participants with relapsing multiple sclerosis treated for at least 12 months. Another phase 3 study of 24 months' treatment with ozanimod in relapsing multiple sclerosis, the RADIANCE phase 3 trial[15] (NCT02047734; EudraCT 2012–002714–40), was conducted concurrently with SUNBEAM and is reported separately.

See Online for appendix

Methods

Study design

SUNBEAM was a multicentre, randomised, double-blind, double-dummy, active-controlled, parallel-group, phase 3 trial (appendix p 5) done in participants with relapsing multiple sclerosis at 152 academic medical centres and clinical practices in 20 countries (appendix p 6). The institutional review board or ethics committee at each site approved the study protocol, which conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles.

Participants

Participants were aged 18–55 years and diagnosed with multiple sclerosis per 2010 McDonald criteria,[16] with a relapsing clinical course (relapsing–remitting, secondary progressive, or progressive–relapsing), history of brain MRI lesions consistent with multiple sclerosis, baseline expanded disability status scale (EDSS) score of 0·0–5·0, and either at least one relapse in the 12 months before screening or at least one relapse in the 24 months before screening plus at least one gadolinium-enhancing lesion in the 12 months before randomisation. Participants had to have no history of relapse or systemic corticosteroid or adrenocorticotrophic hormone use from 30 days before screening up to randomisation and positive varicella zoster virus immunoglobulin G antibody status or varicella zoster virus vaccination at least 30 days before randomisation. Individuals with primary progressive multiple sclerosis; disease duration more than 15 years with an EDSS of 2·0 or less; contraindications to MRI or gadolinium contrast; previous inability to tolerate interferon beta;

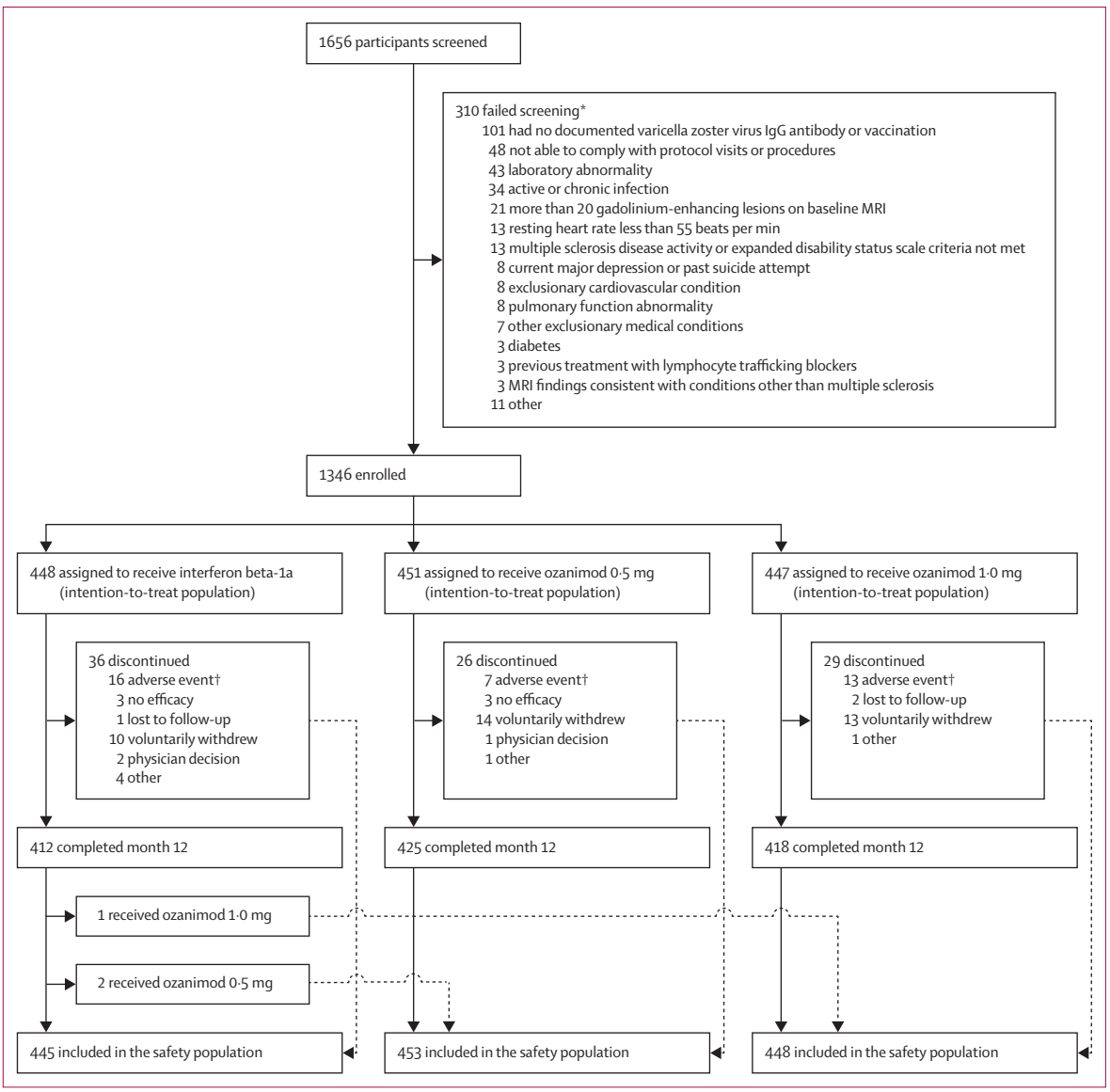


Figure 1: **Trial profile**
*Some individuals are included in more than one category. †Adverse events leading to discontinuation are in the appendix (pp 24–25).

resting heart rate less than 55 beats per min (bpm) at screening; specific cardiac conditions (eg, recent myocardial infarction, stroke, prolonged Fridericia-corrected QT [QTcF]); previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers; or active infections were excluded. Individuals with a history of macular oedema were eligible. Full inclusion and exclusion criteria are in the appendix (pp 6–8). Participants provided written informed consent.

