Supplemental Materials

eAppendix 1

Eligibility criteria for Core/Extension studies

Eligible patients for the Core study were men or women (aged 18-55 years) with relapsing-remitting multiple sclerosis (RRMS) (revised 2005 McDonald Diagnostic Criteria[1]) and Expanded Disability Status Scale (EDSS) score of 0–5.5 and were required to have documented relapses (≥1 within 12 months or ≥2 within 24 months before screening) or ≥1 gadolinium-enhancing (Gd+) lesion on T1 weighted MRI at screening. Women of child-bearing potential had to use appropriate contraception methods and were excluded from the Core study if they were pregnant or breastfeeding. Patients who completed 24-weeks treatment in the Core study were eligible to enter the Extension study. Patients were not eligible for the Extension study if they met the study-specific criteria for permanent treatment discontinuation at Week 24 of the Core study, during the transition period, and/or at visit E1 (Day 1) of the Extension study; or were receiving concomitant medication that was prohibited as per the study protocol; or had any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the patient at risk by participating in the Extension study.

[1]Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Annals of neurology. 2005;58(6):840-846

Study assessments

The brain MRI scans were performed every 4 weeks from week 4 to 24 during Core, every 24 weeks during treatment period 1 (TP1), every 48 weeks during TP2/TP3, at end of treatment (EOT) and at the 30-day follow-up. The EDSS/ functional score (FS) neurological assessments were conducted at Week 24 in the core and at Weeks 24, 48, and 96 in TP1; every 12 weeks during TP2/TP3, and at follow-up 30 and/or 90 days. EDSS and FS scores were based on a standard neurological examination (Kurtzke scale) for assessing neurologic impairment in MS.[2] A 12-lead ECG, blood pressure measurements (systolic and diastolic blood pressure [SBP and DBP]) were performed at all study visits. Clinical laboratory tests were performed at all visits (except Day 1 of the Core study and the Extension study). Spirometry test was performed pre-dose at Day 8, Day 15, followed by every 4 weeks (Weeks 4, 8, 12, 16, 20 and 24) of the Core study and at Day 8, Day 15, followed by every 4 weeks (Weeks 4, 8, 12) and every 24 weeks (Weeks 24, 48, 72, and 96) of TP1 and every 24 weeks during TP2/TP3, and at each follow-up visit. In addition, unscheduled spirometry tests were conducted in the event of respiratory symptoms (e.g., dyspnea) or decreased lung function (forced expiratory volume in 1 second [FEV_1] and/or forced vital capacity [FVC] <80% of baseline value) during treatment. The adverse events were recorded throughout the study and were coded using the preferred terms from Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0.

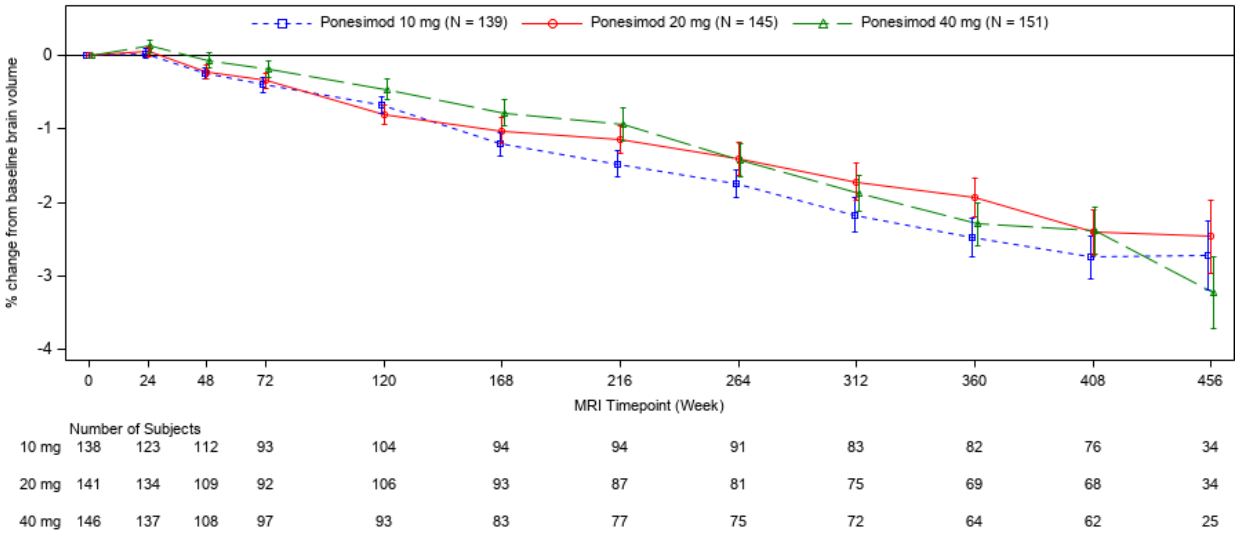
[2]Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-1452.

Statistical analysis

A negative binomial (NB) regression model was used to analyze annualized relapse rate (ARR) and MRI lesion endpoints. A Poisson regression model was additionally used for the analysis of combined unique active lesions (CUAL) due to a poor fit for the data when using a NB distribution. Time to first confirmed relapse and time to first 6-month confirmed disability accumulation (CDA) were analyzed using the Kaplan-Meier method and a Cox proportional hazards model for relative effect size estimate (Hazard ratios [HRs] and 95% CIs) and log-rank test for the p-value. Safety was summarized using descriptive analysis.

