**Table e-1 Additional baseline demographics and disease characteristics for the MRI cohort**

| Characteristic | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Age, mean (SD) years | 36.6 (9.1) | 38.5 (8.9) | 38.2 (9.7) | 36.8 (8.8) |
| Relapses in previous year, mean (SD) | 1.3 (0.6) | 1.3 (0.7) | 1.3 (0.7) | 1.3 (0.7) |
| EDSS score at baseline, mean (SD)[a] | 2.5 (1.1) | 2.5 (1.1) | 2.5 (1.2) | 2.5 (1.3) |

Abbreviations: BID = twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; MS = multiple sclerosis; TID = three times daily.

[a]Score on the EDSS scale, which ranges from 0 to 10, with higher scores indicating greater degree of disability.

[b]From T1-weighted scans.

## Table e-2 Key baseline characteristics for the MRI cohort and non-MRI cohort

| Characteristic | MRI cohort (n = 681) | Non-MRI cohort (n = 736) |
|---|---|---|
| Age, years | | |
| Mean | 37.5 | 37.1 |
| Median | 37.0 | 37.0 |
| Female, n (%) | 478 (70) | 515 (70) |
| Prior approved MS treatment, n (%)[a] | 195 (29) | 220 (30) |
| Time since first MS symptoms, years | | |
| Mean | 7.9 | 7.4 |
| Median | 7.0 | 6.0 |
| Relapses in previous year | | |
| Mean | 1.3 | 1.4 |
| Median | 1.0 | 1.0 |
| EDSS score[b] | | |
| Mean | 2.5 | 2.6 |
| Median | 2.5 | 2.5 |

Abbreviations: DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

[a]Interferon beta-1a, interferon beta-1b, natalizumab, and glatiramer acetate; one patient each in the placebo, DMF BID, and glatiramer acetate groups and three patients in the DMF TID group had previously been exposed to glatiramer acetate. Patients may have received more than one prior MS medication. Patients may also have received other non-approved therapies for MS.

[b]Score on the EDSS scale, which ranges from 0 to 10, with higher scores indicating greater degree of disability.

**Table e-3 T2 lesion number and volume outcomes during the 96-week study (intent-to-treat MRI cohort)**

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Patients included in analysis, n | 139 | 140 | 140 | 153 |
| Number of new/enlarging T2 lesions from baseline to 2 years (week 96)[a] | | | | |
| Mean (SD) | 19.9 (25.27) | 5.7 (11.07) | 5.1 (8.73) | 9.6 (19.11) |
| Median ($25^{th}$, $75^{th}$ percentile) | 11.0 (4.0, 26.0) | 2.0 (0.0, 5.5) | 2.0 (0.0, 6.0) | 3.0 (1.0, 9.0) |
| Adjusted mean (95% CI) | 17.4 (13.5, 22.4) | 5.1 (3.9, 6.6) | 4.7 (3.6, 6.2) | 8.0 (6.3, 10.2) |
| Lesion mean ratio (95% CI) | | 0.29 (0.21, 0.41) | 0.27 (0.20, 0.38) | 0.46 (0.33, 0.63) |
| % reduction vs placebo (95% CI) | | 71 (59, 79) | 73 (62, 80) | 54 (37, 67) |
| *p*-value | | <0.0001 | <0.0001 | <0.0001 |
| Number of new/enlarging T2 lesions from baseline to 1 year (week 48)[a] | | | | |
| Mean (SD) | 10.6 (13.62) | 3.5 (6.17) | 2.9 (4.57) | 5.6 (12.06) |
| Median ($25^{th}$, $75^{th}$ percentile) | 6.0 (2.0, 14.0) | 1.0 (0.0, 4.0) | 1.0 (0.0, 4.0) | 2.0 (0.0, 4.0) |
| Adjusted mean (95% CI) | 9.5 (7.3, 12.3) | 3.1 (2.4, 4.1) | 2.8 (2.2, 3.7) | 4.6 (3.6, 5.8) |
| Lesion mean ratio (95% CI) | | 0.33 (0.24, 0.46) | 0.30 (0.21, 0.42) | 0.48 (0.35, 0.67) |
| % reduction vs placebo (95% CI) | | 67 (54, 76) | 70 (58, 79) | 52 (33, 65) |
| *p*-value | | <0.0001 | <0.0001 | <0.0001 |

