

Table e-1. Patient demographics, and clinical and MRI characteristics at start of core TEMSO study for patients who did not subsequently enter the extension (modified intent-to treat population, core study)

	Teriflunomide 14 mg (n = 107)	Teriflunomide 7 mg (n = 113)	Placebo (n = 126)
Demographics			
Age (years), mean (SD)	36.0 (7.7)	36.2 (9.5)	37.9 (9.7)
Sex (female), n (%)	72 (67.3)	79 (69.9)	96 (76.2)
Caucasian/white, n (%)	100 (93.5)	109 (96.5)	123 (97.6)
Region, n (%)			
Americas	23 (21.5)	21 (18.6)	23 (18.3)
Eastern Europe	34 (321.8)	41 (36.3)	34 (27.0)
Western Europe	50 (46.7)	51 (45.1)	69 (54.8)
Clinical disease characteristics			
Mean (SD) time from first symptoms of MS (years)	7.60 (5.98)	9.11(6.37)	9.54 (8.22)
No. relapses within past 12 months			
Mean (SD)	1.3 (0.7)	1.4 (0.8)	1.5 (0.8)
Median (min:max)	1.0 (0:3)	1.0 (0:6)	1.0 (0:6)
MS subtype			
Relapsing-remitting, n (%)	93 (86.9)	100 (88.5)	111 (88.1)
Secondary progressive, n (%)	6 (5.6)	8 (7.1)	13 (10.3)
Progressive relapsing, n (%)	8 (7.5)	5 (4.4)	2 (1.6)
EDSS score			
Mean (SD)	2.87 (1.38)	2.92 (1.41)	2.87 (1.38)
Median (min:max)	2.50 (0.0:5.5)	3.00 (0.0:6.0)	3.00 (0.0:5.5)
MRI characteristics			

	Teriflunomide	Teriflunomide	Placebo
	14 mg	7 mg	(n = 126)
	(n = 107)	(n = 113)	
Total lesion volume (mL)			
Mean (SD)	19.84 (19.57)	19.93 (21.22)	20.73 (19.82)
Median (min:max)	13.59 (0.3:88.8)	13.94 (0.2:103.8)	14.58 (0.1:78.4)
Gd-enhancing T1 lesions, n			
Mean (SD)	2.33 (5.12)	1.44 (4.33)	2.29 (4.33)
Median (min:max)	0.0 (0.0:32.0)	0.0 (0.0:35.0)	0.0 (0.0:23.0)

EDSS = Expanded Disability Status Scale; Gd = gadolinium.

Table e-2. Efficacy outcomes (end of core TEMSO study) for patients who did and did not enter the extension (modified intent-to-treat population population)

	Patients who entered the extension			Patients who did not enter the extension		
	Teriflunomide 14 mg (n = 251)	Teriflunomide 7 mg (n = 252)	Placebo (n = 237)	Teriflunomide 14 mg (n = 107)	Teriflunomide 7 mg (n = 113)	Placebo (n = 126)
ARR						
Patients with ≥ 1 relapse, n (%)	96 (38.2)	101 (40.1)	117 (49.4)	45 (42.1)	53 (46.9)	67 (53.2)
Adjusted ARR	0.291	0.301	0.440	0.786	0.671	0.878
Relative risk (95% CI)	0.660* (0.508, 0.857)	0.683* (0.535, 0.872)		0.895 (0.635, 1.262)	0.764 (0.544, 1.074)	
12-week Disability Progression						
Patients with progression, n (%)	48 (19.1)	52 (20.6)	63 (26.6)	14 (13.1)	16 (14.2)	23 (18.3)
Probability of Disability Progression at 108 weeks (95% CI)	0.191 (0.143, 0.240)	0.206 (0.156, 0.256)	0.266 (0.210, 0.322)	0.299 (0.122, 0.476)	0.265 (0.140, 0.390)	0.254 (0.150, 0.358)
Hazard ratio vs placebo (95% CI)	0.671† (0.461, 0.978)	0.731 (0.506, 1.056)		0.831 (0.426, 1.621)	0.857 (0.449, 1.637)	

* $P < 0.005$ vs placebo, derived using Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline and region as covariates, and log-transformed standardized duration as an offset variable.