Randomisation and masking

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

To maintain masking, participants assigned to interferon beta-1a received daily oral placebo capsules identical in appearance to ozanimod; those assigned to ozanimod received weekly intramuscular placebo injections. Participants were advised to take acetaminophen or ibuprofen 1 h before each injection and every 6 h for 24 h after the injection as prophylaxis against flu-like symptoms associated with interferon. To prevent potential unmasking

	Interferon beta-1a group (n=448)	Ozanimod 0·5 mg group (n=451)	Ozanimod 1·0 mg group (n=447)
Age, years	35·9 (9·1)	36·0 (9·4)	34·8 (9·2)
Sex			
Female	300 (67·0%)	311 (69·0%)	283 (63·3%)
Male	148 (33·0%)	140 (31·0%)	164 (36·7%)
Race			
White	447 (99·8%)	447 (99·1%)	446 (99·8%)
Black	0	2 (0·4%)	0
Asian	0	1 (0·2%)	1 (0·2%)
Other	1 (0·2%)	1 (0·2%)	0
Bodyweight, kg	70·0 (16·2)	69·3 (15·6)	69·7 (15·5)
Region			
Eastern Europe*	419 (93·5%)	419 (92·9%)	415 (92·8%)
Western Europe	16 (3·6%)	17 (3·8%)	17 (3·8%)
North America	11 (2·5%)	13 (2·9%)	12 (2·7%)
Oceania†	2 (0·4%)	2 (0·4%)	3 (0·7%)
Time since multiple sclerosis symptom onset, years	6·9 (5·9)	7·2 (6·3)	6·9 (6·4)
Time since multiple sclerosis diagnosis, years	3·7 (4·4)	3·7 (4·5)	3·6 (4·2)
Type of multiple sclerosis			
Relapsing-remitting multiple sclerosis	441 (98·4%)	443 (98·2%)	438 (98·0%)
Progressive-relapsing multiple sclerosis	5 (1·1%)	5 (1·1%)	9 (2·0%)
Secondary progressive multiple sclerosis	2 (0·4%)	3 (0·7%)	0
Expanded disability status scale score	2·6 (1·1)	2·7 (1·1)	2·6 (1·2)
Number of relapses in previous 12 months	1·3 (0·6)	1·3 (0·6)	1·3 (0·6)
Number of relapses in previous 24 months	1·7 (0·8)	1·7 (0·8)	1·8 (0·9)
Previous disease-modifying therapy‡	151 (33·7)	132 (29·3)	128 (28·6)
Number of gadolinium-enhancing lesions	1·7 (3·2)	1·6 (3·0)	1·8 (3·4)
Gadolinium-enhancing lesion volume, cm^3	0·18 (0·46)	0·16 (0·41)	0·20 (0·54)
Number of T2 lesions	53·7 (37·8)	53·6 (35·6)	54·5 (39·5)
T2 lesion volume, cm^3	13·6 (15·2)	13·1 (15·3)	12·5 (15·3)
Normalised brain volume, cm^3	1443·4 (78·7)	1447·4 (79·5)	1456·0 (77·9)

Data are mean (SD) or n (%). *Eastern Europe includes Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Serbia, and Ukraine. †The Oceania region included only New Zealand. ‡Disease-modifying therapy includes interferon beta-1a, pegylated interferon beta-1a, interferon beta-1b, glatiramer acetate, daclizumab, dimethyl fumarate, teriflunomide, and mitoxantrone.

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

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

due to observed efficacy, adverse events, or laboratory changes, an independent assessor masked to treatment and previous EDSS scores assessed participants using the EDSS (Neurostatus method) at all visits. Participants were advised not to discuss clinical symptoms or adverse events with the EDSS assessor. The treating investigator did all other study assessments. Treating investigators, EDSS assessors, study personnel, MRI reviewers, participants, and the sponsor 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 once-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 injections of interferon beta-1a 30 µg (manufactured by Biogen, Cambridge, MA, USA). An initial 7-day dose escalation 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 the assigned dose starting on day 8. On day 1, vital signs were measured before administration of the drug and hourly for the first 6 h after, and electrocardiograms (ECGs) were done before and at 6 h after. At the end of the 6-h period, if heart rate was less than 45 bpm or at its lowest value since administration of the drug, or if ECG showed a prolonged QTcF interval or second-degree or third-degree atrioventricular block, then monitoring was continued until resolution. Monitoring was repeated on days 5 and 8 at the investigators' discretion for participants with a cardiac safety issue on the previous day of dose escalation.

Study visits occurred at screening, baseline, month 1, and every 3 months between month 3 and the end of treatment. The EDSS and neurological examinations were done at screening and each visit from month 3 to the end of treatment, and at the time of suspected relapse. Brain MRI was done with and without gadolinium enhancement on the same machine at screening, month 6, and month 12. Adverse events were assessed at each visit.

Liver function tests were assessed at each visit. Optical coherence tomography was done at screening, month 6, month 12, and at the end of treatment (if not done in the previous 6 months). General retinal exams, 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 central foveal thickness increased more than 20% from baseline, or any relevant optical coherence tomography abnormality. Pulmonary function tests were done at screening and months 3, 6, and 12. Diffusing capacity of the lungs for carbon monoxide (if available locally) was assessed at screening and every 12 months. Skin examinations were done at screening and month 12. Treatment was discontinued for participants with alanine aminotransferase or aspartate aminotransferase concentrations of at least five times the upper limit of normal (ULN) after confirmation on retest within 14 days, new or worsening macular oedema, forced expiratory volume in 1 s or forced vital capacity less than 50% predicted, or pregnancy. The investigator followed macular oedema and pulmonary function test abnormalities until resolution or until no further improvement was expected (after ≥3 months of follow-up).

Whole brain volume and cortical grey matter volume were measured using SienaX and thalamic volume was measured using ThalamicVolume software (appendix p 8).

