Sphingosine 1-phosphate receptor modulator therapy for multiple sclerosis: differential downstream receptor signaling and clinical profile effects

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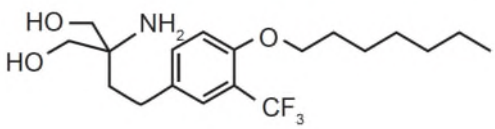
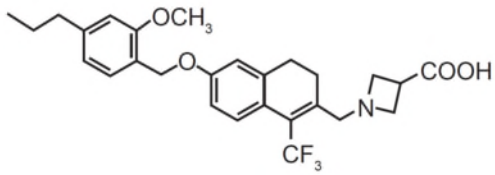
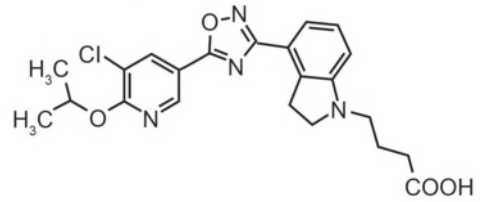
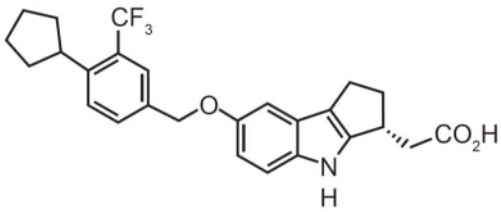
Online Resource Table 1 Sphingosine 1-phosphate receptor (S1PR) modulator structures, receptor subtype interactions and summary of S1PR modulator pharmacokinetics and pharmacodynamics.

	S1PR subtype interaction	Prodrug (requires phosphoryl-ation *in vivo*)	t_{max} (h)	Time to lymphocyte count reduction (h)	Lymphocyte decrease from baseline (%)	$t_{½}$ (h)	Time to lymphocyte count recovery after treatment discontinuation (days)
Amiselimod (MT-1303) [1,2] 	$S1PR_1$ $S1PR_4$ $S1PR_5$	Yes	12–16	N/A	60–66	380–420	49
Ceralifimod (ONO-4641) [3,4] 	$S1PR_1$ $S1PR_5$	No	4–6	N/A	8–56	82–89	N/A
GSK2018682 [2,3] 	$S1PR_1$	No	4–9	6–16	28–76	48–63	1–6

Etrasimod (APD334) [5] 	$S1PR_1$ $S1PR_4$ $S1PR_5$	No	N/A	N/A	N/A	N/A	N/A

N/A, not available; t_{max} time to maximum plasma concentration; $t_{½}$ elimination half-life

Data from:

1. Sugahara *et al*. 2016.
2. Comi *et al*. 2017.
3. Vogt & Stark 2017.
4. Krösser *et al*. 2015.
5. Buzard *et al*. 2014.

Online Resource Table 2. Clinical trial safety summary

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
Fingolimod								
FREEDOMS	Similar proportions of patients with at least one AE were reported in the three groups, *n* (%): Placebo, 387 (92.6%) Fingolimod 0.5 mg, 401 (94.4%) Fingolimod 1.25 mg, 404 (94.2%)	Any SAE, *n* (%): Placebo, 56 (13.4%) Fingolimod 0.5 mg, 43 (10.1%) Fingolimod 1.25 mg, 51 (11.9%) Three deaths were reported, *n* (%): Placebo, 2 (0.5%), pulmonary embolism and traffic accident Fingolimod 1.25 mg, 1 (0.2%), suicide Relationship to study drug	AEs causing study drug discontinuation, *n* (%): Placebo, 32 (7.7%) Fingolimod 0.5 mg, 32 (7.5%) Fingolimod 1.25 mg, 61 (14.2%)	Transient, dose-dependent reduction in heart rate developed 4–5 h after first dose Maximal decreases in heart rate, mean: Fingolimod 0.5 mg, 8 bpm after 5 h Fingolimod 1.25 mg, 10 bpm after 4 h Bradycardia, *n* (%): Placebo, 3 (0.7%) Fingolimod 0.5 mg, 9 (2.1%) Fingolimod 1.25 mg, 14 (3.3%)	Alanine aminotransferase levels ≥3 times the upper limit of normal %: Placebo, 1.7% Fingolimod 0.5 mg, 8.5% Fingolimod 1.25 mg, 12.5%	Macular edema was diagnosed in seven patients, all in the fingolimod 1.25 mg group, three of these cases were reported as SAEs Mean visual acuity and central foveal thickness remained stable in all patients throughout the study	Overall incidence of infection was similar in the fingolimod and placebo groups, in the range 69–72% Similar incidences of URTI and LRTI were seen in the three groups (48–50.5% and 6–11.4%, respectively). The same was true of influenza (9.3–12.9%), herpes virus (5.8–8.7%) and UTI (4.9–11.2%) Serious infections occurred in 1.6–2.6% of patients The only serious infection occurring in more than one patient in a group was UTI, with two	Malignant neoplasms, *n* (%): Placebo, 10 (2.2%) Fingolimod 0.5 mg, 4 (0.9%) Fingolimod 1.25 mg, 4 (0.8%)

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
		unlikely but not discussed		In the fingolimod groups, 20/23 bradycardia cases occurred after first dose. Six cases were symptomatic. All resolved within 24 h. All except two resolved without treatment Second-degree AV block was a rare AE; one in the placebo group, one in the fingolimod 1.25 mg group Asymptomatic cases on day 1: Fingolimod 0.5 mg, *n* = 1 Fingolimod 1.25 mg, *n* = 4 No significant effect on heart rate or AV conduction was			cases reported in the fingolimod 0.5 mg group	

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
				observed with continued fingolimod use				
FREEDOMS extension NCT00662649	Similar proportions of patients with at least one AE were reported in the four groups, *n* (%): Placebo-fingolimod 0.5 mg, 148 (95.5%) Placebo-fingolimod 1.25 mg, 133 (91.7%) Continuous fingolimod 0.5 mg, 314 (94.9%) Continuous fingolimod 1.25 mg, 272 (94.1%)	Any SAE, *n* (%): Placebo-fingolimod 0.5 mg, 11 (7.1%) Placebo-fingolimod 1.25 mg, 17 (11.7%) Continuous fingolimod 0.5 mg, 31 (9.4%) Continuous fingolimod 1.25 mg, 31 (10.7%) There were no deaths	AEs causing study drug discontinuation, *n* (%): Placebo-fingolimod 0.5 mg, 14 (9.0%) Placebo-fingolimod 1.25 mg, 14 (9.7%) Continuous fingolimod 0.5 mg, 15 (4.5%) Continuous fingolimod 1.25 mg, 16 (5.5%)	Transient decrease in heart rate and delayed AV conduction in patients in the switch groups on fingolimod initiation Symptomatic first-dose bradycardia in two patients: one with severe dizziness; one with a mild feeling of cold Transient episode of second-degree AV block on day 1 of therapy in one patient who was asymptomatic	Elevated alanine aminotransferase, *n* (%): Placebo-fingolimod 0.5 mg, 9 (5.8%) Placebo-fingolimod 1.25 mg, 16 11.0%) Continuous fingolimod 0.5 mg, 11 (3.3%) Continuous fingolimod 1.25 mg, 10 (3.5%)	Macular edema was diagnosed in three patients, one each in the placebo-fingolimod 0.5 mg group and the continuous fingolimod 0.5 mg and 1.25 mg group None was classified as serious	Overall incidence of infection was similar across the groups, in the range 69–73% Specific infections also occurred at similar rates across the groups: Nasopharyngitis, 25.4–28.4% URTI, 13.5–17.5% Influenza, 6.2–10.4% Herpes virus, 9.0–12.1%	Benign, malignant and unspecified neoplasms, *n* (%): Placebo-fingolimod 0.5 mg, 2 (1.3%) Placebo-fingolimod 1.25 mg, 3 (2.1%) Continuous fingolimod 0.5 mg, 7 (2.1%) Continuous fingolimod 1.25 mg, 5 (1.7%) There were two cases of uterine leiomyoma in the continuous fingolimod 0.5 mg group