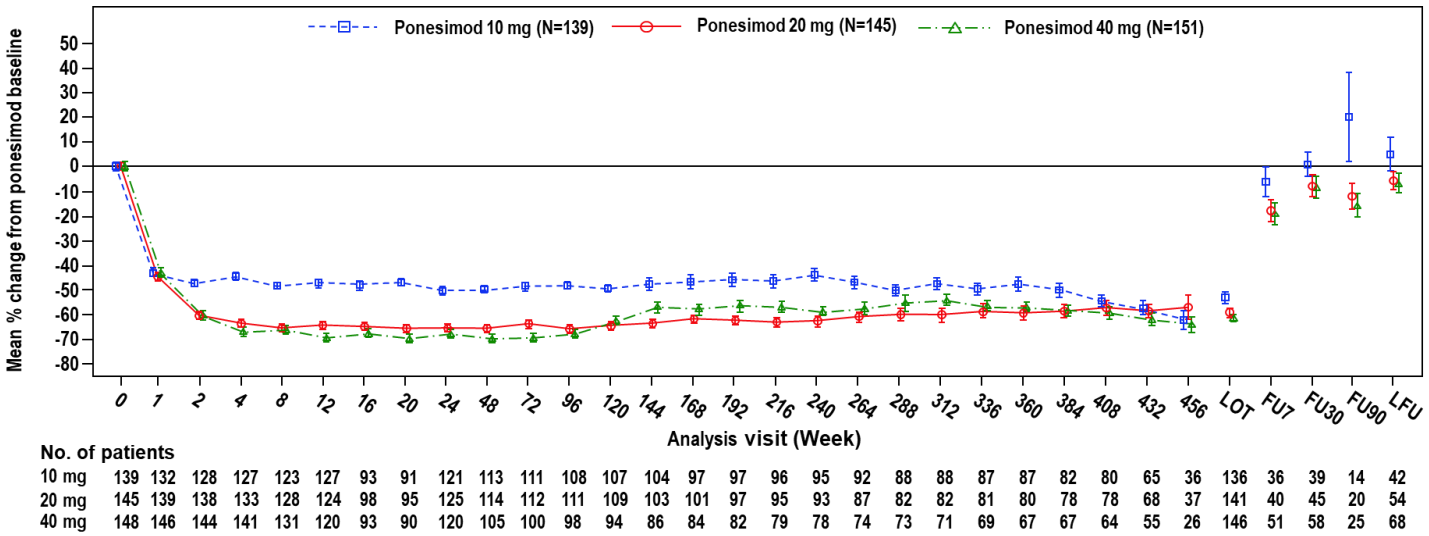
Supplemental Figures

eFigure 1. Percent change from baseline by visit for brain volume up to end of TP3, (Ponesimod Analysis Set)



TP, treatment period. Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eFigure 2. Percentage change from baseline by visit for lymphocytes up to end of TP3 (Ponesimod Analysis Set)

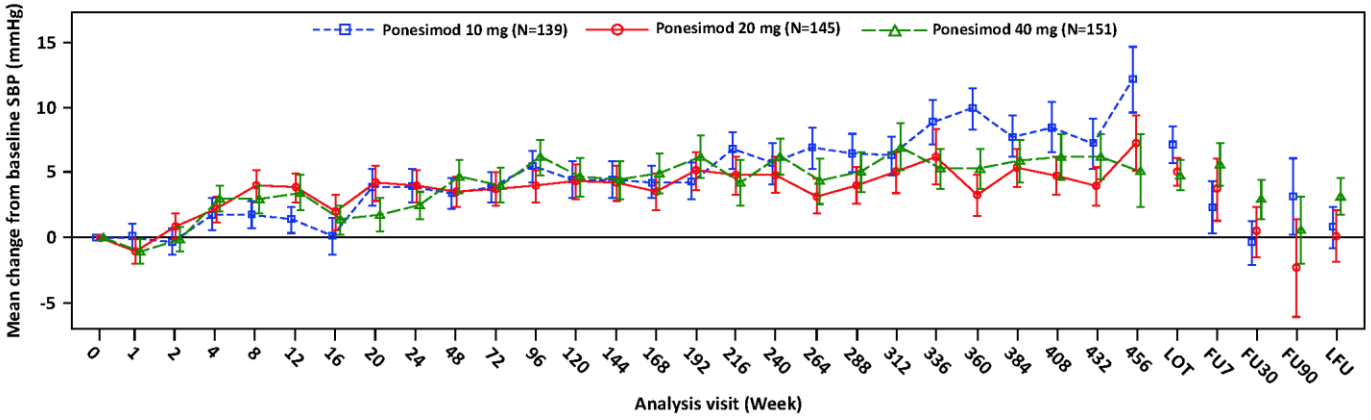


FU7, Follow-up Day 7; FU30, Follow-up Day 30; FU90, Follow-up Day 90; LFU, Last Follow-up Visit; LOT, Last-On-Treatment Visit; TP, Treatment Period.

Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eFigure 3. Absolute change from baseline by visit for Systolic BP (a) and Diastolic BP (b) up to end of TP3 (Ponesimod Analysis Set)

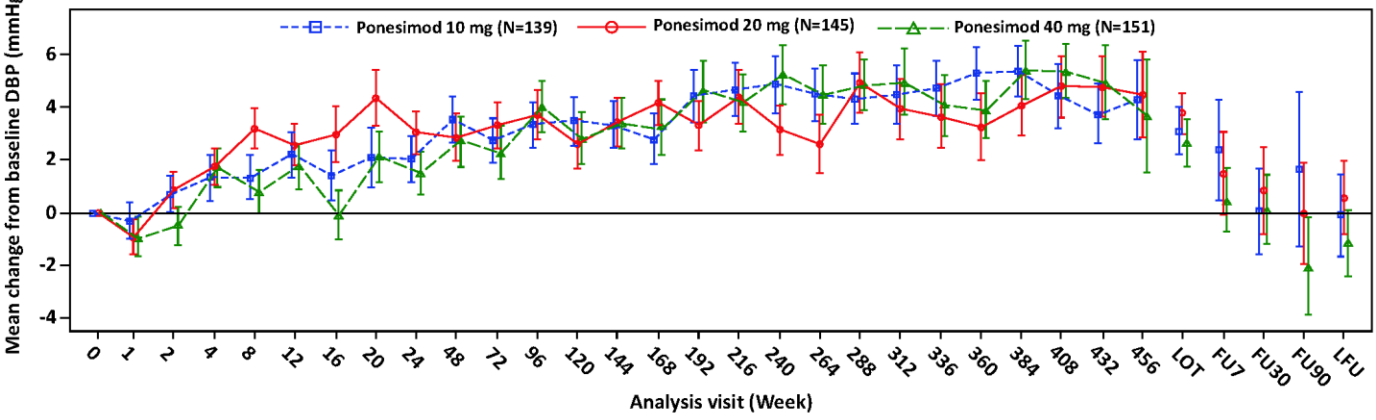
a.