	Interferon beta-1a group (n=448)	Ozanimod 0·5 mg group (n=451)			Ozanimod 1·0 mg group (n=447)		
		Absolute value	Rate ratio *vs* interferon beta-1a*	p value	Absolute value	Rate ratio *vs* interferon beta-1a*	p value
Primary endpoint							
Adjusted ARR through month 12	0·35 (0·28 to 0·44)	0·24 (0·19 to 0·31)	0·69 (0·55 to 0·86)	0·0013	0·18 (0·14 to 0·24)	0·52 (0·41 to 0·66)	<0·0001
Secondary endpoints							
Adjusted mean number of new or enlarging T2 lesions per scan over 12 months	2·84 (2·33 to 3·45)	2·14 (1·78 to 2·58)	0·75 (0·63 to 0·91)	0·0032	1·47 (1·20 to 1·78)	0·52 (0·43 to 0·63)	<0·0001
Adjusted mean number of gadolinium-enhancing lesions at month 12	0·43 (0·30 to 0·64)	0·29 (0·20 to 0·42)	0·66 (0·47 to 0·93)	0·0182	0·16 (0·11 to 0·24)	0·37 (0·26 to 0·54)	<0·0001

Numbers in parentheses are 95% CIs. ARR=annualised relapse rate. *Rate for ozanimod divided by rate for interferon beta-1a.

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

Percentage change in brain volume was calculated using JacobianAtrophy software using longitudinal Jacobian integration.[17]

Participants continued treatment until the last participant was treated for 12 months. Participants who completed the study were eligible for a long-term, open-label extension study (RPC01-3001; NCT02576717, EudraCT 2015-002500-91).

Outcomes

The primary efficacy endpoint was annualised relapse rate (ARR) during the treatment period based on confirmed, protocol-defined relapses (ie, new or worsening neurological symptoms attributable to multiple sclerosis persisting for >24 h, not attributable to confounding clinical factors, and immediately preceded by a mostly stable or improving neurological state for ≥30 days). Relapse was confirmed when accompanied by objective neurological worsening (ie, EDSS score 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 efficacy endpoints were number of new or enlarging T2 brain lesions over 12 months; number of gadolinium-enhancing brain lesions at month 12; and time to onset of disability progression (defined as a sustained worsening in EDSS ≥1-point increase) confirmed after 3 months and 6 months. Disability progression was assessed as a prespecified pooled analysis with the RADIANCE phase 3 trial[15] (treatment duration 24 months); the methods and results are reported with the RADIANCE phase 3 trial. Percentage change from baseline to month 12 in whole brain volume was a secondary endpoint; changes in cortical grey matter and thalamic volume were prespecified exploratory endpoints. Other secondary endpoints were the proportions of participants free of gadolinium-enhancing or new or enlarging T2 lesions at month 12; changes from baseline to month 12 in multiple sclerosis functional composite (MSFC) score; and the physical and mental health composite scores of the 54-item multiple sclerosis quality of life (MSQOL-54) scale. The symbol digit modalities test (SDMT) was included as a component of the MSFC for assessment of cognitive processing speed.

Adverse events were recorded by system organ class, severity, and causality, and were coded per the Medical Dictionary for Regulatory Activities, version 18.1. All adverse events presented are treatment-emergent adverse events (TEAEs), meaning that they 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.

Adverse events of special interest were cardiac abnormalities (eg, bradycardia, conduction abnormalities, or new ischaemic changes on ECG), serious and opportunistic infections, hepatotoxicity (confirmed alanine aminotransferase or aspartate aminotransferase at least three times the ULN, with or without raised bilirubin), ophthalmic abnormalities (including macular oedema), pulmonary function test abnormalities, and dermatological and other malignancies. Suicidality, which is increased in people with multiple sclerosis compared with the general population,[18] was assessed at each visit.

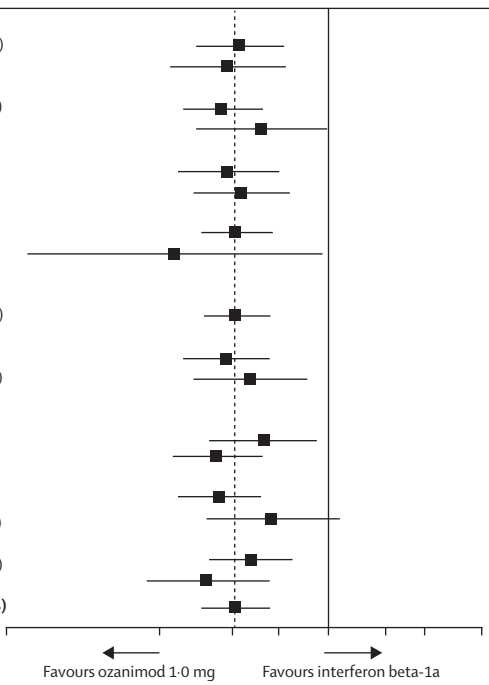
Statistical analysis

Assuming an ARR in the interferon beta-1a group of 0·3,[19] using a Poisson regression model with an extra-Poisson variation of σ^2=1·3,[20] a two-sided α of 0·025, and 12 months of follow-up per participant, the method of Nicholas and colleagues[20] resulted in a sample size of 353 participants per treatment group to provide 80% power to detect a 43% lower ARR among ozanimod-treated participants (ARR 0·17). Assuming a 12% dropout rate, about 400 participants per treatment group were to be randomly assigned to each group.

ARR was compared for each ozanimod dose versus interferon beta-1a using a prespecified Poisson regression