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Number of new/enlarging T2 lesions from 1 year (week 48) to 2 years (week 96)[a] | | | | |
| Mean (SD) | 9.4 (13.14) | 2.2 (5.35) | 2.3 (4.84) | 4.1 (9.15) |
| Median ($25^{th}$, $75^{th}$ percentile) | 4.0 (1.0, 11.0) | 0.5 (0.0, 2.0) | 1.0 (0.0, 3.0) | 1.0 (0.0, 4.0) |
| Adjusted mean (95% CI) | 8.0 (6.0, 10.7) | 2.0 (1.4, 2.7) | 1.9 (1.4, 2.6) | 3.4 (2.6, 4.5) |
| Lesion mean ratio (95% CI) | | 0.24 (0.17, 0.36) | 0.24 (0.16, 0.35) | 0.43 (0.30, 0.62) |
| % reduction vs placebo (95% CI) | | 76 (64, 83) | 76 (65, 84) | 57 (38, 70) |
| *p*-value | | <0.0001 | <0.0001 | <0.0001 |
| Patients with new/enlarging T2 lesions at 2 years (week 96), n (%) | | | | |
| 0 lesions | 17 (12) | 38 (27) | 43 (31) | 36 (24) |
| 1 lesion | 7 (5) | 24 (17) | 21 (15) | 22 (14) |
| 2 lesions | 4 (3) | 16 (11) | 13 (9) | 12 (8) |
| 3 lesions | 5 (4) | 11 (8) | 12 (9) | 9 (6) |
| ≥4 lesions | 106 (76) | 51 (36) | 51 (36) | 74 (48) |
| Volume of T2 lesions at 1 year (week 48), $mm^3$ | | | | |
| Mean (SD) | 13601.3 (11674.71) | 12534.7 (11384.34) | 12557.6 (12458.33) | 13225.2 (13778.81) |
| Median (min, max) | 11341.0 (457, 62417) | 9256.5 (175, 58050) | 8006.5 (394, 68112) | 8733.0 (392, 79780) |

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Change in T2 lesion volume from baseline to 1 year (week 48), $mm^3$ | | | | |
| Mean (SD) | 641.2 (3095.81) | -756.4 (2284.06) | -595.8 (3652.73) | -439.6 (3280.77) |
| Median (min, max) | 367.0 (-18991, 10932) | -378.5 (-9812, 8076) | -100.0 (-31590, 7062) | -259.0 (-12808, 12337) |
| *p*-value[b] | | <0.0001 | 0.0002 | <0.0001 |
| % change in T2 lesion volume from baseline to 1 year (week 48) | | | | |
| Mean (SD) | 11.9 (32.04) | -4.2 (20.05) | 0.0 (21.66) | -0.3 (30.18) |
| Median ($25^{th}$, $75^{th}$ percentile) | 4.8 (-5.0, 17.2) | -4.2 (14.1, 3.6) | -0.3 (-12.4, 9.2) | -3.4 (-14.2, 4.7) |
| *p*-value[b] | | <0.0001 | <0.0001 | <0.0001 |
| Volume of T2 lesions at 2 years (week 96), $mm^3$ | | | | |
| Mean (SD) | 13742.0 (10332.81) | 12235.1 (10837.42) | 12166.1 (10640.00) | 12568.7 (12406.16) |
| Median (min, max) | 13742.0 (451, 53884) | 9752.5 (168, 59615) | 11367.5 (508, 44852) | 9158.0 (304, 68443) |
| Change in T2 lesion volume from baseline to 2 years (week 96), $mm^3$ | | | | |
| Mean (SD) | 744.7 (3662.44) | -1035.8 (2657.15) | -800.5 (3933.29) | -946.0 (3766.58) |
| Median (min, max) | 744.7 (-23104, 17637) | -705.5 (-13758, 9958) | -347.0 (-29064, 7788) | -689.0 (-11537, 24796) |
| *p*-value[b] | | <0.0001 | <0.0001 | <0.0001 |
| % change in T2 lesion volume from baseline to 2 years (week 96) | | | | |
| Mean (SD) | 14.6 (31.48) | -7.4 (20.74) | -1.5 (23.60) | -3.4 (29.29) |
| Median ($25^{th}$, $75^{th}$ percentile) | 14.6 (-2.0, 18.7) | -7.4 (-19.5, 1.2) | -1.5 (-15.0, 7.1) | -6.3 (-16.3, 4.5) |
| *p*-value[b] | | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: BID = twice daily; GA = glatiramer acetate; TID = three times daily.