No. of patients

10 mg	139	138	132	131	129	128	95	93	121	113	111	108	107	104	98	97	96	95	92	88	88	87	87	82	80	66	36	139	38	38	15	44
20 mg	145	141	141	137	132	129	100	98	125	115	112	111	109	102	101	97	95	93	87	82	82	81	80	78	78	69	37	145	41	46	21	53
40 mg	151	148	150	146	138	129	98	98	123	108	104	101	96	89	88	85	82	81	78	76	74	72	70	70	68	60	30	148	51	55	27	67

b.



No. of patients

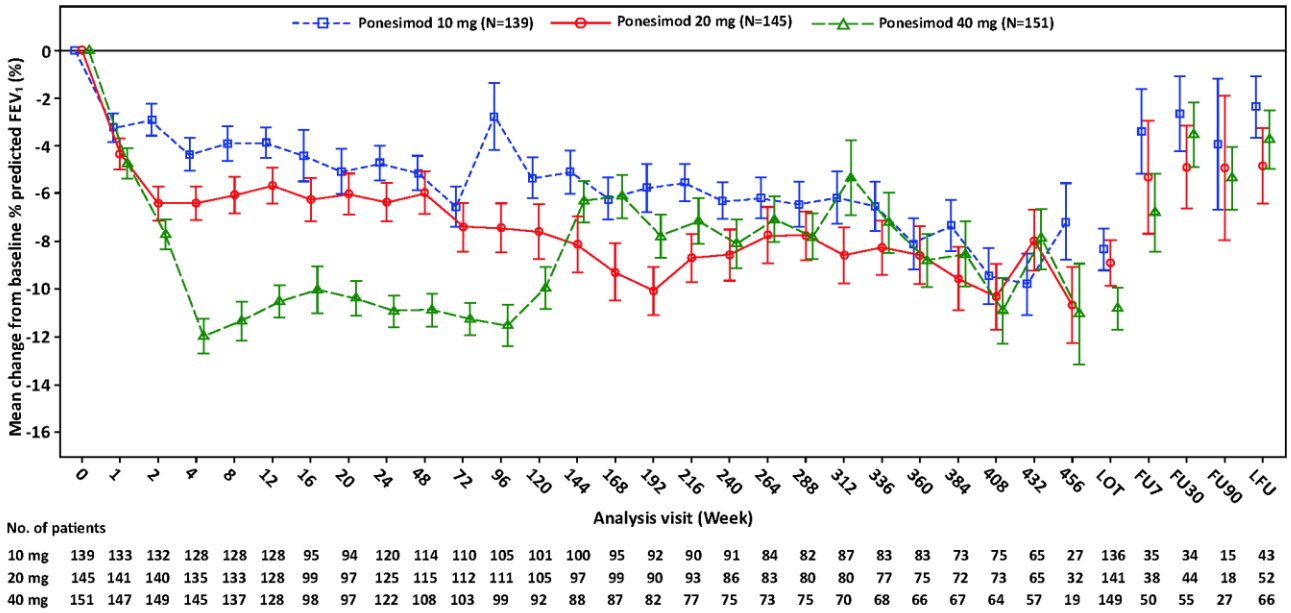
10 mg	139	138	132	131	129	128	95	93	121	113	111	108	107	104	98	97	96	95	92	88	88	87	87	82	80	66	36	139	38	38	15	44
20 mg	145	141	141	137	132	129	100	98	125	115	112	111	109	102	101	97	95	93	87	82	82	81	80	78	78	69	37	145	41	46	21	53
40 mg	151	148	150	146	138	129	98	98	123	108	104	101	96	89	88	85	82	81	78	76	74	72	70	70	68	60	30	148	51	55	27	67

BP, Blood pressure; FU7, Follow-up Day 7; FU30, Follow-up Day 30; FU90, Follow-up Day 90; LFU, Last Follow-up Visit; LOT, Last-On-Treatment Visit; TP, Treatment Period.

Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eFigure 4. Change from baseline by visit for %predicted FEV1 (a) and FVC (b) up to end of TP3 (Ponesimod Analysis Set)