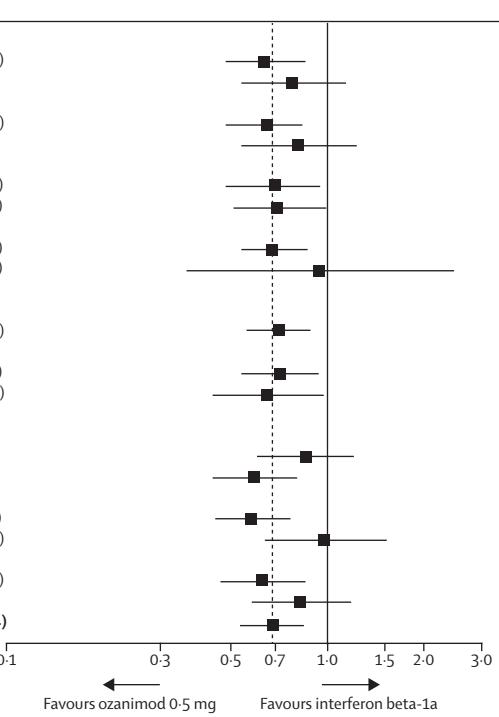
A

	Number of participants in subgroup		Annualised relapse rate (95% CI)		Rate ratio (95% CI)
	Ozanimod 1·0 mg (n=447)	Interferon beta-1a (n=448)	Ozanimod 1·0 mg (n=447)	Interferon beta-1a (n=448)	
Sex					
Female	283	300	0·18 (0·13–0·26)	0·34 (0·26–0·46)	0·53 (0·39–0·73)
Male	164	148	0·17 (0·11–0·26)	0·35 (0·24–0·51)	0·49 (0·32–0·74)
Age (years)					
≤40	324	307	0·22 (0·16–0·29)	0·46 (0·35–0·61)	0·47 (0·35–0·63)
>40	123	141	0·13 (0·08–0·23)	0·21 (0·13–0·33)	0·62 (0·39–1·01)
Baseline body weight					
Less than median (<66·9 kg)	206	230	0·19 (0·12–0·30)	0·38 (0·25–0·57)	0·49 (0·34–0·70)
Median or greater (≥66·9 kg)	241	218	0·18 (0·13–0·25)	0·33 (0·25–0·45)	0·54 (0·39–0·76)
Region					
Eastern Europe	415	419	0·19 (0·15–0·23)	0·35 (0·30–0·41)	0·52 (0·41–0·68)
Rest of world	32	29	0·09 (0·04–0·22)	0·26 (0·13–0·52)	0·34 (0·12–0·97)
Race					
Non-white	1	1			
White	446	447	0·19 (0·14–0·24)	0·36 (0·28–0·45)	0·52 (0·41–0·67)
Number of relapses in previous year					
Less than two	333	337	0·15 (0·11–0·21)	0·31 (0·24–0·42)	0·48 (0·35–0·66)
Two or more	114	111	0·26 (0·17–0·41)	0·46 (0·31–0·69)	0·58 (0·38–0·86)
Baseline gadolinium-enhancing lesions					
Absent	233	232	0·13 (0·08–0·20)	0·21 (0·14–0·31)	0·63 (0·43–0·92)
Present	214	216	0·25 (0·18–0·35)	0·55 (0·42–0·72)	0·45 (0·33–0·63)
Baseline EDSS					
≤3·5	360	370	0·17 (0·13–0·23)	0·37 (0·29–0·47)	0·46 (0·34–0·62)
>3·5	87	78	0·15 (0·05–0·41)	0·22 (0·08–0·60)	0·67 (0·42–1·09)
Previous disease-modifying therapy					
No	319	297	0·20 (0·14–0·27)	0·34 (0·25–0·45)	0·58 (0·43–0·78)
Yes	128	151	0·15 (0·10–0·25)	0·37 (0·25–0·53)	0·42 (0·27–0·66)
Overall	**447**	**448**	**0·18 (0·14–0·24)**	**0·35 (0·28–0·44)**	**0·52 (0·41–0·66)**



B

	Number of participants in subgroup		Annualised relapse rate (95% CI)		Rate ratio (95% CI)
	Ozanimod 0·5 mg (n=451)	Interferon beta-1a (n=448)	Ozanimod 0·5 mg (n=451)	Interferon beta-1a (n=448)	
Sex					
Female	311	300	0·22 (0·16–0·30)	0·34 (0·26–0·46)	0·63 (0·48–0·85)
Male	140	148	0·27 (0·18–0·40)	0·35 (0·24–0·51)	0·77 (0·53–1·12)
Age (years)					
≤40	293	307	0·29 (0·22–0·38)	0·46 (0·35–0·61)	0·62 (0·47–0·82)
>40	158	141	0·17 (0·11–0·28)	0·21 (0·13–0·33)	0·81 (0·54–1·22)
Baseline body weight					
Less than median (<66·9 kg)	236	230	0·26 (0·17–0·40)	0·38 (0·25–0·57)	0·68 (0·48–0·93)
Median or greater (≥66·9 kg)	215	218	0·23 (0·17–0·32)	0·33 (0·25–0·45)	0·70 (0·50–0·97)
Region					
Eastern Europe	419	419	0·24 (0·20–0·29)	0·35 (0·30–0·41)	0·67 (0·53–0·85)
Rest of world	32	29	0·25 (0·13–0·48)	0·26 (0·13–0·52)	0·94 (0·36–2·44)
Race					
Non-white	4	1			
White	447	447	0·25 (0·19–0·32)	0·36 (0·28–0·45)	0·69 (0·55–0·87)
Number of relapses in previous year					
Less than two	337	337	0·22 (0·17–0·30)	0·31 (0·24–0·42)	0·71 (0·54–0·94)
Two or more	114	111	0·30 (0·19–0·46)	0·46 (0·31–0·69)	0·65 (0·44–0·96)
Baseline gadolinium-enhancing lesions					
Absent	249	232	0·17 (0·12–0·26)	0·21 (0·14–0·31)	0·85 (0·60–1·20)
Present	202	216	0·32 (0·23–0·44)	0·55 (0·42–0·72)	0·59 (0·43–0·80)
Baseline EDSS					
≤3·5	360	370	0·21 (0·16–0·28)	0·37 (0·29–0·47)	0·58 (0·44–0·76)
>3·5	91	78	0·21 (0·08–0·57)	0·22 (0·08–0·60)	0·98 (0·64–1·50)
Previous disease-modifying therapy					
No	319	297	0·21 (0·15–0·29)	0·34 (0·25–0·45)	0·52 (0·46–0·84)
Yes	132	151	0·30 (0·20–0·45)	0·37 (0·25–0·53)	0·82 (0·57–1·17)
Overall	**451**	**448**	**0·24 (0·19–0·31)**	**0·35 (0·28–0·44)**	**0·69 (0·55–0·86)**



model adjusted for geographic region (eastern Europe *vs* rest of world), baseline age, and baseline number of gadolinium-enhancing lesions; the natural log transformation of time on study was included as an offset term. To account for multiple comparisons, each ozanimod group was compared with interferon beta-1a at a two-sided α of 0·025. Additional sensitivity analyses were done to assess assumptions regarding the Poisson model (appendix pp 10–11).