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
TRANSFORMS	Similar proportions of patients with at least one AE were reported in the three groups Any AE, *n* (%): IFN β-1a, 395 (91.6%) Fingolimod 0.5 mg, 369 (86.0%) Fingolimod 1.25 mg, 380 (90.5%)	SAEs occurred most frequently in the fingolimod 1.25 mg group; bradycardia and AV block were the most common Most were asymptomatic and only reported as SAEs because symptoms did not resolve within 6 h of first dose All SAEs other than bradycardia and AV block in the fingolimod 1.25 mg group	Discontinuation due to AEs, *n* (%): IFN β-1a, 16 (3.7%) Fingolimod 0.5 mg, 24 (5.6%) Fingolimod 1.25 mg, 42 (10%)	Transient, dose-dependent reduction in heart rate developed within 1 h of first-dose fingolimod, consistent with previous trials Maximal decreases in heart rate occurred 4 –5 h after first dose, mean: Fingolimod 0.5 mg, 8 bpm Fingolimod 1.25 mg, 12 bpm All started to attenuate within 6 h Symptomatic bradycardia (mild-to-moderate), *n* (%):	Alanine aminotransferase levels ≥3 times the upper limit of normal, *n* (%): IFN β-1a, 10 (2%) Fingolimod 0.5 mg, 36 (8%) Fingolimod 1.25 mg, 29 (7%)	Macular edema, *n* (%): Fingolimod 0.5 mg, 2 (0.5%) Fingolimod 1.25 mg, 4 (1%) Macular edema was asymptomatic in three of these patients Mean visual acuity and retinal thickness were similar across the study groups and remained stable over the study period	Percentage of patients with an infection that occurred in more than 5% of patient in any study group: IFN β-1a, 42% Fingolimod 0.5 mg, 42.7% Fingolimod 1.25 mg, 48.6% Percentage of patients with a serious infection that occurred in at least two patients in any study group: IFN β-1a, 0.7% Fingolimod 0.5 mg, 0.2% Fingolimod 1.25 mg, 1.2% Overall incidence of infection was	Basal cell carcinoma, *n* (%): IFN β-1a, 1 (0.2%) Fingolimod 0.5 mg, 3 (0.7%) Fingolimod 1.25 mg, 2 (0.5%) Melanoma, *n* (%): IFN β-1a, 0 (0.0%) Fingolimod 0.5 mg, 3 (0.7%) Fingolimod 1.25 mg, 0 (0.0%) Breast cancer, *n* (%): IFN β-1a, 0 (0.0%)

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
		occurred in <1% of any study group Any SAE, *n* (%): IFN β-1a, 25 (5.8%) Fingolimod 0.5 mg, 30 (7.0%) Fingolimod 1.25 mg, 45 (10.7%) Two deaths occurred on study in the fingolimod 1.25 mg group, one due to varicella zoster infection, the other due to herpes simplex encephalitis		Fingolimod 0.5 mg, 3 (0.7%) Fingolimod 1.25 mg, 4 (0.9%) All resolved within 24 h without treatment Second-degree AV block reported on first day of treatment: Fingolimod 1.25 mg, 3 (0.7%) Fingolimod 0.5 mg, 1 (0.2%) No significant effect on heart rate or AV conduction was observed with continued administration of drug			similar across the study groups	Fingolimod 0.5 mg, 2 (0.5%) Fingolimod 1.25 mg, 2 (0.5%)

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
FREEDOMS II	Similar proportions of patients with at least one AE were reported in the three groups, *n* (%): Placebo, 343 (97%) Fingolimod 0.5 mg, 350 (98%) Fingolimod 1.25 mg, 359 (97%)	Similar proportions of patients with at least one SAE were reported in the three groups, *n* (%): Placebo, 45 (13%) Fingolimod 0.5 mg, 53 (15%) Fingolimod 1.25 mg, 53 (14%)	AEs causing study drug discontinuation, *n* (%): Placebo, 37 (10%) Fingolimod 0.5 mg, 66 (18%) Fingolimod 1.25 mg, 72 (20%)	Most patients were discharged after 6 h of first-dose observation. Patients requiring extended observation, *n* (%): Placebo, 8 (2%) Fingolimod 0.5 mg, 52 (15%) Fingolimod 1.25 mg, 70 (19%) Most first-dose monitoring events were asymptomatic, did not require treatment and resolved within 24 h of onset Patients with bradycardia at first dose, *n* (%):	Asymptomatic increases in liver enzyme levels, mainly alanine aminotransferase, occurred in a dose-dependent manner Patients with increased alanine aminotransferase, *n* (%): Placebo, 6 (2%) Fingolimod 0.5 mg, 29 (8%) Fingolimod 1.25 mg, 35 (10%) Patients with alanine aminotransferase increases >5 times the upper limit of normal, *n* (%): Placebo, 4 (1%) Fingolimod 0.5 mg, 8 (2%) Fingolimod 1.25 mg, 7 (2%)	Macular edema, *n* (%): Placebo, 2 (1%) Fingolimod 0.5 mg, 3 (1%) Fingolimod 1.25 mg, 4 (1%). Four of the macular edema cases were SAEs: Placebo, 1 (<0.5%) Fingolimod 0.5 mg, 1 (<0.5%) Fingolimod 1.25 mg, 2 (<0.5%) The proportions of patients with	All infections, *n* (%): Placebo, 255 (72%) Fingolimod 0.5 mg, 263 (74%) Fingolimod 1.25 mg, 269 (73%) The most common infections were URTIs, UTIs, nasopharyngitis, and sinusitis, with similar incidences across treatment groups Certain infections occurred in more patients in the fingolimod groups than in the placebo group: Bronchitis (8–9% vs 6%), influenza (7–10% vs 7%) and herpes virus (8–10% vs 5%)	Most malignancies were involving the skin with basal cell carcinoma being the most common, *n* (%): Placebo, 2 (1%) Fingolimod 0.5 mg, 10 (3%) Fingolimod 1.25 mg, 6 (2%) Other malignancies occurred with a similarly low frequency. All neoplasms, *n* (%): Placebo, 8 (2%) Fingolimod 0.5 mg, 13 (4%)

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
				Placebo, 1 (<0.5%), symptomatic Fingolimod 0.5 mg, 5 (1%), three were symptomatic Fingolimod 1.25 mg, 21 (6%), 15 were symptomatic Second-degree AV block, one case in the fingolimod 1.25 mg group (<0.5%). No cases of Mobitz type II AV block reported Decrease in mean heart rate with maximum decreases in heart rate at 5 h post first dose, bpm (SD): Fingolimod 0.5 mg, 8.5 bpm (7.84)		changes from baseline in central foveal thickness greater than 20 μm were similar across the study groups	UTIs were slightly more common in the placebo group (13–15% vs 17%) Herpes zoster infections were slightly more common in the fingolimod groups, *n* (%): Placebo, 3 (1%) Fingolimod 0.5 mg, 9 (3%) Fingolimod 1.25 mg, 12 (3%)	Fingolimod 1.25 mg, 14 (4%)

