Figure e-2 MRI outcomes in pre-specified patient subpopulations

Reductions with DMF BID or TID vs placebo in T2 (A, B), T1-hypointense (C, D) and Gd+ (E, F) lesion number in pre-specified subpopulations based on baseline demographic and disease characteristics, over the 2 years of the study.

BID = twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF);

EDSS; Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; MS = multiple sclerosis; OR =

odds ratio; TID = three times daily.

A Number of new/enlarging T2 lesions over 2 years by subgroup: DMF* BID vs placebo

		Favors DMF* BID	Favors placebo	
	No. of patients (placebo, DMF*)			Lesion mean ratio (95% Cl)
MRI cohort	139, 140	-•		0.29 (0.21-0.41)
Gender Male Female	46, 45 93, 95	_ -		0.30 (0.18–0.49) 0.27 (0.18–0.42)
Age (years) <40 ≥40	83, 83 56, 57	_ -		0.33 (0.22–0.48) 0.24 (0.13–0.43)
Relapses in the prior year ≤1 relapse ≥2 relapses	99, 93 40, 47	_ -		0.30 (0.20–0.46) 0.29 (0.17–0.51)
McDonald criteria 1 2, 3 or 4	120, 115 19, 25	_ -		0.26 (0.18–0.38) 0.37 (0.17–0.83)
Prior MS treatment No Yes	88, 84 51, 56	_ + _		0.31 (0.21–0.46) 0.22 (0.13–0.40)
Baseline EDSS ≤2.0 >2.0	70, 71 69, 69	_ -		0.26 (0.17–0.41) 0.35 (0.21–0.56)
Baseline T2 lesion volume ≤median >median	69, 70 70, 70	_ -		0.29 (0.18–0.48) 0.29 (0.19–0.46)
Baseline Gd+ lesions Absent Present	74, 68 64, 72	 		0.28 (0.17–0.45) 0.29 (0.19–0.43)
		0.01 0.1	1 10	
		Lesion mean ratio (95	% CI)	

*DMF, delayed-release DMF (also known as gastro-resistant DMF)

B Number of new/enlarging T2 lesions over 2 years by subgroup: DMF* TID vs placebo

		Favors DMF* TID	Favors placebo
	No. of patients (placebo, DMF*)		Lesion mean ratio (95% CI)
MRI cohort	139, 140	-	0.27 (0.20-0.38)
Gender Male Female	46, 42 93, 98	- <u>+</u>	0.28 (0.17–0.45) 0.25 (0.16–0.39)
Age (years) <40 ≥40	83, 72 56, 68	- <u>*</u> -	0.29 (0.19–0.43) 0.33 (0.19–0.56)
Relapses in the prior year ≤1 relapse ≥2 relapses	99, 89 40, 51	- <u>+</u> -	0.28 (0.19–0.43) 0.24 (0.14–0.42)
McDonald criteria 1 2, 3 or 4	120, 121 19, 19	- <u>+</u>	0.28 (0.19–0.40) 0.22 (0.09–0.53)
Prior MS treatment No Yes	88, 85 51, 55	- <u>+</u> -	0.22 (0.15–0.34) 0.33 (0.19–0.57)
Baseline EDSS ≤2.0 >2.0	70, 67 69, 73	- <u>+</u> -	0.25 (0.16–0.39) 0.31 (0.19–0.49)
Baseline T2 lesion volume ≤median >median	69, 77 70, 62	- <u>+</u> -	0.24 (0.15–0.38) 0.30 (0.19–0.47)
Baseline Gd+ lesions Absent Present	74, 79 64, 59	- <u>*</u> -	0.25 (0.15–0.39) 0.29 (0.19–0.45)
		0.01 0.1	1 10

Lesion mean ratio (95% CI)

Number of new non-enhancing T1-hypointense lesions over 2 years by subgroup: DMF* BID vs placebo

		Favors DMF* BID	Favors placebo	
	No. of patients (placebo, DMF*)			Lesion mean ratio (95% CI)
MRI cohort	139, 140			0.43 (0.30-0.61)
Gender Male Female	46, 45 93, 95	_ -		0.37 (0.22–0.64) 0.42 (0.27–0.67)
Age (years) <40 ≥40	83, 83 56, 57	_ -		0.46 (0.31–0.69) 0.39 (0.21–0.74)
Relapses in the prior year ≤1 relapse ≥2 relapses	99, 93 40, 47	_ -		0.45 (0.29–0.69) 0.42 (0.22–0.77)
McDonald criteria 1 2, 3 or 4	120, 115 19, 25	_ + _	_	0.39 (0.26–0.57) 0.52 (0.21–1.29)
Prior MS treatment No Yes	88, 84 51, 56	_ + _		0.44 (0.29-0.68) 0.38 (0.21-0.70)
Baseline EDSS ≤2.0 >2.0	70, 71 69, 69	- • -		0.46 (0.28-0.74) 0.40 (0.24-0.66)
Baseline T2 lesion volume ≤median >median	69, 70 70, 70	_ • _		0.34 (0.20–0.59) 0.51 (0.34–0.78)
Baseline Gd+ lesions Absent Present	74, 68 64, 72			0.24 (0.13–0.42) 0.48 (0.34–0.70)
		0.01 0.1	1 10	
		Lesion mean ratio (95	% CI)	