A hierarchical testing procedure was used to assess key secondary endpoints (appendix p 8). If both ozanimod doses reached statistical significance on the primary endpoint (ARR), then ozanimod 1·0 mg would be compared with interferon beta-1a for the number of new or enlarging T2 lesions over 12 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 to be followed for number of gadolinium-enhancing lesions at month 12, followed by time to onset of confirmed disability progression (pooled with the RADIANCE phase 3 trial),[15] until a comparison did not reach statistical significance, after which all subsequent comparisons would be considered exploratory. If only one ozanimod dose 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 enlarging T2 lesions over 12 months and number of gadolinium-enhancing lesions at month 12 were analysed using a negative binomial regression model adjusted for geographic region (eastern Europe *vs* rest of world), baseline age, and baseline number of gadolinium-enhancing lesions; the natural log transformation of the number of available MRI scans was included as an offset term.

Prespecified subgroup analyses were done for ARR, new or enlarging T2 lesions, and gadolinium-enhancing lesions for the following subgroups: baseline EDSS score (≤3·5 *vs* >3·5), baseline gadolinium-enhancing lesions (present *vs* absent), treatment-naive versus previous disease-modifying treatment, 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 the preceding 12 months (less than two *vs* two or more; ARR endpoint only), and region (eastern Europe *vs* rest of world). Analyses were not done for subgroups comprising less than 5% of the overall sample size.

Change from baseline in brain volume measures was calculated using descriptive statistics. Comparisons of percentage change from baseline in brain volume between interferon beta-1a and ozanimod 1·0 mg or 0·5 mg were made using an analysis of covariance (ANCOVA) model adjusted for region (eastern Europe *vs* rest of world), baseline EDSS category, and baseline brain volume, with missing data imputed using the last-observation-carried-forward method.

MSFC score was a composite of average Z scores calculated for each MSFC component, using the study population as the reference population. Differences in MSFC score and the physical and mental health composite scores of the MSQOL-54 between each ozanimod group and the interferon beta-1a group were compared using ANCOVA, with models adjusted for region (eastern Europe *vs* rest of world), EDSS score, and baseline value of interest. Safety outcomes were reported as incidence in each treatment group, with inclusion limited to one occurrence of a preferred term per participant. Statistical hypothesis testing was not done on safety results.

Efficacy analyses were done in the intention-to-treat population, defined as all participants who received at least one dose of their assigned study drug. The safety population consisted of all participants who received at least one dose of study drug, categorised by the highest ozanimod dose received.

All statistical analyses were done using SAS, version 9.1 or higher. No interim analyses were planned. The SUNBEAM trial steering committee contributed to development of the protocol and statistical analysis plan and reviewed the data analyses. 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 at ClinicalTrials.gov, number NCT02294058 and EudraCT, number 2014–002320–27.

Role of the funding source

The funders of this study were 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 18, 2014, and Nov 12, 2015, 1656 participants were screened, of whom 1346 were eligible and enrolled. 447 participants were randomly assigned to ozanimod 1·0 mg, 451 to ozanimod 0·5 mg, and 448 to interferon beta-1a; all received at least one dose of study drug and 1255 (93·2%) completed the study (figure 1). 91 (6·8%)

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.

	Interferon beta-1a group (n=448)	Ozanimod 0·5 mg group (n=451)			Ozanimod 1·0 mg group (n=447)		
		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	406	420	..	..	397	..	..
Mean percentage change from baseline to month 12*	−0·61 (0·686)	−0·49 (0·610)	0·12 (0·03 to 0·20)	0·0092	−0·41 (0·640)	0·19 (0·10 to 0·28)	<0·0001
Cortical grey matter volume†							
Participants with data available	407	418	..	..	398	..	..
Mean percentage change from baseline to month 12*	−1·00 (0·969)	−0·34 (0·793)	0·66 (0·54 to 0·78)	<0·0001	−0·16 (0·872)	0·84 (0·72 to 0·96)	<0·0001
Thalamic volume†							
Participants with data available	406	416	..	..	393	..	..
Mean percentage change from baseline to month 12*	−1·72 (1·935)	−1·12 (1·617)	0·59 (0·35 to 0·82)	<0·0001	−1·12 (1·633)	0·55 (0·31 to 0·78)	<0·0001
Proportion of participants who were lesion free at month 12‡							
Gadolinium-enhancing lesion free	63·17 (58·70 to 67·64)	68·29 (64·00 to 72·59)	5·12 (−1·07 to 11·32)	0·1130	74·05 (69·99 to 78·11)	10·88 (4·84 to 16·92)	0·0006
New or enlarging T2 lesion free	23·44 (19·51 to 27·36)	26·39 (22·32 to 30·45)	2·95 (−2·70 to 8·60)	0·3023	27·96 (23·80 to 32·12)	4·53 (−1·19 to 10·24)	0·1180
MSFC score							
Participants with data available	448	450	..	..	447	..	..
Mean change from baseline to month 12	−0·024 (0·366)	−0·004 (0·408)	0·019 (−0·030 to 0·069)	0·4394	0·006 (0·382)	0·040 (−0·009 to 0·090)	0·1091
MSFC score with LCLA measurement of visual function							
Participants with data available	447	450	..	..	447	..	..
Mean change from baseline to month 12	−0·022 (0·334)	−0·007 (0·351)	0·015 (−0·028 to 0·059)	0·4942	0·003 (0·328)	0·034 (−0·010 to 0·077)	0·1290
SDMT Z score							
Participants with data available	448	450	..	..	447	..	..
Mean change from baseline to month 12	−0·029 (0·508)	0·061 (0·552)	0·082 (0·010 to 0·153)	0·0246	0·073 (0·653)	0·111 (0·039 to 0·182)	0·0024
MSQOL-54 physical health composite score							
Participants with data available	445	448	..	..	443	..	..
Mean change from baseline to month 12§	0·046 (12·578)	1·414 (12·343)	1·024 (−0·510 to 2·559)	0·1905	1·925 (11·870)	1·642 (0·104 to 3·180)	0·0364
MSQOL-54 mental health composite score							
Participants with data available	448	451	..	..	446	..	..
Mean change from baseline to month 12§	−0·123 (15·240)	0·283 (15·686)	−0·170 (−2·045 to 1·705)	0·8587	0·260 (15·800)	0·356 (−1·523 to 2·234)	0·7104