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
				Fingolimod 1.25 mg, 12.4 bpm (8.41) No major or consistent changes in left ventricular ejection fraction were observed in any treatment group				
INFORMS NCT00731692	Similar proportions of patients with at least one AE were reported in the two groups, *n* (%): Fingolimod 0.5 mg, 324 (96%) Placebo, 463 (95%)	Any SAE, *n* (%): Fingolimod 0.5 mg, 84 (25%) Placebo, 117 (24%) There were five deaths: 2 of 147 (1%) randomized to fingolimod 1.25 mg (respiratory tract infection; aspiration pneumonia)	AEs causing study drug discontinuation, *n* (%): Fingolimod 0.5 mg, 52 (15%) Placebo, 36 (7%)	Cardiac conduction abnormalities at first dose were in line with results from studies in RRMS Bradycardia: fingolimod 0.5 mg, 5 (1%); placebo, 1 (<1%) First-degree AV block: fingolimod 0.5 mg, 3 (1%); placebo, 6 (1%) Second-degree AV block: fingolimod	Elevated alanine aminotransferase , *n* (%): Fingolimod 0.5 mg, 39 (12%) Placebo, 9 (2%)	Macular edema, *n* (%): Fingolimod 0.5 mg, 6 (2%) Placebo, 6 (1%)	Rates of infection were in line with results from studies in RRMS Nasopharyngitis, fingolimod 0.5 mg, 78 (23%); placebo, 135 (28%) UTI, fingolimod 0.5 mg, 50 (15%); placebo, 79 (16%) URTI, fingolimod 0.5 mg, 37 (11%); placebo, 58 (12%) Influenza, fingolimod	Rates of neoplasms were in line with results from studies in RRMS Basal cell carcinoma, fingolimod 0.5 mg, 14 (4%); placebo, 9 (2%) Squamous cell carcinoma fingolimod 0.5 mg, 6 (2%); placebo, 1 (<1%)

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
		1 of 336 (<1%) on fingolimod 0.5 mg group (metastatic lung cancer) 2 of 487 (<1%) in the combined placebo group (convulsion, pulmonary embolism)		0.5 mg, 1 (<1%); placebo, 0 (0%) Syncope or presyncope: fingolimod 0.5 mg, 7 (2%); placebo, 9 (2%)			0.5 mg, 29 (9%); placebo, 43 (9%) Pneumonia/ broncho-pneumonia, fingolimod 0.5 mg, 6 (2%); placebo, 8 (2%) Herpes zoster, fingolimod 0.5 mg, 10 (3%); placebo, 9 (2%)	
Ponesimod								
AC-058B201	Patients with ≥1 AE, *n* (%), total number of AEs: Placebo, 90 (74.4%), 310 Ponesimod 10 mg, 83 (76.9%), 275 Ponesimod 20 mg, 88 (77.2%), 304 Ponesimod 40 mg, 88 (73.9%), 325	Patients with ≥1 SAE, *n* (%), total number of SAEs: Placebo, 5 (4.1%), 5 Ponesimod 10 mg, 7 (6.5%), 10 Ponesimod 20 mg, 7 (6.1%), 8	Discontinuations due to infections: Placebo, 1 (measles) Ponesimod 10 mg, 1 (ear infection) Ponesimod 40 mg, 1 (sinusitis) Nine patients (2.6%) receiving ponesimod discontinued owing to cardiac AEs:	Cardiac AEs with ponesimod at first dose: First-degree AV block (1.2%) Second-degree AV block (0.9%; no cases of Mobitz type II) Bradycardia (2%) All AEs relating to heart rate and rhythm occurred on day	Hepatic effects observed in the ponesimod treatment groups included liver transaminase increases >3 times the upper limit of normal: Ponesimod 10 mg, 2.8% Ponesimod 20 mg, 4.5% Ponesimod 40 mg, 4.2%	Four macular edema cases were reported, all starting within 3 months of treatment initiation Two cases were reported as SAEs in the ponesimod 20 mg group (1.8% of patients in	The proportions of patients with ≥1 infection-associated AE were similar across the four groups: Placebo, 45.5% Ponesimod 10 mg, 37.0% Ponesimod 20 mg, 32.5% Ponesimod 40 mg, 36.1%	Breast cancer: Ponesimod 10 mg, *n* = 1 Cervix carcinoma: Placebo, *n* = 1

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
	AEs with a higher incidence in ponesimod groups compared with placebo: anxiety, dizziness, dyspnea, increased alanine aminotransferase levels, influenza, insomnia and peripheral edema	Ponesimod 40 mg, 3 (2.5%), 4	Ponesimod groups, 9 (2.6%) Placebo, 0 (0%) In eight of these patients, the onset of cardiac AEs was on day 1, with discontinuations usually occurring during the first 2 weeks Two cases of a macular edema SAE with ponesimod 20 mg resulted in treatment discontinuation Discontinuations due to respiratory criteria: Placebo, *n* = 1 Ponesimod 40 mg, *n* = 2 Discontinuations due to dyspnea: Ponesimod groups, *n* = 7, with	1 when receiving ponesimod 10 mg; all resolved spontaneously and without recurrence Maximum reductions in heart rate occurred at 2–3 h post dose, and returned to baseline by 6 h Up-titration of ponesimod caused small heart rate changes similar to those observed in the placebo group	Placebo, no cases	the group, only one confirmed by optical coherence tomography) and resolved after treatment discontinuation Two cases were reported as AEs: 1 each in the ponesimod 20 mg group (0.9%) and the placebo group (0.8%). Both resolved during study treatment		

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
			6 in the 40 mg group					
Siponimod								
BOLD study	Any AEs over 3 months, *n* (%): Placebo, 13 (81%) Siponimod 0.25 mg, 38 (74%) Siponimod 1.25 mg, 29 (69%) Any AEs over 6 months, *n* (%): Placebo, 36 (80%) Siponimod 0.5 mg, 37 (86%) Siponimod 2 mg, 48 (98%)	Any SAEs over 3 months, *n* (%): Placebo, 0 (0%) Siponimod 0.25 mg, 0 (0%) Siponimod 1.25 mg, 2 (5%) Any SAEs over 6 months, *n* (%): Placebo, 0 (0%) Siponimod 0.5 mg, 8 (19%) Siponimod 2 mg, 4 (8%)	Any AEs leading to discontinuation over 3 months, *n* (%): Placebo, 0 (0%) Siponimod 0.25 mg, 1 (2%) Siponimod 1.25 mg, 1 (2%) Any AEs leading to discontinuation over 6 months, *n* (%): Placebo, 2 (4%) Siponimod 0.5 mg, 5 (12%) Siponimod 2 mg, 6 (12%) Siponimod 10 mg, 10 (20%) Cardiac AEs caused discontinuation of	Dose-dependent decrease in heart rate observed at first dose in patients in whom treatment was initiated without dose titration. Maximum decrease in heart rate was reached after approximately 3 h and returned to placebo levels within 24 h First-degree AV block: Siponimod, *n* = 4 Second-degree (Mobitz I) AV block: Siponimod, *n* = 13	Increased alanine aminotransferase, aspartate transaminase and gamma glutamyltransferase concentrations were reported more frequently in the siponimod treatment groups than in the placebo group AEs of alanine aminotransferase increases, over 3 months, *n* (%): Placebo, 0 (0%) Siponimod 0.25 mg, 1 (2%) Siponimod 1.25 mg, 1 (2%) AEs of alanine aminotransferase increases, over 6 months *n* (%):	One patient with a history of uveitis developed macular edema with siponimod 10 mg, but this was not classified as an AE	Reported infection AEs, *n* (%). UTIs over 3 months: Placebo, 0 (0%) Siponimod 0.25 mg, 1 (2%) Siponimod 1.25 mg, 3 (7%) UTIs over 6 months: Placebo, 2 (4%) Siponimod 0.5 mg, 2 (5%) Siponimod 2 mg, 2 (4%) Siponimod 10 mg, 2 (4%) URTIs over 3 months:	A patient in the siponimod 0.5 mg group had a basal cell carcinoma diagnosed and completed 6 months of treatment