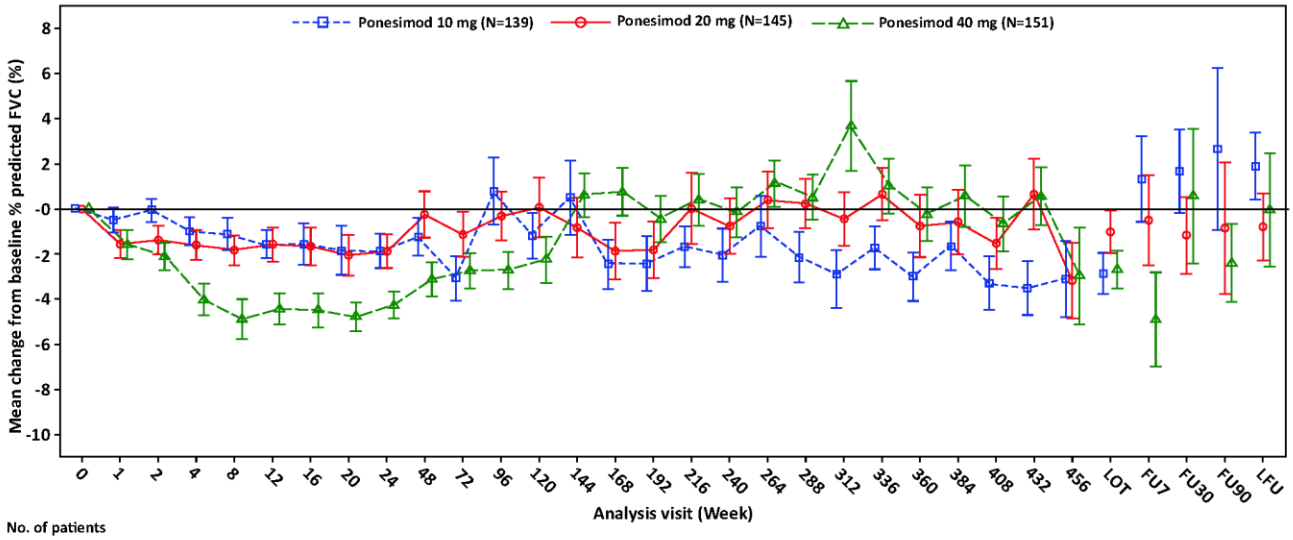
a.



No. of patients

10 mg	139	133	132	128	128	128	95	94	120	114	110	105	101	100	95	92	90	91	84	82	87	83	83	73	75	65	27	136	35	34	15	43
20 mg	145	141	140	135	133	128	99	97	125	115	112	111	105	97	99	90	93	86	83	80	80	77	75	72	73	65	32	141	38	44	18	52
40 mg	151	147	149	145	137	128	98	97	122	108	103	99	92	88	87	82	77	75	73	75	70	68	66	67	64	57	19	149	50	55	27	66

b.



No. of patients

10 mg	139	133	132	128	128	128	95	94	120	114	110	105	101	100	95	92	90	91	84	82	87	83	83	73	75	65	27	136	35	34	15	43
20 mg	145	141	140	135	133	128	99	97	125	115	112	111	105	97	99	90	93	86	83	80	80	77	75	72	73	65	32	141	38	44	18	52
40 mg	151	147	149	145	137	128	98	97	122	108	103	99	92	88	87	82	77	75	73	75	70	68	66	67	64	57	19	149	50	55	27	66

FU7, Follow-up Day 7; FU30, Follow-up Day 30; FU90, Follow-up Day 90; LFU, Last Follow-up Visit; LOT, Last-On-Treatment Visit; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TP, Treatment Period.

Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

Supplemental Tables

eTable 1. Summary of treatment-emergent adverse events up to end of TP1

Event, n (%)	Ponesimod 10 mg (n=139)	Ponesimod 20 mg (n=145)	Ponesimod 40 mg (n=151)
Patients with any TEAE	99 (71.2)	103 (71.0)	122 (80.8)
Most common TEAEs (≥10% of patients in any ponesimod group)			
Nasopharyngitis	27 (19.4)	25 (17.2)	35 (23.2)
Headache	26 (18.7)	23 (15.9)	31 (20.5)
Upper respiratory tract infection	13 (9.4)	14 (9.7)	27 (17.9)
Dyspnea	7 (5.0)	9 (6.2)	21 (13.9)
Cough	6 (4.3)	8 (5.5)	19 (12.6)
Dizziness	15 (10.8)	9 (6.2)	16 (10.6)
Edema peripheral	1 (0.7)	8 (5.5)	16 (10.6)
Alanine aminotransferase increased	10 (7.2)	12 (8.3)	15 (9.9)
Influenza	14 (10.1)	11 (7.6)	14 (9.3)

TEAE, treatment emergent adverse event; TP, Treatment Period. Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 2: Summary of treatment-emergent adverse events up to end of TP2

Event, n (%)	Ponesimod 10 mg (n=139)	Ponesimod 20 mg (n=145)	Ponesimod 40 mg (n=151)
Patients with any TEAE	119 (85.6)	121 (83.4)	135 (89.4)
Most common TEAEs (≥10% of patients in any ponesimod group)			
Nasopharyngitis	40 (28.8)	41 (28.3)	42 (27.8)
Headache	35 (25.2)	29 (20.0)	36 (23.8)
Upper respiratory tract infection	23 (16.5)	25 (17.2)	36 (23.8)
Cough	11 (7.9)	12 (8.3)	25 (16.6)
Dyspnea	8 (5.8)	11 (7.6)	22 (14.6)
Urinary tract infection	17 (12.2)	18 (12.4)	21 (13.9)
Back pain	13 (9.4)	18 (12.4)	20 (13.2)
Influenza	19 (13.7)	16 (11.0)	18 (11.9)
Alanine aminotransferase increased	13 (9.4)	16 (11.0)	18 (11.9)
Dizziness	18 (12.9)	12 (8.3)	18 (11.9)
Bronchitis	19 (13.7)	18 (12.4)	17 (11.3)
Edema peripheral	1 (0.7)	8 (5.5)	16 (10.6)
Fatigue	13 (9.4)	18 (12.4)	12 (7.9)
Rhinitis	14 (10.1)	10 (6.9)	2 (1.3)

TEAE, treatment emergent adverse event; TP, Treatment Period. Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 3. ARR (confirmed relapses) in patients who completed or discontinued prematurely vs patients with treatment ongoing up to end of TP3

	Ponesimod 10 mg		Ponesimod 20 mg		Ponesimod 40 mg	
	N	**ARR**	**N**	**ARR**	**N**	**ARR**
Up to end of TP1[a]						
All	139	0.25	145	0.21	151	0.19
Ongoing	104	0.20	106	0.18	95	0.11
Completed/discontinued	35	0.64	39	0.45	56	0.55
Up to end of TP2[a]						
All	139	0.23	145	0.16	151	0.16
Ongoing	82	0.15	78	0.11	68	0.08
Completed/discontinued	57	0.47	67	0.29	83	0.33
Up to end of TP3[a]						
All	139	0.22	145	0.15	151	0.16
Ongoing	73	0.13	75	0.10	68	0.08
Completed/discontinued	66	0.39	70	0.28	83	0.34

ARR, annualized relapse rate; TP, treatment period.