Data are n, mean (SD), or % (95% CI). Differences 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), EDSS category at baseline, and baseline value of interest. Differences in proportions between ozanimod and interferon beta-1a are based on Wald 95% CI; p values based on the Cochran-Mantel-Haenszel test were stratified by region (eastern Europe *vs* rest of world) and EDSS 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 SDMT score was missing, due to 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 SDMT; if the scores were missing for some other reason, then last observation carried forward was used to impute the Z score for that visit. EDSS=expanded disability status scale. LCLA=low-contrast letter acuity. MSFC=multiple sclerosis functional composite. MSQOL-54=54-item multiple sclerosis quality of life. SDMT=symbol digit modalities test. *Missing data imputed using last observation carried forward. †Exploratory endpoint. ‡Calculated using non-responder imputation to account for missing data. §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)**

participants discontinued the study drug (29 in the ozanimod 1·0 mg group; 26 in the ozanimod 0·5 mg group; and 36 in the interferon beta-1a group). The primary reasons for discontinuation in all groups were voluntary withdrawal and TEAEs. Mean duration of study drug exposure was 13·6 months (SD 2·7) for each ozanimod group and 13·5 months (2·9) for interferon beta-1a. Three participants assigned to interferon beta-1a erroneously received ozanimod 1·0 mg (one participant) or 0·5 mg (two participants) and completed the study; thus, the safety population comprised 448 participants in the ozanimod 1·0 mg group, 453 in the 0·5-mg group, and 445 in the interferon beta-1a group. Baseline demographics and disease characteristics were similar across

	Interferon beta-1a group (n=445)	Ozanimod 0·5 mg group (n=453)	Ozanimod 1·0 mg group (n=448)
Adverse events	336 (75·5%)	259 (57·2%)	268 (59·8%)
Severe adverse events	10 (2·2%)	10 (2·2%)	7 (1·6%)
Serious adverse events	11 (2·5%)	16 (3·5%)	13 (2·9%)
Adverse events leading to discontinuation of study drug	16 (3·6%)	7 (1·5%)	13 (2·9%)
Death	0	0	0
Adverse events occurring in at least 2% of ozanimod-treated participants and with an incidence at least 1% higher than in the interferon beta-1a group			
Nasopharyngitis	36 (8·1%)	44 (9·7%)	30 (6·7%)
Headache	25 (5·6%)	27 (6·0%)	34 (7·6%)
Upper respiratory tract infection	24 (5·4%)	31 (6·8%)	18 (4·0%)
Alanine aminotransferase increased	8 (1·8%)	12 (2·6%)	21 (4·7%)
Back pain	9 (2·0%)	10 (2·2%)	17 (3·8%)
γ-glutamyltransferase increased	2 (0·4%)	10 (2·2%)	15 (3·3%)
Respiratory tract infection, viral	3 (0·7%)	10 (2·2%)	15 (3·3%)
Urinary tract infection	10 (2·2%)	8 (1·8%)	17 (3·8%)
Hypercholesterolaemia	5 (1·1%)	6 (1·3%)	11 (2·5%)
Hypertension	4 (0·9%)	11 (2·4%)	6 (1·3%)
Pharyngitis	5 (1·1%)	6 (1·3%)	11 (2·5%)
Rhinitis	3 (0·7%)	8 (1·8%)	9 (2·0%)
Upper abdominal pain	3 (0·7%)	9 (2·0%)	6 (1·3%)

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)**

treatment groups (table 1); mean age was 35·6 years (SD 9·3), 894 (66%) of 1346 participants were women, mean time since multiple sclerosis symptom onset was 7·0 years (6·2), and mean time since diagnosis was 3·7 years (4·4). Changes to the original protocol and statistical analysis plan implemented after enrolment commenced are summarised in the appendix (p 9).

Adjusted ARRs were 0·18 (95% CI 0·14–0·24) for ozanimod 1·0 mg, 0·24 (0·19–0·31) for ozanimod 0·5 mg, and 0·35 (0·28–0·44) for interferon beta-1a. Versus the interferon beta-1a group, the rate ratio (RR) was 0·52 (0·41–0·66) with ozanimod 1·0 mg (p<0·0001) and 0·69 (0·55–0·86) with ozanimod 0·5 mg (p=0·0013; table 2; appendix p 10).

The adjusted mean number of new or enlarging T2 lesions per scan over 12 months was 1·47 (95% CI 1·20–1·78) for ozanimod 1·0 mg, 2·14 (1·78–2·58) for ozanimod 0·5 mg, and 2·84 (2·33–3·45) for interferon beta-1a, with an RR versus interferon beta-1a of 0·52 (0·43–0·63) with ozanimod 1·0 mg (p<0·0001) and 0·75 (0·63–0·91) with ozanimod 0·5 mg (p=0·0032; table 2; appendix p 12). Adjusted mean number (95% CI) of gadolinium-enhancing lesions at month 12 was 0·16 (0·11–0·24) for ozanimod 1·0 mg, 0·29 (0·20–0·42) for ozanimod 0·5 mg, and 0·43 (0·30–0·64) for interferon beta-1a, with an RR versus interferon beta-1a of 0·37 (0·26–0·54) with ozanimod 1·0 mg (p<0·0001) and 0·66 (0·47–0·93) with ozanimod 0·5 mg (p=0·0182; table 2; appendix p 13).

RRs and 95% CIs for ARR, new or enlarging T2 lesions over 12 months, and gadolinium-enhancing lesions at 12 months 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 wide CIs for the analyses of the subgroups of non-eastern European region and baseline EDSS score more than 3·5, and no RRs could be calculated for the non-white subgroup because of the very small sample size.

Both ozanimod doses reduced loss of whole brain volume, cortical grey matter, and thalamic volume from baseline to month 12 compared with interferon beta-1a (table 3, appendix pp 18–20). Brain volume data were not normally distributed; consequently, median percentage change in brain volume from baseline to month 12 was also compared between each ozanimod dose and interferon beta-1a using rank ANCOVA (observed data; appendix pp 21–22). Mean change in MSFC score from baseline to month 12 was similar across treatment groups, but mean change in SDMT Z score was greater for both ozanimod groups than in the interferon beta-1a group. Other endpoints were not different between groups, except the physical health composite score of the MSQOL-54 and proportion of participants who were gadolinium-enhancing lesion-free at month 12 for ozanimod 1·0 mg versus interferon beta-1a (table 3).