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
	Siponimod 10 mg, 48 (96%) The most frequent AEs across all groups were headache, bradycardia, dizziness and nasopharyngitis	Siponimod 10 mg, 3 (6%) SAEs occurring in ≥2 patients in the same treatment group, *n* (%): Siponimod 2 mg, second-degree AV block, 3 (6%) One death reported in a patient 27 days after discontinuing treatment from the siponimod 1.25 mg group on day 52 owing to chest pain. The patient was a 43-year-old man, a smoker with a family history of heart disease	siponimod in eight patients (3.4% of the 235 patients receiving siponimod)	Placebo, *n* = 1 Second-degree 2:1 AV block: Siponimod, *n* = 5 Most AV events occurred in the siponimod 10 mg and 2 mg groups. No patients had Mobitz type II AV block Bradycardia on day 1, *n* (%): Siponimod 0.5 mg, 2 (5%) (one was recorded as an SAE) Siponimod 2 mg, 3 (6%) Siponimod 10 mg, 14 (28%) Second-degree AV block AEs	Placebo, 0 (0%) Siponimod 0.5 mg, 0 (0%) Siponimod 2 mg, 4 (8%) Siponimod 10 mg, 3 (6%)		Placebo, 0 (0%) Siponimod 0.25 mg, 0 (0%) Siponimod 1.25 mg, 1 (2%) URTIs over 6 months: Placebo, 7 (16%) Siponimod 0.5 mg, 3 (7%) Siponimod 2 mg, 4 (8%) Siponimod 10 mg, 2 (4%) Incidence of infections was not clearly related to dose	

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
		One myocardial infarction suspected to be related to the study drug occurred in a 42-year-old male who smoked, 45 days after the last dose of study drug (siponimod 10 mg) One suicide attempt occurred via an intentional overdose (siponimod 2 mg group, 41 mg overdose), without serious signs of toxicity		associated with symptomatic bradycardia, *n* = 5: Siponimod 10 mg, *n* = 2 Siponimod 2 mg, *n* = 3 All but one were classified as SAEs; all occurred approximately 2 h after the first dose, and recovered within 24 h Second-degree AV block AEs in placebo group, *n* = 2				
EXPAND study	Any AE, *n* (%) Placebo, 445 (82%)	Any SAE, *n* (%) Placebo, 83 (15%)	Non-serious AE leading to discontinuation, *n* (%) Placebo, 15 (3%)	Bradycardia during treatment initiation, *n* (%)	SAE of alanine aminotransferase increased, *n* (%) Placebo, 2 (<1%)	Macular edema, *n* (%) Placebo, 1 (<1%)	Infections and infestations (SOC), *n* (%) Placebo, 268 (49%)	Rates of malignancies, including basal cell carcinoma, were similar in the two

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
	Siponimod, 975 (89%) The most frequent AEs were headache, nasopharyngitis, UTIs and falls, being reported in more than 10% of patients in both groups	Siponimod, 197 (18%) Four deaths occurred in each treatment group Deaths in the siponimod group were due to: metastatic gastrointestinal melanoma within 4 months of commencing siponimod; septic shock in a patient with terminal colon cancer; urosepsis more than 10 weeks after discontinuation of siponimod and after two doses of rituximab; and suicide	Siponimod, 48 (4%) SAE leading to discontinuation, *n* (%) Placebo, 13 (2%) Siponimod, 36 (3%)	Placebo, 14 (3%) Siponimod, 48 (4%) Bradyarrhythmia (including conduction defects and disorders of sinus node function) during treatment initiation, *n* (%) Placebo, 2 (0.4%) Siponimod, 29 (3%) Sinus bradycardia during treatment initiation, *n* (%) Placebo, 1 (<1%) Siponimod, 14 (1%) No cases of Mobitz type II or	Siponimod, 10 (1%) SAE of aspartate aminotransferase increased, *n* (%) Placebo, 1 (<1%) Siponimod, 5 (<1%)	Siponimod, 18 (2%)	Siponimod, 539 (49%) Herpes viral infections, *n* (%) Placebo, 15 (3%) Siponimod, 53 (5%) Herpes zoster, *n* (%) Placebo, 4 (1%) Siponimod, 25 (2%) One case of herpes zoster meningitis was reported in the siponimod group	treatment groups

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
		One additional patient withdrew consent from the study with metastatic lung carcinoma, having been on siponimod for 11 months; this patient died (unspecified reason) about 5 months after discontinuing study medication Deaths in the placebo group were due to hemorrhagic stroke, lung cancer, gastric cancer and for an unknown reason		high-degree AV block were observed during double-blind treatment				
Ozanimod								

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
RADIANCE (phase 2)	Any AE, *n* (%): Placebo, 52 (59%) Ozanimod 0.5 mg, 57 (66%) Ozanimod 1 mg, 47 (57%) Any AE judged as possibly related to treatment, *n* (%): Placebo, 11 (13%) Ozanimod 0.5 mg, 19 (22%) Ozanimod 1 mg, 15 (18%) Most common AEs in ozanimod-treated	Any SAE, *n* (%): Placebo, 0 (0%) Ozanimod 0.5 mg, 3 (3%) Ozanimod 1 mg, 0 (0%) The three SAEs were optic neuritis (attributed to underlying multiple sclerosis) Somatoform autonomic dysfunction (related to anxiety/ stress) Uterine cervical squamous metaplasia (secondary to human papilloma virus on	No discontinuations occurred due to an AE	No notable cardiovascular AEs were recorded. The most common cardiovascular AE was orthostatic hypotension, with 6 of the 9 events occurring on day 1 and resolving spontaneously without intervention No reduction in heart rate greater than 2 bpm was seen with ozanimod in the first 6 h Second-degree AV block type 1 was seen in two patients receiving placebo (2%) and four patients (2%) with ozanimod	Alanine aminotransferase level increases >3 times the upper limit of normal, *n* (%): Placebo, 0 (0%) Ozanimod 0.5 mg, 2 (2%) Ozanimod 1 mg, 1 (1%) All resolved despite continuing treatment	No cases of macular edema were noted	No notable infectious AEs were recorded	No notable malignancy-related AEs were recorded

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
	patients, *n* (%): Nasopharyngitis: Placebo, 12 (14%) Ozanimod 0.5 mg, 11 (13%) Ozanimod 1 mg, 5 (6%) Headache: Placebo, 8 (9%) Ozanimod 0.5 mg, 5 (6%) Ozanimod 1 mg, 3 (4%) UTI: Placebo, 2 (2%) Ozanimod 0.5 mg, 6 (7%) Ozanimod 1 mg, 2 (2%)	planned conization procedure)		No cases of second-degree type 2 or third-degree AV block were reported				

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
RADIANCE (phase 3)	Any AE, *n* (%): IFN β-1a, 365 (83.0%) Ozanimod 0.5 mg, 326 (74.3%) Ozanimod 1.0 mg, 324 (74.7%) Any severe AE, *n* (%): IFN β-1a, 19 (4.3%) Ozanimod 0.5 mg, 19 (4.3%) Ozanimod 1.0 mg, 15 (3.5%)	Any SAE, *n* (%): IFN β-1a, 28 (6.4%) Ozanimod 0.5 mg, 31 (7.1%) Ozanimod 1.0 mg, 28 (6.5%) One patient in the ozanimod 0.5 mg group died because of accidental drowning, which was considered unrelated to study drug	AE leading to discontinuation, *n* (%) IFN β-1a, 18 (4.1%) Ozanimod 0.5 mg, 14 (3.2%) Ozanimod 1.0 mg, 13 (3.0%)	An AE of symptomatic bradycardia was reported in one patient after the initial ozanimod dose (0.25 mg) No clinically meaningful cardiac AEs considered related to study drug were reported during dose escalation. No ECG findings or AEs of second-degree or third-degree AV block were reported on day 1 or thereafter. Serious cardiac AEs were infrequent and similar across treatment groups, with none reported in the ozanimod 1.0 mg group	Alanine aminotransferase level increases >3 times the upper limit of normal, *n* (%): IFN β-1a, 17 (3.9%) Ozanimod 0.5 mg, 26 (5.9%) Ozanimod 1.0 mg, 29 (6.7%)	Macular edema, *n* (%) IFN β-1a, 2 (0.5%) Ozanimod 0.5 mg, 1 (0.2%) Ozanimod 1.0 mg, 1 (0.2%) Cystoid macular edema was reported in one additional participant (0.2%) receiving ozanimod 0.5 mg	Incidence of infection-related AEs was similar across treatment groups Serious infections were infrequent, and no serious opportunistic infections occurred Herpes zoster, *n* (%) IFN β-1a, 1 (0.2%) Ozanimod 0.5 mg, 2 (0.5%) Ozanimod 1.0 mg, 4 (0.9%)	Malignancies, *n* (%) IFN β-1a, 2 (0.5%) Ozanimod 0.5 mg, 3 (0.7%) Ozanimod 1.0 mg, 4 (0.9%)