[a]From ponesimod baseline to end of extension treatment period 1 or EoS; [b]From ponesimod baseline to end of extension treatment period 2 or EoS, [c]From ponesimod baseline to extension treatment period 3 (up to data cut-off date or EoS).

eTable 4: Percent change from baseline by visit for brain volume up to end of TP3, (Ponesimod Analysis Set)

Analysis visit (n)	Ponesimod 10 mg (N=139)	Ponesimod 20 mg (N=145)	Ponesimod 40 mg (N=151)
Week 24	123	134	137
Mean (SD)	0.03 (0.72)	0.05 (0.76)	0.13 (0.97)
Week 48	112	109	108
Mean (SD)	-0.24 (0.87)	-0.23 (0.97)	-0.07 (1.05)
Week 72	93	92	97
Mean (SD)	-0.40 (1.05)	-0.34 (0.99)	-0.19 (1.13)
Week 120	104	106	93
Mean (SD)	-0.67 (1.16)	-0.8 (1.4)	-0.46 (1.33)
Week 168	94	93	83
Mean (SD)	-1.20 (1.56)	-1.03 (1.72)	-0.78 (1.65)
Week 216	94	87	77
Mean (SD)	-1.47 (1.7)	-1.14 (1.72)	-0.93 (2.00)
Week 264	91	81	75
Mean (SD)	-1.75 (1.76)	-1.41 (2.02)	-1.43 (2.00)
Week 312	83	75	72
Mean (SD)	-2.17 (2.15)	-1.72 (2.19)	-1.87 (2.04)
Week 360	82	69	64
Mean (SD)	-2.47 (2.4)	-1.94 (2.18)	-2.29 (2.35)
Week 408	76	68	62
Mean (SD)	-2.75 (2.55)	-2.40 (2.56)	-2.38 (2.56)

TP, treatment period. Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 5: Summary of treatment-emergent adverse events up to end of TP3

Event, n (%)	Ponesimod 10 mg (n=139)	Ponesimod 20 mg (n=145)	Ponesimod 40 mg (n=151)	Total (n=435)
Patients with any TEAE	132 (95.0)	132 (91.0)	148 (98.0)	412 (94.7)
Most common TEAEs (≥10% of patients in any ponesimod group)				
Nasopharyngitis	43 (30.9)	45 (31.0)	43 (28.5)	131 (30.1)
Headache	36 (25.9)	29 (20.0)	38 (25.2)	103 (23.7)
Upper respiratory tract infection	26 (18.7)	27 (18.6)	38 (25.2)	91 (20.9)
Cough	11 (7.9)	12 (8.3)	27 (17.9)	50 (11.5)
Dyspnea	10 (7.2)	11 (7.6)	22 (14.6)	43 (9.9)
Back pain	15 (10.8)	20 (13.8)	21 (13.9)	56 (12.9)
Urinary tract infection	18 (12.9)	18 (12.4)	21 (13.9)	57 (13.1)
Bronchitis	21 (15.1)	20 (13.8)	20 (13.2)	61 (14.0)
Influenza	20 (14.4)	16 (11.0)	20 (13.2)	56 (12.9)
Alanine aminotransferase increased	16 (11.5)	18 (12.4)	18 (11.9)	52 (12.0)
Dizziness	18 (12.9)	12 (8.3)	18 (11.9)	48 (11.0)
Forced expiratory volume decreased	9 (6.5)	11 (7.6)	16 (10.6)	36 (8.3)
Edema peripheral	1 (0.7)	8 (5.5)	16 (10.6)	25 (5.7)
Fatigue	13 (9.4)	18 (12.4)	14 (9.3)	45 (10.3)
Hypertension	14 (10.1)	13 (9.0)	14 (9.3)	41 (9.4)
Arthralgia	14 (10.1)	12 (8.3)	11 (7.3)	37 (8.5)
Hypercholesterolemia	12 (8.6)	15 (10.3)	10 (6.6)	37 (8.5)
Rhinitis	14 (10.1)	11 (7.6)	2 (1.3)	27 (6.2)

TEAE, treatment emergent adverse event; TP, Treatment Period. Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 6: Summary of treatment-emergent adverse events of special interest up to end of TP3

AESI categories and preferred terms within the categories, n (%)	Ponesimod 10 mg (n=139)	Ponesimod 20 mg (n=145)	Ponesimod 40 mg (n=151)	Total (n=435)
Patients with at least one AESI	81 (58.3)	87 (60.0)	109 (72.2)	277 (63.7)
Pulmonary	31 (22.3)	39 (26.9)	64 (42.4)	134 (30.8)
Dyspnea	10 (7.2)	11 (7.6)	22 (14.6)	43 (9.9)
Forced expiratory volume decreased	9 (6.5)	11 (7.6)	16 (10.6)	36 (8.3)
Hepatobiliary disorders / Liver enzyme abnormality	23 (16.5)	27 (18.6)	29 (19.2)	79 (18.2)
Alanine aminotransferase increased	16 (11.5)	18 (12.4)	18 (11.9)	52 (12.0)
Hypertension	16 (11.5)	15 (10.3)	19 (12.6)	50 (11.5)
Herpetic infection	11 (7.9)	14 (9.7)	15 (9.9)	40 (9.2)
Effect on heart rate and rhythm (including hypotension)	15 (10.8)	12 (8.3)	15 (9.9)	42 (9.7)
Infection	4 (2.9)	5 (3.4)	13 (8.6)	22 (5.1)
Seizure	3 (2.2)	3 (2.1)	2 (1.3)	8 (1.8)
Macular edema	1 (0.7)	4 (2.8)	3 (2.0)	8 (1.8)
Skin malignancy	2 (1.4)	2 (1.4)	2 (1.3)	6 (1.4)
Non-skin malignancy	3 (2.2)	3 (2.1)	2 (1.3)	8 (1.8)