[a]Adjusted mean, percentage reduction, 95% CI and *p*-value for comparison between active and placebo groups, based on negative binomial regression, adjusted for region and baseline volume of T2 lesions.

[b]*p*-value for comparison between active and placebo groups, based on analysis of covariance on ranked data, adjusted for region and baseline T2 lesion volume.

**Table e-4 T1-hypointense lesion number and volume outcomes during the 96-week study (intent-to-treat MRI cohort)**

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Patients included in analysis, n | 139 | 140 | 140 | 154 |
| Number of new T1-hypointense lesions from baseline to 2 years (week 96)[a] | | | | |
| Mean (SD) | 8.1 (10.43) | 3.8 (6.91) | 2.7 (5.09) | 4.5 (8.13) |
| Median ($25^{th}$, $75^{th}$ percentile) | 4.0 (1.0, 11.0) | 1.0 (0.0, 5.0) | 1.0 (0.0, 3.0) | 2.0 (0.0, 5.0) |
| Adjusted mean (95% CI) | 7.0 (5.3, 9.2) | 3.0 (2.3, 4.0) | 2.4 (1.8, 3.2) | 4.1 (3.2, 5.3) |
| Lesion mean ratio (95% CI) | | 0.43 (0.30, 0.61) | 0.35 (0.24, 0.49) | 0.59 (0.42, 0.82) |
| % reduction vs placebo (95% CI) | | 57 (39, 70) | 65 (51, 76) | 41 (18, 58) |
| *p*-value | | <0.0001 | <0.0001 | 0.0021 |
| Number of new T1-hypointense lesions from baseline to 1 year (week 48)[a] | | | | |
| Mean (SD) | 4.2 (5.33) | 2.7 (5.30) | 1.6 (2.54) | 2.8 (5.07) |
| Median ($25^{th}$, $75^{th}$ percentile) | 2.0 (0.0, 6.0) | 1.0 (0.0, 3.0) | 1.0 (0.0, 2.0) | 1.0 (0.0, 3.0) |
| Adjusted mean (95% CI) | 3.7 (2.8, 4.8) | 2.2 (1.7, 2.9) | 1.5 (1.1, 2.0) | 2.6 (2.0, 3.4) |
| Lesion mean ratio (95% CI) | | 0.59 (0.42, 0.84) | 0.40 (0.28, 0.57) | 0.70 (0.50, 0.98) |
| % reduction vs placebo (95% CI) | | 41 (16, 58) | 60 (43, 72) | 30 (2, 50) |
| *p*-value | | 0.0030 | <0.0001 | 0.0402 |