Study name	AEs	SAEs	Discontinuation due to AEs	First-dose effects	Liver enzyme elevation	Macular edema	Infections	Malignancies
SUNBEAM	Any AE, *n* (%): IFN β-1a, 336 (75.5%) Ozanimod 0.5 mg, 259 (57.2%) Ozanimod 1.0 mg, 268 (59.8%) Any severe AE, *n* (%): IFN β-1a, 10 (2.2%) Ozanimod 0.5 mg, 10 (2.2%) Ozanimod 1.0 mg, 7 (1.6%)	Any SAE, *n* (%): IFN β-1a, 11 (2.5%) Ozanimod 0.5 mg, 16 (3.5%) Ozanimod 1.0 mg, 13 (2.9%)	AE leading to discontinuation, *n* (%) IFN β-1a, 16 (3.6%) Ozanimod 0.5 mg, 7 (1.5%) Ozanimod 1.0 mg, 13 (2.9%)	No AEs of second-degree or third-degree AV block were reported during the study. An AE of symptomatic bradycardia was reported in one patient after the initial ozanimod dose (0.25 mg), but there was no evidence of bradycardia on heart rate monitoring. One participant had extended monitoring, during which a serious AE of asymptomatic sinus bradycardia was reported; the event resolved	Alanine aminotransferase level increases >3 times the upper limit of normal, *n* (%): IFN β-1a, 10 (2.2%) Ozanimod 0.5 mg, 8 (1.8%) Ozanimod 1.0 mg, 19 (4.3%)	Macular edema, *n* (%) IFN β-1a, 1 (0.2%) Ozanimod 0.5 mg, 0 (0.0%) Ozanimod 1.0 mg, 1 (0.2%) Cystoid macular edema was reported in one participant (0.2%) receiving ozanimod 0.5 mg	The proportions of participants with an infection were similar across treatment groups (26.7%–28.9%) Herpes infections (oral herpes, herpes zoster, herpes simplex, or herpes virus infection), *n* (%) IFN β-1a, 5 (1.1%) Ozanimod 0.5 mg, 3 (0.7%) Ozanimod 1.0 mg, 4 (0.9%) Herpes zoster, *n* (%) IFN β-1a, 1 (0.2%) Ozanimod 0.5 mg, 1 (0.2%) Ozanimod 1.0 mg, 1 (0.2%)	Malignancies, *n* (%) IFN β-1a, 0 (0.0%) Ozanimod 0.5 mg, 2 (0.4%) Ozanimod 1.0 mg, 1 (0.2%)

AE adverse event, *AV* atrioventricular, *BOLD* BAF312 on MRI lesion given once-daily, bpm beats per minute, *ECG* electrocardiogram, *FIRST* fingolimod initiation and cardiac safety trial, *FIRST LATAM* FIRST in Latin American patients, *FREEDOMS* FTY720 research evaluating effects of daily oral therapy in multiple sclerosis, *iDTM* injectable disease-modifying therapy, *IFN* interferon, *PREFERMS* evaluation of patient retention of fingolimod versus currently approved disease-modifying therapy in patients with relapsing–remitting multiple sclerosis, *RADIANCE* safety and efficacy of the selective sphingosine-1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis, *RRMS* relapsing–remitting multiple sclerosis, *SAE* serious adverse event, *SD* standard deviation, *TRANSFORMS* trial assessing injectable interferon versus FTY720 oral in relapsing–remitting multiple sclerosis, *URTI* upper respiratory tract infection, *UTI* urinary tract infection.

Online Resource Table 3. Clinical trial efficacy summary

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
Fingolimod						
FREEDOMS NCT00289978	ARR over 24 months, mean (95% CI): Placebo, 0.40 (0.34–0.47) Fingolimod 1.25 mg, 0.16 (0.13–0.19), *P* < 0.001 vs placebo Fingolimod 0.5 mg, 0.18 (0.15–0.22), *P* < 0.001 vs placebo	Number of Gd+ lesions at 24 months, mean (SD): Placebo, 1.1 (2.4) Fingolimod 1.25 mg, 0.2 (1.1), *P* < 0.001 vs placebo Fingolimod 0.5 mg, 0.2 (0.8), *P* < 0.001 vs placebo	Percentage change from baseline to 24 months in volume of hypointense lesions on T1 weighted images, mean (SD): Placebo, 50.7 (388.3) Fingolimod 1.25 mg, 12.2 (85.5), *P* = 0.02 vs placebo Fingolimod 0.5 mg, 8.8 (76.3), *P* = 0.01 vs placebo	Number of new or enlarged lesions on T2 weighted images at 24 months, mean (SD): Placebo, 9.8 (13.2) Fingolimod 1.25 mg, 2.5 (5.5), *P* < 0.001 vs placebo Fingolimod 0.5 mg, 2.5 (7.2), *P* < 0.001 vs placebo	Percentage change from baseline to 12 months in brain volume, mean (SD): Placebo, −0.65 (1.05) Fingolimod 1.25 mg, −0.44 (1.08), *P* < 0.001 vs placebo Fingolimod 0.5 mg, −0.50 (1.05), *P* = 0.03 vs placebo Percentage change from baseline to 24 months in brain volume, mean (SD): Placebo, −1.31 (1.50) Fingolimod 1.25 mg, −0.89 (1.39), *P* < 0.001 vs placebo Fingolimod 0.5 mg, −0.84 (1.31),	Percentage of patients with no CDP over 24 months: a) confirmed after 3 months, mean (95% CI): Placebo, 75.9 (71.7–80.2) Fingolimod 1.25 mg, 83.4 (79.7–87.1), *P* = 0.01 vs placebo, hazard ratio vs placebo 0.68 (0.50–0.93), *P* = 0.02 Fingolimod 0.5 mg, 82.3 (78.6–86.1), *P* = 0.03 vs placebo, hazard ratio vs placebo 0.70 (0.52–0.96), *P* = 0.02 b) confirmed after 6 months, mean (95% CI): Placebo, 81.0 (77.1–84.9)

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
					P < 0.001 vs placebo	Fingolimod 1.25 mg, 88.5 (85.3–91.6), *P* = 0.004 vs placebo, hazard ratio vs placebo 0.60 (0.41–0.86), *P* = 0.006 Fingolimod 0.5 mg, 87.5 (84.3–90.7), *P* = 0.01 vs placebo, hazard ratio vs placebo 0.63 (0.44–0.90), *P* = 0.01
FREEDOMS extension NCT00662649	ARR (95% CI) from month 0 to end of study: Placebo-fingolimod (*n*=418), 0.36 (0.31–0.41) Continuous fingolimod 0.5 mg (*n*=425), 0.19 (0.16–0.22); *P* < 0.0001 vs placebo Continuous fingolimod 1.25 mg (*n*=429), 0.16 (0.14–0.20); *P* < 0.0001 vs placebo	Cumulative Gd+ lesions (95% CI) from month 0 to end of study: Placebo-fingolimod (*n*=233), 3.7 (3.42–3.91) Continuous fingolimod 0.5 mg (*n*=285), 1.1 (0.98–1.23); *P* < 0.0001 vs placebo Continuous fingolimod 1.25 mg (*n*=233), 0.8 (0.70–0.94);	Not reported	Cumulative new or newly enlarged T2 lesions (95% CI) from month 0 to end of study Placebo-fingolimod (*n*=365), 11.0 (10.68–11.36) Continuous fingolimod 0.5 mg (*n*=395), 4.5 (4.27–4.68); *P* < 0.0001 vs placebo Continuous fingolimod 1.25 mg (*n*=373), 4.0 (3.80–4.21);	Percentage change in brain volume (95% CI) from month 0 to end of study Placebo-fingolimod (*n*=259), −2.2 (−2.51, −1.97) Continuous fingolimod 0.5 mg (*n*=299), −1.7 (−1.91, −1.43); *P* = 0.0013 vs placebo Continuous fingolimod 1.25 mg (*n*=250), −1.6 (−1.88, −1.40);	Proportion of patients (95% CI) free from 3-month CDP at end of study: Placebo-fingolimod (*n*=418), 66.3% (61.3–71.3%) Continuous fingolimod 0.5 mg (*n*=425), 73.9% (69.4–78.4%); *P* = 0.0171 vs placebo Continuous fingolimod 1.25 mg (*n*=429), 74.2% (69.5–78.8%);