AESI, adverse events of special interest; TP, Treatment Period. Preferred Terms are based on MedDRA version 21.0. Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 7. Percentage change from baseline by visit for lymphocytes up to end of TP3

	Ponesimod		
	10 mg (n=139)	**20 mg (n=145)**	**40 mg (n=151)**
Week 1	–42.9 (21.77)	–44.5 (18.08)	–43.0 (20.51)
Week 2	–47.0 (17.94)	–60.5 (15.28)	–60.4 (16.96)
Week 4	–44.4 (23.03)	–63.4 (14.30)	–67.0 (17.83)
Week 8	–48.3 (19.66)	–65.3 (13.37)	–65.9 (21.24)
Week 12	–47.0 (20.92)	–64.4 (15.80)	–69.2 (14.92)
Week 16	–47.8 (19.30)	–64.9 (13.37)	–67.5 (17.91)
Week 20	–46.9 (19.59)	–65.4 (12.06)	–69.6 (15.44)
Week 24	–50.3 (17.81)	–65.3 (14.33)	–67.9 (17.52)
Week 48	–49.8 (18.03)	–65.5 (13.19)	–69.7 (15.77)
Week 72	–48.5 (19.83)	–64.0 (18.23)	–69.3 (14.47)
Week 96	–48.2 (19.44)	–65.7 (17.13)	–67.8 (17.33)
Week 120	–49.6 (19.78)	–64.4 (16.52)	–62.6 (19.2)
Week 144	–47.6 (24.41)	–63.8 (17.03)	–57.1 (20.45)
Week 168	–46.8 (27.07)	–61.9 (19.11)	–57.6 (20.43)
Week 192	–45.8 (27.48)	–62.5 (19.88)	–56.6 (19.09)
Week 216	–46.5 (24.71)	–63.0 (16.95)	–56.8 (20.50)
Week 240	–44.1 (24.52)	–62.8 (16.23)	–58.6 (15.74)
Week 264	–47.2 (23.10)	–60.6 (20.19)	–57.4 (19.62)
Week 288	–50.0 (17.67)	–59.8 (22.44)	–55.3 (30.10)
Week 312	–47.5 (23.25)	–60.2 (23.29)	–54.2 (20.25)
Week 336	–49.6 (21.04)	–58.6 (24.74)	–56.6 (16.60)
Week 360	–47.6 (25.49)	–59.3 (24.12)	–56.9 (17.80)
Week 384	–50.3 (23.58)	–58.8 (23.73)	–58.4 (16.88)
Week 408	–54.3 (22.89)	–57.5 (24.7)	–59.4 (18.32)
Week 432	–57.3 (21.26)	–58.8 (22.15)	–61.7 (18.05)
Week 456	–61.8 (20.64)	–57.0 (30.08)	–63.9 (15.61)
Week 480	–54.3 (13.14)	–61.1 (16.82)	–58.2 (8.72)
LOT	–53.3 (22.37)	–59.6 (21.0)	–61.5 (20.70)
FU Day 7	–6.5 (35.71)	–17.7 (29.01)	–19.0 (30.24)
FU Day 30	0.7 (31.05)	–7.9 (27.66)	–8.5 (32.49)
FU Day 90	20.2 (67.34)	–12.1 (21.79)	–15.7 (23.43)
Last FU Visit	5.4 (44.89)	–5.6 (27.14)	–6.7 (30.41)

LOT, last on treatment, FU, follow-up. LOT, last on treatment, FU, follow-up; TP, treatment period. Data are mean (SD). Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 8. Absolute change from baseline by visit for systolic blood pressure up to end of TP3

	Ponesimod		
	10 mg (n=139)	**20 mg (n=145)**	**40 mg (n=151)**
Week 1	0.1 (11.5)	–1.1 (11.3)	–1.1 (10.8)
Week 2	–0.3 (11.8)	0.9 (11.7)	–0.1 (11.6)
Week 4	1.8 (13.5)	2.2 (11.9)	3.0 (12.2)
Week 8	1.7 (11.9)	3.9 (13.9)	2.9 (12.1)
Week 12	1.4 (11.6)	3.8 (12.4)	3.4 (14.9)
Week 16	0.2 (13.8)	2.0 (13.6)	1.4 (11.3)
Week 20	3.9 (13.4)	4.2 (13.6)	1.8 (12.7)
Week 24	3.9 (14.2)	4.0 (14.0)	2.4 (12.1)
Week 48	3.4 (12.3)	3.5 (12.5)	4.7 (13.6)
Week 72	3.8 (12.4)	3.8 (13.8)	4.0 (13.9)
Week 96	5.5 (12.8)	3.9 (12.5)	6.1 (14.1)
Week 120	4.4 (14.7)	4.3 (14.2)	4.6 (14.2)
Week 144	4.5 (14.3)	4.1 (13.6)	4.4 (13.9)
Week 168	4.2 (12.3)	3.5 (14.0)	5.0 (14.4)
Week 192	4.3 (14.3)	5.1 (14.8)	6.2 (15.1)
Week 216	6.8 (12.7)	4.8 (14.2)	4.2 (16.0)
Week 240	5.7 (15.2)	4.8 (13.2)	6.2 (12.8)
Week 264	7.0 (13.5)	3.2 (12.8)	4.3 (15.0)
Week 288	6.4 (13.7)	4.0 (12.9)	5.0 (13.1)
Week 312	6.3 (13.7)	5.0 (14.4)	6.9 (15.5)
Week 336	8.9 (15.8)	6.2 (18.7)	5.3 (13.3)
Week 360	9.9 (14.6)	3.2 (13.9)	5.3 (13.1)
Week 384	7.8 (14.7)	5.4 (12.9)	5.8 (13.3)
Week 408	8.5 (17.4)	4.7 (13.1)	6.2 (14.5)
Week 432	7.2 (15.7)	3.9 (11.9)	6.2 (14.0)
Week 456	12.1 (15.2)	7.3 (12.7)	5.1 (15.3)
Week 480	11.1 (14.9)	13.6 (14.1)	5.6 (7.4)
LOT	7.1 (16.8)	5.0 (12.8)	4.8 (14.2)
FU Day 7	2.3 (12.4)	3.7 (15.4)	5.6 (11.8)
FU Day 30	–0.4 (10.5)	0.4 (13.1)	2.9 (11.6)
FU Day 90	3.1 (11.3)	–2.4 (17.2)	0.6 (13.3)
Last FU Visit	0.8 (10.5)	0.1 (14.6)	3.1 (11.6)