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Number of new T1-hypointense lesions from 1 year (week 48) to 2 years (week 96)[a] | | | | |
| Mean (SD) | 4.0 (5.82) | 1.2 (3.61) | 1.1 (3.02) | 1.7 (3.91) |
| Median ($25^{th}$, $75^{th}$ percentile) | 2.0 (0.0, 6.0) | 0.0 (0.0, 1.0) | 0.0 (0.0, 1.0) | 0.0 (0.0, 2.0) |
| Adjusted mean (95% CI) | 3.3 (2.4, 4.6) | 1.0 (0.7, 1.4) | 0.9 (0.7, 1.4) | 1.5 (1.1, 2.1) |
| Lesion mean ratio (95% CI) | | 0.30 (0.19, 0.46) | 0.29 (0.18, 0.45) | 0.45 (0.29, 0.69) |
| % reduction vs placebo (95% CI) | | 70 (54, 81) | 71 (55, 82) | 55 (31, 71) |
| *p*-value | | <0.0001 | <0.0001 | 0.0002 |
| Patients with new T1-hypointense lesions from baseline to 2 years (week 96), n (%) | | | | |
| 0 lesions | 29 (21) | 55 (39) | 61 (44) | 53 (34) |
| 1 lesion | 8 (6) | 21 (15) | 21 (15) | 19 (12) |
| 2 lesions | 10 (7) | 15 (11) | 19 (14) | 22 (14) |
| 3–4 lesions | 29 (21) | 12 (9) | 9 (6) | 18 (12) |
| ≥5 lesions | 63 (45) | 37 (26) | 30 (21) | 42 (27) |
| Volume of T1-hypointense lesions at 1 year (week 48), $mm^3$ | | | | |
| Mean (SD) | 3745.4 (5509.00) | 3329.5 (4541.46) | 3569.5 (5139.88) | 3245.2 (4462.43) |
| Median (min, max) | 1871.0 (0, 33014) | 1657.0 (0, 29530) | 1829.0 (0, 39195) | 1328.0 (0, 26480) |

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Change in T1-hypointense lesion volume from baseline to 1 year (week 48), $mm^3$ | | | | |
| Mean (SD) | 179.9 (1054.51) | 154.6 (1253.73) | 180.9 (1117.33) | 81.5 (1258.38) |
| Median (min, max) | 67.5 (-2717, 6223 ) | 3.5 (-2212, 10956) | 22.0 (-3614, 6977) | 2.5 (-5152, 6426) |
| *p*-value[b] | | 0.2607 | 0.6719 | 0.1412 |
| % change in T1-hypointense lesion volume from baseline to 1 year (week 48) | | | | |
| Mean (SD) | 16.0 (83.45) | 10.5 (64.43) | 11.4 (45.81) | 10.3 (60.33) |
| Median ($25^{th}$, $75^{th}$ percentile) | 7.9 (-11.5, 26.8) | 1.5 (-13.8, 19.6) | 2.8 (-9.6, 25.2) | 2.5 (-17.2, 27.9) |
| *p*-value[b] | | 0.2587 | 0.6540 | 0.2741 |
| Volume of T1-hypointense lesions at 2 years (week 96), $mm^3$ | | | | |
| Mean (SD ) | 3878.0 (4684.08) | 3352.1 (4154.05) | 3421.9 (3851.61) | 3393.6 (4360.81) |
| Median (min, max) | 3878.0 (0, 33114) | 2125.0 (0, 28492) | 2681.5 (0, 17922) | 1884.5 (0, 21863) |
| Change in T1-hypointense lesion volume from baseline to 2 years (week 96), $mm^3$ | | | | |
| Mean (SD) | 342.4 (878.46) | 198.1 (1380.00) | 190.7 (1204.16) | 214.7 (1389.03) |
| Median (min, max) | 335.7 (-2866, 4989) | 92.0 (-5746, 9918) | 64.0 (-5908, 5956) | 79.0 (-4604, 7646) |
| *p*-value[b] | | 0.0022 | 0.0011 | 0.0009 |
| % change in T1-hypointense lesion volume from baseline to 2 years (week 96) | | | | |
| Mean (SD) | 35.1 (96.52) | 14.1 (54.55) | 14.4 (63.82) | 20.1 (103.02) |
| Median ($25^{th}$, $75^{th}$ percentile) | 19.5 (0.7, 35.1) | 10.7 (-14.3, 20.1) | 8.5 (-9.3, 24.0) | 8.6 (-18.4, 26.5) |
| *p*-value[b] | | 0.0005 | 0.0015 | 0.0013 |

Abbreviations: BID = twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); GA = glatiramer acetate; TID = three times daily.