TEAEs were reported in 268 (59·8%) of 448 participants who received ozanimod 1·0 mg, 259 (57·2%) of 453 who received ozanimod 0·5 mg, and 336 (75·5%) of 445 who received interferon beta-1a (table 4). TEAEs occurring in at least 5% of ozanimod-treated participants and with a

numerical difference of at least 1% versus interferon beta-1a were nasopharyngitis, headache, and upper respiratory tract infection. The most frequently occurring TEAEs (≥5%) among interferon beta-1a treated participants were influenza-like illness, nasopharyngitis, pyrexia, headache, and upper respiratory tract infection (appendix p 23). Serious TEAEs occurred in 13 (2·9%) of 448 participants in the ozanimod 1·0 mg group, 16 (3·5%) of 453 in the ozanimod 0·5 mg group, and 11 (2·5%) of 445 in the interferon beta-1a group (appendix pp 23, 24). Few participants discontinued treatment due to TEAEs (13 [2·9%] who received ozanimod 1·0 mg; seven [1·5%] who received ozanimod 0·5 mg; and 16 [3·6%] who received interferon beta-1a); influenza-like illness, back pain, headache, and alanine aminotransferase increases were the only events leading to discontinuation in more than one participant in any treatment group (appendix pp 24, 25). No deaths occurred during the study.

Maximum reduction in mean supine heart rate over 1–6 h after administration of ozanimod 0·25 mg on day 1 was –1·8 bpm at 5 h; no participant had a heart rate less than 45 bpm. No TEAEs of second-degree or third-degree atrioventricular block occurred during the study. One participant with a predose supine heart rate of 76 bpm was reported as having symptomatic bradycardia (headache) after the initial dose of ozanimod 0·25 mg, but there was no evidence of bradycardia on heart rate monitoring (lowest supine heart rate 71 bpm); the participant remained in the study. One participant with a baseline heart rate of 60 bpm and lowest heart rate of 50 bpm at 6 h had extended monitoring, during which a serious TEAE of asymptomatic sinus bradycardia was reported; the event resolved.

The proportion of participants with an infection was similar across treatment groups (range 26·7–28·9%). The incidence of herpes infections (oral herpes, herpes zoster, herpes simplex, or herpes virus infection) was low and similar across treatment groups (four [0·9%] with ozanimod 1·0 mg; three [0·7%] with ozanimod 0·5 mg; and five [1·1%] with interferon beta-1a). The herpes zoster cases were in a single dermatome and mild (one case in each ozanimod group) or moderate (one case in the interferon beta-1a group); all cases resolved on treatment and all participants completed the study. No serious opportunistic infections were reported in participants treated with ozanimod.

Mean absolute lymphocyte count (ALC) decreased from baseline at month 3 and remained stable through month 12 in both ozanimod groups (appendix p 26). Mean ALC at month 12 was $0·759\times10^9$ cells per L (SD 0·427; 42·8% of baseline) in the ozanimod 1·0 mg group, $0·963\times10^9$ cells per L (0·461; 54·1% of baseline) in the ozanimod 0·5 mg group, and $1·764\times10^9$ cells per L (0·641; 97·7% of baseline) in the interferon beta-1a group. Mean minimum ALC at any time point was $0·557\times10^9$ cells per L (SD 0·290) in the ozanimod 1·0 mg group, $0·755\times10^9$ cells per L (0·351) in the ozanimod 0·5 mg group, and $1·324\times10^9$ cells per L (0·498) in the interferon beta-1a group. 11 (2·5%) participants, all treated with ozanimod 1·0 mg, had an ALC of less than $0·2\times10^9$ cells per L after baseline (appendix p 26); none were associated with serious or opportunistic infections.

Alanine aminotransferase increase to at least three times the ULN occurred in 19 (4·3%) of 447 participants treated with ozanimod 1·0 mg, eight (1·8%) of 453 treated with ozanimod 0·5 mg, and ten (2·2%) of 445 treated with interferon beta-1a (appendix p 25). Most TEAEs related to alanine aminotransferase increase were transient and resolved without study drug discontinuation. Four (0·9%) participants treated with ozanimod 1·0 mg, one (0·2%) treated with ozanimod 0·5 mg, and one (0·2%) treated with interferon beta-1a had TEAEs of hepatobiliary dysfunction or related investigations that led to discontinuation of study drug (appendix pp 24–25).

Macular oedema was reported as a TEAE in one (0·2%) participant in the ozanimod 1·0 mg group and one (0·2%) participant in the interferon beta-1a group; cystoid macular oedema was reported in one (0·2%) participant in the ozanimod 0·5 mg group. The expert review panel confirmed two cases of macular oedema, both with predisposing factors: one participant in the ozanimod 0·5 mg group had macular oedema secondary to ocular trauma; and the baseline optical coherence tomography of one participant in the ozanimod 1·0 mg group showed evidence of previous intraocular inflammation in the affected eye.

A low incidence of pulmonary-specific TEAEs was observed across treatment groups without association to pulmonary function test findings; no participants discontinued study drug because of these events. Malignancies occurred in one (0·2%) participant in the ozanimod 1·0 mg group (testicular seminoma; diagnosed on study day 51), two (0·4%) in the ozanimod 0·5 mg group (invasive breast cancer and basal cell carcinoma), and none in the interferon beta-1a group. The incidence of TEAEs of depression was low and balanced across groups, with no reported suicide attempts or ideation.

Discussion

In SUNBEAM, relapsing multiple sclerosis participants randomly assigned to receive ozanimod had significantly lower ARRs and new or enlarging T2 and gadolinium-enhancing lesion counts on brain MRI compared with participants randomly assigned to receive interferon beta-1. The study was adequately powered with a sufficient sample size to assess the primary efficacy endpoint. Although this study was not designed to show a difference between ozanimod doses, ARR and new or enlarging T2 and gadolinium-enhancing lesion counts were numerically lower with ozanimod 1·0 mg than with ozanimod 0·5 mg. Demographics and baseline characteristics in the overall study population were consistent with the populations of other phase 3 studies in patients with clinically active relapsing multiple sclerosis,[21–28] except that participants from eastern Europe were over-represented in SUNBEAM.