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
		P < 0.0001 vs placebo		*P* < 0.0001 vs placebo	*P* = 0.0010 vs placebo Significantly less brain volume was lost after switching to fingolimod 0.5 mg from placebo Mean brain volume change within group, months 24–48 vs months 0–24: Placebo-fingolimod 0.5 mg (n=49), p=0.0084 Placebo-fingolimod 1.25 mg (n=41), p=0.0621 Continuous fingolimod 0.5 mg (n=109), p=0.2218 Continuous fingolimod 1.25 mg (n=75), p=0.3974	*P* = 0.0165 vs placebo
TRANSFORMS NCT01281657	ARR over 12 months, mean (95% CI): IFN β-1a, 0.33 (0.26–0.42)	Number of Gd+ lesions on T1-weighted images, mean (SD): IFN β-1a, 0.51 (1.86)	Percentage change from baseline in volume of hypointense lesions on T1 weighted images, mean (SD):	Number of new or enlarged lesions on T2 weighted images, mean (SD): IFN β-1a, 2.6 (5.8)	Percentage change from baseline to 12 months in brain volume, mean (SD): IFN β-1a, −0.45 (0.73)	No significant between-group differences observed in the time to CDP or the proportion of patients with CDP

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
	Fingolimod 1.25 mg, 0.20 (0.16–0.26), *P* < 0.001 vs IFN β-1a Fingolimod 0.5 mg, 0.16 (0.12–0.21), *P* < 0.001 vs IFN β-1a	Fingolimod 1.25 mg, 0.14 (0.58), *P* < 0.001 vs IFN β-1a Fingolimod 0.5 mg, 0.23 (0.97), *P* < 0.001 vs IFN β-1a	IFN β-1a, 15.0 (70.3) Fingolimod 1.25 mg, 34.7 (122.3), *P* = 0.09 vs IFN β-1a Fingolimod 0.5 mg, 24.1 (127.3), *P* = 0.17 vs IFN β-1a	Fingolimod 1.25 mg, 1.5 (2.7), *P* < 0.001 vs IFN β-1a Fingolimod 0.5 mg, 1.7 (3.9), *P* = 0.004 vs IFN β-1a	Fingolimod 1.25 mg, −0.3 (0.65), *P* < 0.001 vs IFN β-1a Fingolimod 0.5 mg, −0.31 (0.65), *P* < 0.001 vs IFN β-1a	Percentage of patients with no CDP, mean (95% CI): IFN β-1a, 92.1 (89.4–94.7) Fingolimod 1.25 mg, 93.3 (90.9–95.8), *P* = 0.50 vs IFN β-1a Fingolimod 0.5 mg, 94.1 (91.8–96.3), *P* = 0.25 vs IFN β-1a.
FREEDOMS II NCT00355134	ARR over 24 months, mean (95% CI): Placebo, 0.40 (0.34–0.48) Fingolimod 1.25 mg, 0.20 (0.17–0.25), rate ratio 0.50 (0.39–0.65) vs placebo, *P* < 0.0001 Fingolimod 5.0 mg, 0.21 (0.17–0.25), rate ratio 0.52 (0.40–0.66) vs placebo, *P* < 0.0001	Number of Gd+ lesions at 24 months, mean (SD): Placebo, 1.2 (2.97) Fingolimod 1.25 mg, 0.2 (2.40), *P* < 0.0001 vs placebo Fingolimod 0.5 mg, 0.4 (1.84), *P* < 0.0001 vs placebo	Percentage change from baseline to 24 months in volume of hypointense lesions on T1 weighted images, mean (SD): Placebo, 26.42 (148.80) Fingolimod 1.25 mg, −4.69 (53.55), *P* = 0.205 vs placebo Fingolimod 0.5 mg, 12.64 (211.07),	Number of new or enlarged lesions on T2 weighted images at 24 months, mean (SD): Placebo, 8.9 (13.86) Fingolimod 1.25 mg, 1.6 (5.41), *P* < 0.0001 vs placebo Fingolimod 0.5 mg, 2.3 (7.26), *P* < 0.0001 vs placebo	Percentage change from baseline to 12 months in brain volume, mean (SD): Placebo, −0.629 (1.053) Fingolimod 1.25 mg, −0.354 (1.200), *P* < 0.0001 vs placebo Fingolimod 0.5 mg, −0.377 (0.965), *P* = 0.0004 vs placebo	Percentage of patients with no CDP over 24 months: a) when confirmed after 3 months, mean (standard error; 95% CI): Placebo, 71.0 (2.6; 65.9–76.1) Fingolimod 1.25 mg, 78.3 (2.3; 73.7–82.9), *P* = 0.056 vs placebo, hazard ratio vs placebo

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
			P = 0.372 vs placebo		Percentage change from baseline to 24 months in brain volume, mean (SD): Placebo, −1.279 (1.503) Fingolimod 1.25 mg, −0.595 (1.390), treatment difference vs placebo −0.63 (−0.86–−0.42), *P* < 0.0001 Fingolimod 0.5 mg, −0.858 (1.222), treatment difference vs placebo −0.41 (−0.62–−0.2), *P* = 0.0002	0.72 (0.53–0.99), *P* = 0.041 Fingolimod 0.5 mg, 74.7 (2.5; 69.9–79.5), *P* = 0.320 vs placebo, hazard ratio vs placebo 0.83 (0.61–1.12), *P* = 0.227 b) when confirmed after 6 months, mean (95% CI): Placebo, 82.2 (2.2; 77.9–86.4) Fingolimod 1.25 mg, 86.9 (1.9; 83.2–90.6), hazard ratio vs placebo 0.72 (0.48–1.08), *P* = 0.113 Fingolimod 0.5 mg, 86.2 (1.9; 82.3–90.0), hazard ratio vs placebo 0.72 (0.48–1.07), *P* = 0.101
INFORMS NCT00731692	Confirmed relapses: Fingolimod (*n*=336), 6 (2%)	Number of Gd+ lesions (95% CI) per scan at month 36:	Number of T1 black holes (95% CI) per year at month 36:	Number of new or newly enlarging T2 lesions (95% CI) per year at month 36:	Percentage change in brain volume (95% CI) at month 36:	Kaplan–Meier estimate of patients with 3-month CDP (95% CI) based on the composite