[a]Adjusted mean, percentage reduction, 95% CI and *p*-value for comparison between the active and placebo groups based on negative binomial regression, adjusted for region and baseline volume of T1-hypointense lesions.

[b]*p*-value for comparison between active and placebo groups, based on analysis of covariance on ranked data, adjusted for region and baseline T1-hypointense lesion volume.

**Table e-5 Gd+ lesion number and volume outcomes during the 96-week study (intent-to-treat MRI cohort)**

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Patients included in analysis, n | 144 | 147 | 144 | 161 |
| Number of Gd+ lesions at 6 months (week 24)[a] | | | | |
| Mean (unadjusted 95% CI)[b] | 1.7 (1.0, 2.3) | 0.5 (0.2, 0.7) | 0.5 (0.3, 0.6) | 1.6 (0.4, 2.7) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (0.0, 2.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 1.0) |
| Odds ratio (95% CI) | | 0.20 (0.11, 0.34) | 0.31 (0.18, 0.52) | 0.58 (0.37, 0.92) |
| % reduction vs placebo (95% CI) | | 81 (66, 89) | 69 (48, 82) | 42 (8.2, 63) |
| *p*-value | | <0.0001 | <0.0001 | 0.0201 |
| Number of Gd+ lesions at 1 year (week 48)[a] | | | | |
| Mean (unadjusted 95% CI)[b] | 2.2 (1.3, 3.2) | 0.4 (0.1, 0.7) | 0.4 (0.2, 0.6) | 0.7 (0.4, 1.0) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (0.0, 2.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 1.0) |
| Odds ratio (95% CI) | | 0.13 (0.07, 0.23) | 0.23 (0.13, 0.39) | 0.37 (0.23, 0.59) |
| % reduction vs placebo (95% CI) | | 87 (77, 93) | 77 (61, 87) | 63 (41, 77) |
| *p*-value | | <0.0001 | <0.0001 | <0.0001 |

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Number of Gd+ lesions at 2 years (week 96)[a] | | | | |
| Mean (unadjusted 95% CI)[b] | 2.0 (1.0, 2.9) | 0.5 (0.2, 0.8) | 0.4 (0.2, 0.6) | 0.7 (0.4, 0.9) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (0.0, 1.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) |
| Odds ratio (95% CI) | | 0.26 (0.15, 0.46) | 0.35 (0.20, 0.59) | 0.39 (0.24, 0.65) |
| % reduction vs placebo (95% CI) | | 74 (54, 85) | 65 (41, 80) | 61 (35, 76) |
| *p*-value | | <0.0001 | 0.0001 | 0.0003 |
| Patients with Gd+ lesions at 2 years (week 96), n (%) | | | | |
| 0 lesions | 88 (61) | 118 (80) | 116 (81) | 124 (77) |
| 1 lesion | 25 (17) | 16 (11) | 16 (11) | 19 (12) |
| 2 lesions | 8 (6) | 4 (3) | 7 (5) | 6 (4) |
| 3–4 lesions | 3 (2) | 4 (3) | 4 (3) | 3 (2) |
| ≥5 lesions | 20 (14) | 5 (3) | 1 (<1) | 9 (6) |
| Patients included in analysis, n | 143 | 147 | 142 | 161 |
| Volume of Gd+ lesions at 6 months (week 24), $mm^3$ | | | | |
| Mean (SD) | 143.6 (489.96) | 46.0 (179.60) | 30.9 (107.39) | 162.5 (686.12) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (0.0, 142.6) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 66.0) |
| *p*-value[c,d] | | <0.0001 | <0.0001 | 0.0544 |