Ozanimod 1·0 mg demonstrated smaller losses of whole brain volume, cortical grey matter volume, and thalamic volume at month 12 relative to interferon beta-1a. To our knowledge, SUNBEAM and RADIANCE phase 3[15] (reported separately), are the first reports of reductions in cortical grey matter and thalamic volume loss in a phase 3 study of a multiple sclerosis intervention. The observed slowing of brain volume loss suggests that ozanimod might protect against structural changes associated with disease progression over time. This hypothesis is supported by improvements in measures of cognition and physical function that contribute to patients' overall quality of life. Although the clinical relevance of our findings requires further exploration, losses in brain volume, including whole brain volume, cortical grey matter, and thalamic volume, correlate with the long-term disability progression and cognitive impairment shown in other studies.[29,30]

Mean change in SDMT Z score was numerically greater (nominal $p<0·05$) in both ozanimod groups versus interferon beta-1a, suggesting potential beneficial effects on cognitive processing speed. Although the MSFC was originally designed to include the paced auditory serial addition test as an assessment of cognitive processing, the SDMT is considered an acceptable alternative that is at least as sensitive, if not more so.[31] SDMT has been used as an assessment of cognitive processing speed in studies of patients with multiple sclerosis versus healthy controls and in studies of other disease-modifying therapies for multiple sclerosis.[32,33]

Ozanimod was well tolerated, with a lower incidence of TEAEs than interferon beta-1a. The incidence of serious TEAEs was low and similar across treatment groups. No clinically significant bradycardia or second-degree or third-degree atrioventricular block were observed during dose escalation in the ozanimod-treated participants. The incidence of infections was similar for participants who received ozanimod and those who received interferon beta-1a; no serious opportunistic infections occurred in ozanimod-treated participants. ALC less than $0·2\times10^9$ cells per L occurred in 2·5% of participants (all in the ozanimod 1·0 mg group) at least once during the study; no serious or opportunistic infections were reported when ALC was less than $0·2\times10^9$ cells per L. Although transaminase increases of three or more times the ULN were more common with ozanimod 1·0 mg than the other groups, the incidence was low across all groups, asymptomatic, and resolved on treatment in all but two participants who discontinued the study drug.

The results of this larger and longer trial confirm the efficacy and tolerability of ozanimod in participants with active relapsing multiple sclerosis, as observed in the RADIANCE phase 2 trial.[14] Direct comparison to an immunomodulator approved for the treatment of relapsing multiple sclerosis provides important information to clinicians when considering therapeutic options. Nearly all SUNBEAM participants were white, and most were of eastern European descent, which might limit generalisability; however, geographic region was adjusted for in the statistical analyses. Subgroup analyses for eastern Europe versus the rest of the world were done; however, because few participants were from outside eastern Europe, the CIs were wide, prohibiting any clear conclusions. The 12-month duration is insufficient to assess long-term safety. Additional studies are needed to draw conclusions on those efficacy and safety outcomes requiring longer drug exposures. The 24-month RADIANCE phase 3 trial[15] and an ongoing open-label extension study allow further analysis of efficacy and safety of ozanimod.

In SUNBEAM, treatment of participants with relapsing multiple sclerosis with ozanimod for at least 12 months more effectively reduced active disease based on relapses and MRI lesion counts compared with interferon beta-1a. Ozanimod 1·0 mg consistently provided numerically greater efficacy than ozanimod 0·5 mg. Both doses were well tolerated. These findings provide support for ozanimod as an oral therapy for individuals with relapsing multiple sclerosis.

Contributors

All authors contributed to the study concept and design, acquisition, analysis, or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors vouch for data accuracy, reviewed all drafts, and approved the final manuscript. KR and ND did the statistical analysis.

Declaration of interests

GC has received compensation for consulting or speaking activities from Almirall, Biogen, Celgene Corporation, Excemed, Forward Pharma, Merck, Novartis, Roche, Sanofi, Genzyme, and Teva. LK's institution (University Hospital Basel) has received the following, which was used exclusively for research support: steering committee, advisory board, and consultancy fees (Actelion, Addex, Bayer, Biogen, Biotica, Celgene Corporation, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Sanofi, Santhera, Siemens, Teva, UCB, and Xenoport); speaker fees (Bayer, Biogen, Merck, Novartis, Sanofi, and Teva); support for educational activities (Bayer, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, and Teva); license fees for Neurostatus products; and grants (Bayer, Biogen, European Union, Merck, Novartis, Roche, Swiss Multiple Sclerosis Society, and Swiss National Research Foundation). KWS has served as a consultant for Biogen, Celgene Corporation, Genzyme, Merck, Novartis, Ono Pharma, Roche, Synthon, and Teva. AB-O has received personal compensation for consulting from Biogen, Celgene Corporation, EMD Serono, Genzyme, MedImmune, Novartis, and Roche. DLA has received personal fees for consulting from Acorda, Biogen, Celgene Corporation, MedImmune, Mitsubishi Pharma, Novartis, Roche, and Sanofi; grants from Biogen and Novartis; and holds an equity interest in NeuroRx Research. LS has served as a consultant for AbbVie, Atreca, Celgene Corporation, Novartis, Teva, Tolerion, and EMD Serono and has received research support from Atara, Biogen, and Celgene Corporation. H-PH has received fees for consulting, serving on steering committees, and speaking from Bayer, Biogen, GeNeuro, Genzyme, Merck, MedImmune, Novartis, Octapharma, Opexa, Roche, Sanofi, and Teva. XM has received speaking honoraria and travel expenses for scientific meetings or has participated in steering committees or in advisory boards for clinical trials with Almirall, Bayer Schering Pharma, Biogen, Genentech, Genzyme, GlaxoSmithKline, Merck Serono, MS International Federation, National Multiple Sclerosis Society, Novartis, Roche, Sanofi-Aventis, and Teva, and is editor for Clinical Cases for *Multiple Sclerosis Journal*. EKH has received personal compensation for consulting and speaking for Actelion, Biogen, Celgene Corporation, Merck, Novartis, Roche, Sanofi, and Teva and is supported by Czech Ministry of Education, project PROGRES Q27/LF1. BACC has

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Data sharing

Celgene is committed to responsible and transparent sharing of clinical trial data with patients, health-care practitioners, and independent researchers to improve scientific and medical knowledge as well as foster innovative treatment approaches. For more information, please visit the Celgene website.

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

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