LOT, last on treatment, FU, follow-up; TP, treatment period. Data are mean (SD). Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 9. Absolute change from baseline by visit for diastolic blood pressure up to end of TP3

	Ponesimod		
	10 mg (n=139)	**20 mg (n=145)**	**40 mg (n=151)**
Week 1	–0.3 (8.2)	–0.9 (7.8)	–0.9 (9.2)
Week 2	0.6 (8.7)	0.8 (8.3)	–0.5 (8.8)
Week 4	1.3 (10.3)	1.7 (8.0)	1.7 (8.8)
Week 8	1.3 (9.7)	3.2 (8.8)	0.8 (9.6)
Week 12	2.2 (9.8)	2.6 (9.0)	1.8 (9.7)
Week 16	1.4 (9.6)	3 (10.6)	–0.1 (9.2)
Week 20	2.1 (10.5)	4.3 (10.3)	2.1 (9.4)
Week 24	2.0 (9.7)	3.0 (9.2)	1.5 (8.9)
Week 48	3.5 (9.2)	2.9 (9.9)	2.7 (10.2)
Week 72	2.7 (8.7)	3.3 (9.3)	2.3 (10.4)
Week 96	3.3 (8.9)	3.7 (9.9)	4.0 (10.0)
Week 120	3.4 (9.5)	2.6 (9.6)	2.8 (9.8)
Week 144	3.3 (9.4)	3.4 (9.6)	3.4 (8.9)
Week 168	2.8 (9.6)	4.1 (8.6)	3.2 (10.0)
Week 192	4.4 (9.8)	3.3 (9.1)	4.6 (10.6)
Week 216	4.7 (10.1)	4.4 (9.9)	4.2 (9.9)
Week 240	4.9 (10.4)	3.1 (9.1)	5.2 (10.0)
Week 264	4.5 (9.6)	2.6 (10.2)	4.5 (9.9)
Week 288	4.3 (9.1)	4.9 (10.5)	4.8 (8.4)
Week 312	4.5 (10.6)	3.9 (10.2)	5.0 (10.8)
Week 336	4.7 (9.7)	3.7 (11.1)	4.1 (9.9)
Week 360	5.3 (9.3)	3.3 (11.5)	3.9 (9.1)
Week 384	5.4 (8.7)	4.1 (10.0)	5.4 (9.3)
Week 408	4.4 (11.1)	4.8 (10.5)	5.4 (8.6)
Week 432	3.7 (9.3)	4.8 (9.5)	5 (11.0)
Week 456	4.3 (9.0)	4.5 (9.9)	3.7 (11.8)
Week 480	5.7 (7.0)	7.1 (6.9)	6.0 (4.2)
LOT	3.1 (10.8)	3.7 (9.6)	2.6 (11.0)
FU Day 7	2.4 (11.7)	1.5 (10.2)	0.5 (8.5)
FU Day 30	0.1 (10.1)	0.8 (11.1)	0.1 (9.7)
FU Day 90	1.7 (11.4)	0 (8.8)	–2.0 (9.7)
Last FU Visit	–0.1 (10.2)	0.5 (10.2)	–1.1 (10.2)

LOT, last on treatment, FU, follow-up; TP, treatment period. Data are mean (SD). Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 10. Change from baseline by visit for %predicted FEV1 up to end of TP3