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Change in Gd+ lesion volume from baseline to 6 months (week 24), $mm^3$ | | | | |
| Mean (SD) | -31.1 (506.99) | -284.5 (805.53) | -184.5 (745.04) | -91.7 (560.41) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (-53.0, 14.0) | -21.0 (-246.0, 0.0) | 0.0 (-64.0, 0.0) | 0.0 (-103.0, 0.0) |
| *p*-value[c] | | <0.0001 | 0.0085 | 0.0764 |
| % change in Gd+ lesion volume from baseline to 6 months (week 24) | | | | |
| Mean (SD) | 163.2 (676.03) | -92.6 (21.64) | -56.1 (105.53) | 28.0 (326.03) |
| Median (min, max) | -72.5 (-100, 4560) | -100.0 (-100, 31) | -100.0 (-100, 522) | -92.1 (-100, 1579) |
| *p*-value[c] | | <0.0001 | 0.0001 | 0.0105 |
| Volume of Gd+ lesions at 1 year (week 48), $mm^3$ | | | | |
| Mean (SD) | 189.5 (437.18) | 27.0 (101.19) | 56.2 (237.12) | 77.0 (244.64) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (0.0, 188.2) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 38.0) |
| *p*-value[c,d] | | <0.0001 | <0.0001 | <0.0001 |
| Change in Gd+ lesion volume from baseline to 1 year (week 48), $mm^3$ | | | | |
| Mean (SD) | 31.2 (529.48) | -321.4 (807.79) | -162.1 (674.31) | -181.7 (611.95) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (0.0, 38.0) | -37.0 (-321.4, 0.0) | 0.0 (-99.0, 0.0) | 0.0 (-181.7, 0.0) |
| *p*-value[c] | | <0.0001 | <0.0001 | <0.0001 |

| MRI assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| % change in Gd+ lesion volume from baseline to 1 year (week 48) | | | | |
| Mean (SD) | 424.3 (1401.61) | -35.6 (346.32) | -19.0 (310.24) | -13.8 (310.10) |
| Median (min, max) | -31.1 (-100, 8080) | -100.0 (-100, 2783) | -100.0 (-100, 1938) | -100.0 (-100, 1950) |
| *p*-value[c] | | <0.0001 | <0.0001 | <0.0001 |
| Volume of Gd+ lesions at 2 years (week 96), $mm^3$ | | | | |
| Mean (SD) | 141.8 (339.14) | 35.9 (128.46) | 42.6 (149.94) | 45.6 (135.77) |
| Median ($25^{th}$, $75^{th}$ percentile) | 21.0 (0.0, 140.8) | 0.0 (0.0, 35.9) | 0.0 (0.0, 42.0) | 0.0 (0.0, 45.6) |
| *p*-value[c,d] | | <0.0001 | <0.0001 | <0.0001 |
| Change in Gd+ lesion volume from baseline to 2 years (week 96), $mm^3$ | | | | |
| Mean (SD) | -7.2 (448.59) | -251.8 (595.55) | -181.7 (738.54) | -202.5 (573.45) |
| Median ($25^{th}$, $75^{th}$ percentile) | 0.0 (-7.2, 0.0) | -61.0 (-251.8, 0.0) | 0.0 (-181.7, 0.0) | -21.0 (-202.5, 0.0) |
| *p*-value[c] | | <0.0001 | 0.1151 | 0.0031 |
| % change in Gd+ lesion volume from baseline to 2 years (week 96) | | | | |
| Mean (SD) | 408.0 (1711.26) | -67.6 (132.79) | -27.0 (194.77) | -35.1 (261.11) |
| Median (min, max) | 14.1 (-100, 13460) | -100.0 (-100, 976) | -100.0 (-100, 1122) | -100.0 (-100, 2041) |
| *p*-value[c] | | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: BID =twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); Gd+ = gadolinium-enhancing; GA = glatiramer acetate; TID = three times daily.

[a]Odds ratio, percentage reduction and *p*-value for comparison between active and placebo groups based on ordinal logistic regression, adjusted for region and baseline number of Gd+ lesions.

[b]95% CI of the mean is calculated using t distribution under the large sample assumption.

[c]*p*-value for comparison between active and placebo groups, based on analysis of covariance on ranked data, adjusted for region and baseline Gd+ volume.
[d]Post hoc analysis.