*DMF, delayed-release DMF (also known as gastro-resistant DMF)

D

Number of new non-enhancing T1-hypointense lesions over 2 years by subgroup: DMF* TID vs placebo

		Favors DMF* TID	Favors placebo	
	No. of patients (placebo, DMF*)			Lesion mean ratio (95% Cl)
MRI cohort	139, 140			0.35 (0.24-0.49)
Gender Male Female	46, 42 93, 98	- <u>+</u>		0.41 (0.24–0.71) 0.29 (0.18–0.46)
Age (years) <40 ≥40	83, 72 56, 68			0.39 (0.26–0.59) 0.37 (0.20–0.69)
Relapses in the prior year ≤1 relapse ≥2 relapses	99, 89 40, 51	 		0.40 (0.26–0.63) 0.25 (0.14–0.45)
McDonald criteria 1 2, 3 or 4	120, 121 19, 19	<u>+</u>		0.37 (0.25–0.54) 0.21 (0.08–0.59)
Prior MS treatment No Yes	88, 85 51, 55	- <u>*</u>		0.26 (0.16-0.40) 0.51 (0.28-0.92)
Baseline EDSS ≤2.0 >2.0	70, 67 69, 73	 		0.38 (0.23–0.62) 0.30 (0.18–0.50)
Baseline T2 lesion volume ≤median >median	69, 77 70, 62	— <u>*</u> —		0.25 (0.15–0.43) 0.42 (0.27–0.65)
Baseline Gd+ lesions Absent Present	74, 79 64, 59	<u>*</u>		0.25 (0.15–0.44) 0.41 (0.28–0.60)
		0.01 0.1	1 10	

Lesion mean ratio (95% CI)

		Favors DMF* BID	Favors placebo	
	No. of patients (placebo, DMF*)	•		OR (95% CI)
MRI cohort	144, 147	_ • _		0.26 (0.15-0.46)
Gender Male Female	47, 46 97, 101	_		0.35 (0.13–0.95) 0.21 (0.11–0.43)
Age (years) <40 ≥40	87, 86 57, 61	_		0.25 (0.13–0.49) 0.21 (0.07–0.65)
Relapses in the prior year ≤1 relapse ≥2 relapses	103, 96 41, 51	_ -		0.23 (0.12–0.45) 0.39 (0.14–1.07)
McDonald criteria 1 2, 3 or 4	125, 120 19, 27	-		0.27 (0.14-0.50) 0.20 (0.05-0.73)
Prior MS treatment No Yes	91, 89 53, 58	_		0.32 (0.16–0.64) 0.17 (0.06–0.44)
Baseline EDSS ≤2.0 >2.0	73, 76 71, 71	_		0.29 (0.14-0.61) 0.23 (0.10-0.56)
Baseline T2 lesion volume ≲median >median	71, 74 73, 73	 •		0.42 (0.18-0.96) 0.18 (0.09-0.39)
Baseline Gd+ lesions Absent Present	76, 73 67, 74		_	0.60 (0.24–1.48) 0.24 (0.12–0.46)
		0.01 0.1	10	
		OR (95% CI)		

*DMF, delayed-release DMF (also known as gastro-resistant DMF)

F

Number of Gd+ lesions at 2 years by subgroup: DMF* TID vs placebo

		Favors DMF* TID	Favors placebo
	No. of patients (placebo, DMF*)		OR (95% Cl)
MRI cohort	144, 144	_ _	0.35 (0.20-0.59)
Gender Male Female	47, 43 97, 101	_	0.28 (0.10–0.81) 0.38 (0.20–0.71)
Age (years) <40 ≥40	87, 75 57, 69		0.27 (0.14–0.55) 0.59 (0.24–1.44)
Relapses in the prior year ≤1 relapse ≥2 relapses	103, 93 41, 51		0.33 (0.17–0.62) 0.40 (0.14–1.10)
McDonald criteria 1 2, 3 or 4	125, 123 19, 21	_	0.40 (0.22–0.71) 0.15 (0.03–0.68)
Prior MS treatment No Yes	91, 86 53, 58	— <u> </u>	0.20 (0.09–0.45) 0.57 (0.26–1.23)
Baseline EDSS ≤2.0 >2.0	73, 69 71, 75		0.30 (0.14–0.64) 0.41 (0.19–0.88)
Baseline T2 lesion volume ≤median >median	71, 79 73, 64	k	0.19 (0.07–0.51) 0.45 (0.23–0.90)
Baseline Gd+ lesions Absent Present	76, 81 67, 61	k	0.45 (0.18–1.15) 0.29 (0.15–0.58)
		0.01 0.1	1 10
		OR (95% CI)	