	Ponesimod		
	10 mg (n=139)	**20 mg (n=145)**	**40 mg (n=151)**
Week 1	–3.2 (6.88)	–4.3 (7.86)	–4.7 (7.66)
Week 2	–2.9 (7.71)	–6.4 (8.91)	–7.7 (7.59)
Week 4	–4.3 (7.87)	–6.4 (8.39)	–12.0 (8.87)
Week 8	–3.9 (8.15)	–6.1 (8.60)	–11.4 (9.69)
Week 12	–3.9 (7.15)	–5.7 (8.35)	–10.5 (7.73)
Week 16	–4.4 (10.30)	–6.3 (8.91)	–10.0 (9.76)
Week 20	–5.1 (9.20)	–6.0 (8.46)	–10.4 (7.33)
Week 24	–4.7 (8.06)	–6.4 (9.05)	–10.9 (7.30)
Week 48	–5.2 (7.80)	–6.0 (9.77)	–10.9 (7.28)
Week 72	–6.6 (8.73)	–7.4 (10.63)	–11.3 (7.05)
Week 96	–2.8 (14.52)	–7.4 (10.89)	–11.5 (8.58)
Week 120	–5.4 (8.69)	–7.6 (11.89)	–10.0 (8.49)
Week 144	–5.1 (8.96)	–8.1 (11.71)	–6.3 (8.57)
Week 168	–6.2 (8.79)	–9.3 (11.82)	–6.1 (8.77)
Week 192	–5.8 (9.63)	–10.1 (9.75)	–7.8 (8.17)
Week 216	–5.5 (7.46)	–8.7 (9.88)	–7.2 (8.49)
Week 240	–6.3 (7.36)	–8.6 (9.94)	–8.1 (8.66)
Week 264	–6.2 (7.85)	–7.7 (10.77)	–7.1 (8.26)
Week 288	–6.5 (8.56)	–7.8 (8.99)	–7.8 (8.21)
Week 312	–6.2 (10.34)	–8.6 (10.65)	–5.3 (13.02)
Week 336	–6.5 (9.34)	–8.3 (9.92)	–7.2 (10.21)
Week 360	–8.1 (9.54)	–8.6 (10.50)	–8.8 (8.99)
Week 384	–7.3 (9.25)	–9.6 (11.32)	–8.6 (11.20)
Week 408	–9.5 (10.20)	–10.3 (11.77)	–10.9 (10.98)
Week 432	–9.8 (10.47)	–8.0 (10.31)	–7.9 (9.49)
Week 456	–7.2 (8.33)	–10.7 (9.02)	–11.0 (9.10)
Week 480	–11.8 (8.95)	–8.0 (4.46)	–10.7 (13.09)
LOT	–8.3 (10.12)	–8.9 (11.33)	–10.8 (10.40)
FU Day 7	–3.4 (10.43)	–5.3 (14.61)	–6.8 (11.63)
FU Day 30	–2.7 (9.12)	–4.9 (11.57)	–3.5 (10.23)
FU Day 90	–3.9 (10.68)	–4.9 (12.68)	–5.3 (6.77)
Last FU Visit	–2.4 (8.56)	–4.8 (11.37)	–3.7 (9.95)

LOT, last on treatment, FEV1, forced expiratory volume in 1 second, FU, follow-up; TP, treatment period. Data are mean (SD).

Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.

eTable 11. Change from baseline by visit for %predicted FVC up to end of TP3

	Ponesimod		
	10 mg (n=139)	**20 mg (n=145)**	**40 mg (n=151)**
Week 1	–0.5 (6.34)	–1.6 (7.37)	–1.6 (8.22)
Week 2	0.0 (5.90)	–1.4 (7.46)	–2.1 (7.59)
Week 4	–1.0 (6.85)	–1.6 (7.71)	–4.0 (8.41)
Week 8	–1.1 (8.23)	–1.8 (7.61)	–4.9 (10.41)
Week 12	–1.6 (7.15)	–1.6 (8.61)	–4.4 (7.69)
Week 16	–1.6 (8.87)	–1.7 (8.40)	–4.5 (7.65)
Week 20	–1.8 (10.61)	–2.1 (8.79)	–4.8 (6.46)
Week 24	–1.9 (8.60)	–1.9 (8.40)	–4.3 (6.65)
Week 48	–1.2 (8.68)	–0.3 (11.10)	–3.1 (7.77)
Week 72	–3.1 (10.28)	–1.2 (10.90)	–2.7 (7.90)
Week 96	0.8 (15.35)	–0.3 (11.30)	–2.7 (8.29)
Week 120	–1.2 (10.06)	0.1 (13.53)	–2.3 (9.71)
Week 144	0.5 (16.47)	–0.8 (13.05)	0.6 (9.11)
Week 168	–2.4 (10.44)	–1.9 (12.49)	0.8 (9.81)
Week 192	–2.4 (11.71)	–1.8 (11.82)	–0.5 (9.22)
Week 216	–1.7 (8.44)	0.0 (15.11)	0.4 (10.14)
Week 240	–2.1 (11.35)	–0.8 (11.58)	–0.2 (9.67)
Week 264	–0.8 (12.66)	0.4 (11.54)	1.1 (8.71)
Week 288	–2.1 (10.17)	0.2 (9.67)	0.5 (8.58)
Week 312	–2.9 (10.05)	–0.5 (10.49)	3.7 (16.72)
Week 336	–1.7 (8.79)	0.7 (10.17)	1.0 (9.99)
Week 360	–3.0 (9.75)	–0.8 (11.95)	–0.2 (9.58)
Week 384	–1.7 (9.15)	–0.6 (12.25)	0.6 (11.17)
Week 408	–3.3 (10.18)	–1.5 (9.77)	–0.7 (9.59)
Week 432	–3.5 (9.55)	0.7 (12.49)	0.6 (9.72)
Week 456	–3.1 (8.73)	–3.2 (9.68)	–2.9 (9.28)
Week 480	–6.6 (4.70)	1.5 (2.04)	–7.1 (9.99)
LOT	–2.9 (10.50)	–1.0 (11.56)	–2.7 (10.12)
FU Day 7	1.3 (11.15)	–0.5 (12.23)	–4.9 (14.75)
FU Day 30	1.7 (10.72)	–1.2 (11.26)	0.5 (21.99)
FU Day 90	2.6 (13.86)	–0.9 (12.44)	–2.4 (8.97)
Last FU Visit	1.9 (9.55)	–0.8 (10.84)	0.0 (20.34)

LOT, last on-treatment; FU, follow-up; FVC, forced vital capacity; TP, treatment period. Data are mean (SD). Placebo period was excluded from the analysis. Patients are summarized under their first randomized dose of ponesimod; patients initially randomized to ponesimod 40 mg were re-randomized to 10 mg or 20 mg in TP2; all patients received ponesimod 20 mg in TP3.