**Table e-6 Whole brain volume outcomes (percentage brain volume change) during the 96-week study (intent-to-treat MRI cohort)**

| Assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Patients included in analysis, n | 144 | 147 | 144 | 161 |
| Percentage change from baseline to week 24 | | | | |
| Mean (SD) | -0.230 (0.8935) | -0.157 (0.8851) | -0.200 (0.7657) | -0.304 (0.7049) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.233 (-0.690, 0.205) | -0.035 (-0.630, 0.320) | -0.110 (-0.630, 0.290) | -0.300 (-0.690, 0.030) |
| *p*-value[a] | | 0.1053 | 0.4299 | 0.3816 |
| Percentage change from baseline to week 48 | | | | |
| Mean (SD) | -0.434 (1.0437) | -0.500 (1.2476) | -0.432 (0.9130) | -0.516 (0.8886) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.440 (-1.005, 0.150) | -0.320 (-0.960, 0.100) | -0.450 (-0.930, 0.070) | -0.580 (-1.060, 0.020) |
| *p*-value[a] | | 0.6645 | 0.9299 | 0.2593 |
| Percentage change from baseline to week 96 | | | | |
| Mean (SD) | -1.026 (1.7315) | -0.889 (2.1690) | -0.844 (1.5673) | -0.956 (1.4056) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.945 (-1.890, -0.040) | -0.660 (-1.290, -0.110) | -0.750 (-1.530, -0.210) | -0.960 (-1.540, -0.350) |
| *p*-value[a] | | 0.0645 | 0.2636 | 0.8802 |

| Assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Percentage change from week 24 to week 48 | | | | |
| Mean (SD) | -0.186 (0.8039) | -0.408 (0.7251) | -0.229 (0.6260) | -0.279 (0.6936) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.205 (-0.600, 0.210) | -0.250 (-0.680, 0.070) | -0.270 (-0.575, 0.110) | -0.280 (-0.670, 0.040) |
| *p*-value[b] | | 0.0857 | 0.4636 | 0.1190 |
| Percentage change from week 24 to week 96 | | | | |
| Mean (SD) | -0.801 (1.4016) | -0.886 (1.7165) | -0.636 (1.4250) | -0.645 (1.4064) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.765 (-1.345, -0.135) | -0.720 (-1.340, -0.120) | -0.745 (-1.290, -0.095) | -0.640 (-1.060, -0.140) |
| *p*-value[b] | | 0.8306 | 0.5621 | 0.7063 |
| Percentage change from week 48 to week 96 | | | | |
| Mean (SD) | -0.601 (0.9683) | -0.454 (1.1988) | -0.419 (1.0091) | -0.432 (0.8459) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.590 (-1.110, –0.020) | -0.400 (-0.870, 0.040) | -0.400 (-0.920, 0.045) | -0.420 (-0.940, 0.010) |
| *p*-value[b] | | 0.0359 | 0.0755 | 0.0805 |

Abbreviations: BID = twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); GA = glatiramer acetate; MS = multiple sclerosis; TID = three times daily.

Analysis based on observed data after excluding patients who switched to alternative MS medications. Missing data prior to alternative MS medications and visits after patients switched are included and imputed using constant rate assumptions.

[a]*p*-value for comparison between active and placebo groups, based on analysis of covariance on ranked data, adjusted for region and normalized brain volume at baseline.

[b]*p*-value for comparison between active and placebo groups, based on analysis of covariance on ranked data, adjusted for region and normalized brain volume at week 24.