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
	Placebo (*n*=487), 41 (8%)	Fingolimod (*n*=223), 0.05 (0.02–0.09) Placebo (*n*=320), 0.21 (0.15–0.30) Risk reduction (95% CI) fingolimod vs placebo: 0.217 (0.102–0.463); *P* < 0.0001 Number of patients free from Gd+ lesions at study end: Fingolimod (*n*=299), 260 (87%) Placebo (*n*=432), 335 (78%) Odds ratio (95% CI) fingolimod vs placebo: 2.15 (1.39–3.33); *P* = 0.0006	Fingolimod (*n*=298), 0.09 (0.06–0.13) Placebo (*n*=433), 0.24 (0.18–0.31). Risk reduction (95% CI) fingolimod vs placebo: 0.375 (0.240–0.587); *P* < 0.0001 Number of patients free from new T1 black holes at study end: Fingolimod (*n*=298), 243 (82%) Placebo (*n*=433), 312 (72%) Odds ratio (95% CI) fingolimod vs placebo: 1.75 (1.21–2.53); *P* = 0.003	Fingolimod (*n*=298), 0.13 (0.10–0.18) Placebo (*n*=431), 0.50 (0.40–0.61) Risk reduction (95% CI) fingolimod vs placebo: 0.267 (0.185–0.386); *P* < 0.0001 Number of patients free from new or newly enlarging T2 lesions at study end: Fingolimod (*n*=298), 238 (80%) Placebo (*n*=431), 260 (60%) Odds ratio (95% CI) fingolimod vs placebo: 2.79 (1.95–4.00); *P* < 0.0001	Fingolimod (*n*=293), −1.49 (−1.64, −1.35) Placebo (*n*=421), −1.53 (−1.65, −1.41) Adjusted mean difference (95% CI): 0.04% (−0.15 – 0.23%); *P* = 0.673	endpoint at end of study: Fingolimod, 77.2% (71.87–82.51%) Placebo, 80.3% (73.31–87.25%) Risk reduction 5.05%; hazard ratio (95% CI): 0.95 (0.80–1.12); *P* = 0.544 No significant between-group difference was seen in time to 3-month CDP based on EDSS score, 9-HPT or 25'TWT.
Ponesimod						
AC-058B201 NCT01006265	ARR up to week 24, mean (95% CI), % reduction vs placebo, treatment	Cumulative number of new T1 Gd+ lesions from week 12 to 24, mean	Mean cumulative number of combined unique active lesions from	Cumulative number of new or enlarged nonenhancing T2 lesions from week	Percentage change in brain volume from baseline to week 24, mean (SD):	–

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
	effect ratio (95% CI): Placebo, 0.525 (0.358–0.770) Ponesimod 10 mg, 0.332 (0.198–0.557), 37% reduction, ratio 0.632 (0.332–1.202), *P* = 0.1619 Ponesimod 20 mg, 0.417 (0.266–0.653), 21% reduction, ratio 0.793 (0.440–1.432), *P* = 0.4420 Ponesimod 40 mg, 0.251 (0.141–0.446), 52% reduction, ratio 0.478 (0.240–0.954), *P* = 0.0363	lesion number, % reduction from placebo, treatment effect ratio (95% CI): Placebo, 6.2 lesions Ponesimod 10 mg, 3.5, 43% reduction, ratio 0.57 (0.337–0.952), *P* = 0.0318 Ponesimod 20 mg, 1.1, 83% reduction, ratio 0.17 (0.100–0.289), *P* < 0.0001 Ponesimod 40 mg, 1.4, 77% reduction, ratio 0.23 (0.133–0.384), *P* < 0.0001	week 12 to 24, mean lesion number, % reduction from placebo, treatment effect ratio (95% CI): Placebo, 6.9 lesions Ponesimod 10 mg, 4.0, 42% reduction, ratio 0.580 (0.353–0.954), *P* = 0.0318 Ponesimod 20 mg, 1.4, 80% reduction, ratio 0.199 (0.121–0.329), *P* < 0.0001 Ponesimod 40 mg, 1.9, 73% reduction, ratio 0.272 (0.165–0.449), *P* < 0.0001	12 to 24, mean lesion number, % reduction from placebo, treatment effect ratio (95% CI): Placebo, 0.7 lesions Ponesimod 10 mg, 0.5, 31% reduction, ratio 0.694 (0.353–1.367), *P* = 0.2194 Ponesimod 20 mg, 0.3, 56% reduction, ratio 0.443 (0.223–0.883), *P* = 0.0208 Ponesimod 40 mg, 0.5, 34% reduction, ratio 0.657 (0.336–1.284), *P* = 0.2194	Placebo, −0.26 (1.006) Ponesimod 10 mg, 0.02 (0.718) Ponesimod 20 mg, 0.05 (0.758) Ponesimod 40 mg, 0.23 (1.053) *P* values not reported	
Siponimod						
BOLD study NCT00879658	ARR over 6 months, mean (95% CI): Placebo, 0.58 (0.34–1.00) Siponimod 0.25 mg, N/A	Monthly new Gd+ lesions at 3 months, relative reduction vs placebo (%): Siponimod 0.25 mg, 52%, *P* = 0.0618	Relative reductions in combined unique active lesions at 3 months compared with placebo, % (95% CI); lesion ratio vs placebo (95% CI):	Monthly new or enlarged T2 lesions at 3 months, relative reduction vs placebo (%): Siponimod 0.25 mg, 41%, *P* = 0.1421	–	–

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
	Siponimod 0.5 mg, 0.61, *P* = 0.8986 Siponimod 1.25 mg, N/A Siponimod 2 mg, 0.20 (0.08–0.48), *P* = 0.0408 Siponimod 10 mg, 0.30, *P* = 0.1478	Siponimod 0.5 mg, 63%, *P* = 0.0205 Siponimod 1.25 mg, 88%, *P* = 0.0002 Siponimod 2 mg, 69%, *P* = 0.0119 Siponimod 10 mg, 86%, *P* = 0.0003 Monthly new Gd+ lesions at 6 months, relative reduction vs placebo (%): Siponimod 0.25 mg, n/a Siponimod 0.5 mg, 81%, *P* = 0.0010 Siponimod 1.25 mg, n/a Siponimod 2 mg, 77%, *P* = 0.0051 Siponimod 10 mg, 85%, *P* < 0.0001	Siponimod 0.25 mg, 35% (17–57); 0.557 (0.259–1.197), *P* = 0.1338 Siponimod 0.5 mg, 50% (29–69); 0.385 (0.172–0.864), *P* = 0.0206 Siponimod 1.25 mg, 66% (48–80); 0.139 (0.045–0.432), *P* = 0.0006 Siponimod 2 mg, 72% (57–84); 0.303 (0.120–0.762), *P* = 0.0112 Siponimod 10 mg, 82% (70–90); 0.257 (0.094–0.699), *P* = 0.0078	Siponimod 0.5 mg, 32%, *P* = 0.4852 Siponimod 1.25 mg, 88%, *P* = 0.0007 Siponimod 2 mg, 72%, *P* = 0.0049 Siponimod 10 mg, 74%, *P* = 0.0053 Monthly new or enlarged T2 lesions at 6 months, relative reduction vs placebo (%): Siponimod 0.25 mg, n/a Siponimod 0.5 mg, 58%, *P* = 0.1392 Siponimod 1.25 mg, n/a Siponimod 2 mg, 80%, *P* = 0.0012 Siponimod 10 mg, 84%, *P* = 0.0002		

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
EXPAND study NCT01665144	ARR, adjusted mean (95% CI); rate ratio vs placebo (95% CI): Placebo, 0.16 (0.12–0.21) Siponimod, 0.07 (0.06–0.09); 0.45 (0.34–0.59), *P* < 0.0001	Cumulative number of Gd+ lesions up to and including month 24, adjusted mean (95% CI); rate ratio vs placebo (95% CI): Placebo, 0.60 (0.47–0.76) Siponimod, 0.08 (0.07–0.10); 0.14 (0.10–0.19), *P* < 0.0001	–	New or enlarged T2 lesions over all visits, adjusted mean (95% CI); rate ratio vs placebo (95% CI): Placebo, 3.60 (3.03–4.29) Siponimod, 0.70 (0.58–0.84); 0.19 (0.16–0.24), *P* < 0.0001	Percentage change in brain volume from baseline to month 12, adjusted mean (95% CI); difference vs placebo (95% CI): Placebo, –0.46 (–0.52 to –0.39) Siponimod, –0.28 (–0.34 to –0.23); 0.18 (0.10–0.25), *P* < 0.0001 Percentage change in brain volume from baseline to month 24, adjusted mean difference vs placebo (95% CI): Placebo, –0.84 (–0.93 to –0.75) Siponimod, –0.71 (–0.78 to –0.64); 0.13 (0.02–0.24), *P* = 0.020	CDP at 3 months, n (%); hazard ratio vs placebo (95% CI): Placebo, 173/545 (32%) Siponimod, 288/1096 (26%); 0.79 (0.65–0.95), *P* = 0.013 CDP at 6 months, n (%); hazard ratio vs placebo (95% CI): Placebo, 139/545 (26%) Siponimod, 218/1096 (20%); 0.74 (0.60–0.92), *P* = 0.0058
Ozanimod						
RADIANCE (phase 2 portion) NCT01628393	ARR over 24 weeks, mean (95% CI); odds ratio vs placebo (95% CI):	Cumulative number of Gd+ lesions between weeks 12 and 24, mean (SD);	–	Cumulative number of new or enlarged T2 lesions between weeks 12–24, mean	–	–