ARR, annualized relapse rate

† $P < 0.05$ vs placebo, derived from a log-rank test with treatment group as test variable, and region and baseline EDSS score as stratification factors.

Table e-3A. Serious AEs (≥ 2 events in any treatment group)

	Crude incidence, n (%)			
	Teriflunomide 14 mg/14 mg (n = 250)	Placebo/ teriflunomide 14 mg (n = 106)	Teriflunomide 7 mg/7 mg (n = 254)	Placebo/ teriflunomide 7 mg (n = 130)
Infections and infestations				
Urinary tract infection	2 (0.8)	0	1 (0.4)	1 (0.8)
Gastroenteritis	0	0	2 (0.8)	0
Pneumonia	1 (0.4)	0	2 (0.8)	0
Erysipelas	2 (0.8)	0	0	0
Appendicitis	1 (0.4)	0	2 (0.8)	0
Pyelonephritis	0	0	0	2 (1.5)
Neoplasms benign, malignant, and unspecified				
Uterine leiomyoma	1 (0.4)	2 (1.9)	0	1 (0.8)
Psychiatric disorders				
Suicidal ideation	2 (0.8)	0	0	0
Nervous system disorders				
Cerebrovascular insufficiency	0	0	2 (0.8)	0
Vascular disorders				
Venous stenosis	1 (0.4)	0	3 (1.2)	0
Gastrointestinal disorders				
Abdominal pain	2 (0.8)	0	0	0
Inguinal hernia	2 (0.8)	0	2 (0.8)	0
Musculoskeletal and connective tissue disorders				
Intervertebral disc protrusion	2 (0.8)	0	4 (1.6)	1 (0.8)
Reproductive system and breast disorders				
Endometriosis	2 (0.8)	0	0	0
Investigations				
ALT increased	7 (2.8)	3 (2.8)	3 (1.2)	4 (3.1)
Injury, poisoning, and procedural complications				
Fall	0	0	2 (0.8)	1 (0.8)
Hand fracture	2 (0.8)	0	0	0

AE = adverse event; ALT = alanine aminotransferase.

Table e-3B. AEs leading to treatment discontinuation (≥ 2 events in any treatment group)

	Crude incidence, n (%)			
	Teriflunomide 14 mg/14 mg (n = 250)	Placebo/ teriflunomide 14 mg (n = 106)	Teriflunomide 7 mg/7 mg (n = 254)	Placebo/ teriflunomide 7 mg (n = 130)
Vascular disorders				
Venous stenosis	0	0	2 (0.8)	0
Pregnancy, puerperium and perinatal conditions				
Pregnancy ^a	2 (0.8)	1 (0.9)	1 (0.4)	0
Investigations				
ALT increased	9 (3.6)	4 (3.8)	7 (2.8)	5 (3.8)
Neutrophil count decreased	0	0	1 (0.4)	2 (1.5)
Hepatic enzyme increased	1 (0.4)	0	3 (1.2)	0

^aDiscontinuations were also reported for 1 event of 'Unintended pregnancy' and 1 event of 'Abortion spontaneous.'

AE = adverse event; ALT = alanine aminotransferase.

Table e-3C. Frequency of AEs (≥10% crude incidence in any treatment group)