**Table e-7 Whole brain volume outcomes (percentage brain volume change) relative to baseline at Week 96 – based on re-analysis data by MRI center**

| Re-analysis data | Placebo | DMF BID | DMF TID | GA |
|---|---|---|---|---|
| Observed + missing imputed analysis[a] | | | | |
| Sample size per group re-analysis (sample size in original analysis) | 140 (144) | 138 (147) | 134 (143) | 153 (161) |
| Mean/median | -1.302/ -1.205 | -0.864/-0.770 | -0.973/-0.875 | -1.320/-1.162 |
| % improvement relative to placebo based on median value | | 36% (p=0.0026) | 27% (p=0.0110) | 4% (p=0.6488) |
| Observed value only analysis[b] | | | | |
| Sample size per group (sample size in original analysis) | 83 (107) | 97 (121) | 89 (119) | 98 (131) |
| Mean/median | -1.253/-1.030 | -0.982/-0.770 | -0.999/-0.860 | -1.162/-1.030 |
| % improvement relative to placebo based on median value | | 25% (p=0.0687) | 17% (p=0.0767) | 0 (p=0.7976) |

Abbreviations: BID = twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); GA = glatiramer acetate; TID = three times daily.

[a]Primary analysis: observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are imputed using the constant rate assumption.

[b] Observed data after subjects switched to alternative MS medications are excluded

P-value for comparison between the active and placebo groups are based on analysis of covariance (ANCOVA) on ranked data, adjusted for region and baseline normalized brain volume.

**Table e-8 Whole brain MTR outcomes (percentage change) during the 96-week study (intent-to-treat MRI cohort) – observed data**

| Assessment | Placebo (n = 167) | DMF BID (n = 169) | DMF TID (n = 170) | GA (n = 175) |
|---|---|---|---|---|
| Percentage change from baseline to week 48, n | 86 | 87 | 78 | 90 |
| Mean (SD) | -0.370 (1.3399) | -0.315 (1.1573) | -0.203 (1.4162) | -0.099 (1.4609) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.386 (-1.146, 0.332) | -0.332 (-1.016, 0.320) | 0.000 (-0.942, 0.645) | -0.119 (-0.970, 0.677) |
| *p*-value[a] | | 0.7188 | 0.4847 | 0.1985 |
| Percentage change from baseline to week 96, n | 74 | 83 | 78 | 91 |
| Mean (SD) | -0.419 (1.6721) | -0.167 (1.5690) | -0.008 (1.6252) | 0.010 (1.5733) |
| Median ($25^{th}$, $75^{th}$ percentile) | -0.323 (-1.245, 0.327) | 0.000 (-0.672, 0.640) | 0.000 (-0.997, 0.957) | 0.000 (-0.976, 0.954) |
| *p*-value[a] | | 0.2827 | 0.1071 | 0.0901 |

Abbreviations: BID = twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); GA = glatiramer acetate; TID = three times daily.

Observed data after subjects switched to alternative MS medications are excluded

[a]*p*-value for comparison between active and placebo groups, based on analysis of covariance, adjusted for region and whole brain MTR value at baseline.

**Table e-9 Linear relationship[a] between MRI endpoints and clinical endpoints**

| MRI variable | Clinical variable | Placebo | DMF BID | DMF TID | GA | Overall | p-value[b] | No. of patients |
|---|---|---|---|---|---|---|---|---|
| New T2 count | Subject relapse rate | 0.19276 | 0.14650 | 0.20053 | 0.16095 | 0.21093 | <.0001 | 572 |
| New T1 count | Subject relapse rate | 0.16153 | 0.18711 | 0.21713 | 0.08188 | 0.17718 | <.0001 | 573 |
| % change of T2 volume | Subject relapse rate | 0.10500 | 0.05081 | 0.03044 | 0.16539 | 0.11132 | 0.0078 | 571 |
| % change of T1 volume | Subject relapse rate | 0.10926 | 0.00113 | 0.08113 | 0.07055 | 0.08630 | 0.0473 | 529 |
| PBVC | EDSS | 0.05967 | -0.03710 | -0.08224 | 0.10387 | 0.01301 | 0.7739 | 490 |

Abbreviations: BID = twice daily; DMF = delayed-release dimethyl fumarate (also known as gastro-resistant DMF); EDSS = Expanded Disability Scale Score; GA = glatiramer acetate; PBVC = Percentage Brain Volume Change; TID = three times daily.

[a]Linear relationship between a MRI variable and a clinical variable is calculate using Spearman's rank correlation coefficient.
[b]*p*-values are based on overall correlation, using t test.