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
	Placebo, 0.5 (0.2–1.2) Ozanimod 0.5 mg, 0.35 (0.2–0.8); 0.69 (0.36–1.34), *P* = 0.2714 Ozanimod 1 mg, 0.24 (0.1–0.6); 0.47 (0.22–1.01), *P* = 0.0531	odds ratio vs placebo (95% CI): Placebo, 11.1 (29.9) Ozanimod 0.5 mg, 1.5 (3.7); 0.16 (0.08–0.30), *P* < 0.0001 Ozanimod 1 mg, 1.5 (3.4); 0.11 (0.06–0.21), *P* < 0.0001		(SD); odds ratio vs placebo (95% CI): Placebo, 9.0 (20.9) Ozanimod 0.5 mg, 1.4 (3.2); 0.17 (0.10–0.30), *P* < 0.0001 Ozanimod 1 mg, 0.8 (1.9); 0.08 (0.04–0.14), *P* < 0.0001		
RADIANCE (phase 3 portion) NCT02047734	ARR over 24 months, adjusted mean (95% CI); rate ratio vs IFN β-1a (95% CI): IFN β-1a, 0.28 (0.23–0.32) Ozanimod 0.5 mg, 0.22 (0.18–0.26); 0.79 (0.65–0.96), *P* = 0.0167 Ozanimod 1.0 mg, 0.17 (0.14–0.21); 0.62 (0.51–0.77), *P* < 0.0001	Number of Gd+ lesions at month 24, adjusted mean (95% CI), rate ratio vs IFN β-1a (95% CI): IFN β-1a, 0.37 (0.26–0.54) Ozanimod 0.5 mg, 0.20 (0.13–0.30); 0.53 (0.35–0.81), *P* = 0.0030 Ozanimod 1.0 mg, 0.18 (0.12–0.27); 0.47 (0.31–0.73), *P* = 0.0006	–	Number of new or enlarging T2 lesions per scan over 24 months, adjusted mean (95% CI), ratio vs IFN β-1a (95% CI): IFN β-1a, 3.18 (2.64–3.84) Ozanimod 0.5 mg, 2.09 (1.74–2.51); 0.66 (0.53–0.81), *P* = 0.0001 Ozanimod 1.0 mg, 1.84 (1.52–2.21); 0.58 (0.47–0.71), *P* < 0.0001	Percentage change in whole brain volume from baseline to month 24, mean (SD); difference vs IFN β-1a (95% CI): IFN β-1a, –0.937 (0.944) Ozanimod 0.5 mg, –0.707 (0.746); 0.224 (0.106–0.342) *P* = 0.0002 Ozanimod 1.0 mg, –0.707 (0.878); 0.244 (0.125–0.363) *P* < 0.0001	CDP at 3 months, n/N (%); hazard ratio vs IFN β-1a (95% CI): IFN β-1a, 50/441 (11.3%) Ozanimod 0.5 mg, 41/439 (9.3%); 0.80 (0.53–1.21), *P* = 0.2849 Ozanimod 1.0 mg, 54/433 (12.5%); 1.05 (0.71–1.54), *P* = 0.8224 CDP at 6 months, *n* (%); hazard ratio vs IFN β-1a (95% CI):

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
						IFN β-1a, 29/441 (6.6%) Ozanimod 0.5 mg, 32/439 (7.3%); 1.10 (0.66–1.82), *P* = 0.7154 Ozanimod 1.0 mg, 42/433 (9.7%); 1.44 (0.89–2.31), *P* = 0.1353
SUNBEAM NCT02294058	ARR over 12 months, adjusted mean (95% CI); rate ratio vs IFN β-1a (95% CI): IFN β-1a, 0.35 (0.28–0.44) Ozanimod 0.5 mg, 0.24 (0.19–0.31); 0.69 (0.55–0.86), *P* = 0.0013 Ozanimod 1.0 mg, 0.18 (0.14–0.24); 0.52 (0.41–0.66), *P* < 0.0001	Number of Gd+ lesions at month 12, adjusted mean (95% CI), rate ratio vs IFN β-1a (95% CI): IFN β-1a, 0.43 (0.30–0.64) Ozanimod 0.5 mg, 0.29 (0.20–0.42); 0.66 (0.47–0.93), *P* = 0.0182 Ozanimod 1.0 mg, 0.16 (0.11–0.24); 0.37 (0.26–0.54), *P* < 0.0001	–	Number of new or enlarging T2 lesions per scan over 12 months, adjusted mean (95% CI), ratio vs IFN β-1a (95% CI): IFN β-1a, 2.84 (2.33–3.45) Ozanimod 0.5 mg, 2.14 (1.78–2.58); 0.75 (0.63–0.91), *P* = 0.0032 Ozanimod 1.0 mg, 1.47 (1.20–1.78); 0.52 (0.43–0.63), *P* < 0.0001	Percentage change in whole brain volume from baseline to month 12, mean (SD); difference vs IFN β-1a (95% CI): IFN β-1a, –0.61 (0.686) Ozanimod 0.5 mg, –0.49 (0.610); 0.12 (0.03–0.20) *P* = 0.0092 Ozanimod 1.0 mg, –0.41 (0.640); 0.19 (0.10–0.28) *P* < 0.0001	CDP at 3 months, n/N (%); hazard ratio vs IFN β-1a (95% CI):[b] IFN β-1a, 69/889 (7.8%) Ozanimod 0.5 mg, 58/890 (6.5%); 0.82 (0.58–1.17), *P* = 0.2698 Ozanimod 1.0 mg, 67/880 (7.6%); 0.95 (0.68–1.33), *P* = 0.7651 CDP at 6 months, n/N (%); hazard ratio vs IFN β-1a (95% CI):[b]

Study name	ARR/relapses	Gd+ lesions	T1 black holes/CUALS	T2 lesions	Change in brain volume	CDP
						IFN β-1a, 36/889 (4.0%) Ozanimod 0.5 mg, 43/890 (4.8%); 1.19 (0.76–1.85), *P* = 0.4447 Ozanimod 1.0 mg, 51/880 (5.8%); 1.41 (0.92–2.17), *P* = 0.1126

[a]Study was powered for the primary end-point only (retention on treatment); *P* values for other outcomes are for descriptive purposes only

[b]Pooled analysis of RADIANCE phase 3 and SUNBEAM (duration ≥12 months) was the prespecified analysis for disability progression for the two studies

9-HPT 9-hole peg test, *25'TWT* 25-foot Timed Walk Test, *ARR* annualized relapse rate, *BOLD* BAF312 on MRI lesion given once-daily, *BV* brain volume, *CDP* confirmed disability progression, *CI* confidence interval, *CUAL* combined unique active lesions, *EDSS* Expanded Disability Status Scale, *FREEDOMS* FTY720 research evaluating effects of daily oral therapy in multiple sclerosis, *Gd+* gadolinium-enhancing, *iDMT* injectable disease-modifying therapy, *IFN* interferon, n/a not available, *PREFERMS* evaluation of patient retention of fingolimod versus currently approved disease-modifying therapy in patients with relapsing–remitting multiple sclerosis, *RADIANCE* safety and efficacy of the selective sphingosine-1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis, *SD* standard deviation, *TRANSFORMS* trial assessing injectable interferon versus FTY720 oral in relapsing–remitting multiple sclerosis.