	Crude incidence, n (%)				Episodes of AEs per patient, n1 (n2/n)			
	14 mg/14 mg (n = 250)	Placebo/ 14 mg (n = 106)	7 mg/7 mg (n = 254)	Placebo/ 7 mg (n = 130)	14 mg/14 mg (n = 250)	Placebo/ 14 mg (n = 106)	7 mg/7 mg (n = 254)	Placebo/ 7 mg (n = 130)
Infections and infestations								
Nasopharyngitis	80 (32.0)	28 (26.4)	66 (26.0)	32 (24.6)	2.2 (174/80)	1.8 (50/28)	2.5 (167/66)	2.1 (66/32)
Influenza	33 (13.2)	19 (17.9)	37 (14.6)	19 (14.6)	1.6 (54/33)	1.5 (29/19)	1.5 (55/37)	1.4 (27/19)
Urinary tract infection	32 (12.8)	13 (12.3)	27 (10.6)	18 (13.8)	2 (63/32)	1.7 (22/13)	1.7 (46/27)	1.1 (20/18)
Sinusitis	27 (10.8)	4 (3.8)	16 (6.3)	7 (5.4)	1.8 (48/27)	2.5 (10/4)	1.6 (25/16)	1.1 (8/7)
Upper respiratory tract infection	26 (10.4)	11 (10.4)	26 (10.2)	15 (11.5)	1.8 (47/26)	1.5 (16/11)	2 (51/26)	1.5 (22/15)
Psychiatric disorders								
Depression	13 (5.2)	11 (10.4)	22 (8.7)	8 (6.2)	1.1 (14/13)	1.2 (13/11)	1.1 (24/22)	1 (8/8)
Nervous system disorders								
Headache	39 (15.6)	17 (16.0)	40 (15.7)	20 (15.4)	2.7 (106/39)	2.7 (46/17)	2.2 (86/40)	1.6 (31/20)
Paresthesia	23 (9.2)	12 (11.3)	24 (9.4)	6 (4.6)	1.2 (28/23)	1.3 (16/12)	1.3 (32/24)	1.2 (7/6)
Vascular disorders								
Hypertension	27 (10.8)	7 (6.6)	16 (6.3)	9 (6.9)	1.1 (31/27)	1 (7/7)	1.2 (19/16)	1.3 (12/9)
Respiratory, thoracic, and mediastinal disorders								
Cough	19 (7.6)	7 (6.6)	18 (7.1)	14 (10.8)	1.2 (23/19)	1.1 (8/7)	1.2 (20/18)	1 (14/14)
Gastrointestinal disorders								
Diarrhea	30 (12.0)	18 (17.0)	23 (9.1)	17 (13.1)	1.4 (41/30)	1.3 (24/18)	1.4 (32/23)	1.1 (18/17)
Skin and subcutaneous tissue disorders								
Hair thinning	5 (2.0)	18 (17.0)	12 (4.7)	10 (7.7)	1.6 (8/5)	1.1 (19/18)	1.1 (13/12)	1 (10/10)

Musculoskeletal and connective tissue disorders									
Back pain	36 (14.4)	16 (15.1)	34 (13.4)	10 (7.7)	1.2 (42/36)	1.3 (21/16)	1.4 (47/34)	1 (10/10)	
Pain in extremity	29 (11.6)	18 (17.0)	26 (10.2)	13 (10.0)	1.4 (41/29)	1.2 (22/18)	1.4 (37/26)	1.3 (17/13)	
Arthralgia	26 (10.4)	9 (8.5)	27 (10.6)	14 (10.8)	1.3 (33/26)	1.2 (11/9)	1.3 (34/27)	1.2 (17/14)	
General disorders									
Fatigue	23 (9.2)	17 (16.0)	35 (13.8)	16 (12.3)	1.3 (30/23)	1.6 (28/17)	1.2 (42/35)	1.2 (19/16)	
Investigations									
ALT increased	36 (14.4)	19 (17.9)	39 (15.4)	20 (15.4)	1.4 (50/36)	1.3 (25/19)	1.5 (57/39)	1.3 (26/20)	
Injury, poisoning, and procedural complications									
Fall	27 (10.8)	8 (7.5)	23 (9.1)	8 (6.2)	1.8 (48/27)	1.1 (9/8)	1.5 (34/23)	1 (8/8)	

Data presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Events presented by decreasing order of crude incidence in the teriflunomide 14-mg/14-mg group by preferred term, organized by system organ class.

AE = Adverse Event; ALT = alanine aminotransferase; n1 = episodes per patient; n2 = episodes in study; n = total number of patients with at least one AE.