**Supplemental material 5**

**Remaining secondary efficacy endpoints**

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| --- | --- | --- | --- | --- |
|  | **Endpoint values** | **Treatment effects, dimethyl fumarate vs placebo (n=54)a** |  |  |
| **Efficacy measure** | **Placebo (n=24)** | **Dimethyl fumarate (n=26)** | **Estimate**b | ***95% CI*** | ***p-valuec*** |
| IgG index at baseline | 0.6 (0.5–0.9) | 0.6 (0.5–0.8) |  |  | 0.74 |
| IgG index change | -0.03(0.12) | -0.03 (0.08) | -0.01  | -0.07–0.06 | 0.82 |
| Albumin quotient at baseline | 5.8 (5.0–7.6) | 8.4 (6.5–9.0) |  |  | 0.02 |
| Albumin quotient change | 0.1 (1.0) | -0.8 (1.7) | -0.6  | -1.4–0.1 | 0.10 |
| FA in NAWM at baseline | 0.39 (0.38–0.40) | 0.39 (0.37–0.40) |  |  | 0.22 |
| FA in NAWM change | -0.001 (0.014) | -0.000 (0.010) | -0.001  | -0.011–0.010 | 0.89 |
| T2 lesion volume at baseline (ml) | 4.6 (1.8–14.9) | 5.5 (3.0–14.2) |  |  | 0.47 |
| T2 lesion volume change (ml) | 0.6 (1.4) | 0.7 (1.1) | 0.2  | -0.5–0.8 | 0.64 |
| MTR in lesions at baseline | 26.3 (25.2–29.2) | 27.6 (24.0–29.0) |  |  | 0.94 |
| MTR in lesions change | 0.4 (1.5) | 0.2 (1.3) | -0.1  | 0.8–0.6 | 0.80 |
| Thalamicd volume at baseline (ml) | 9.5 (8.9–10.2) | 9.7 (8.9–10.2) |  |  | 0.68 |
| Thalamic volumee change (ml) | 0.1 (0.6) | -0.9 (0.1) | -0.2  | -0.5–0.1 | 0.16 |
| T25FW (average) baseline (s) | 5.7 (4.8–7.0) | 6.4 (5.0–8.8) |  |  | 0.34 |
| T25FW (average) change (s) | -0.1 (1.4) | 0.9 (2.7) | 0.9  | -0.0–2.1 | 0.12 |
| 9HPT |  |  |  |  |  |
| Dominant Hand, Average baseline (s) | 23.5 (20.8– 26.8) | 26.3 (24.0–32.6) |  |  | 0.03 |
| Dominant Hand, Average change (s) | 1.9 (9) | -1.4 (6) | -2.4  | -6.6–1.8 | 0.26 |
| Nondominant Hand, Average baseline (s) | 25.8 (21.7–33.1) | 25.8 (24.0–28.3) |  |  | 0.94 |
| Nondominant Hand, Average change (s) | 0.0 (28) | 5 (24) | 4.7  | -8.8–18.3 | 0.49 |
| SDMT baseline | 45.0 (37.8–52.3) | 39.5 (34.3–46.0) |  |  | 0.17 |
| SDMT change | 3.7 (5.3) | 2.5 (6.1) | -1.2  | -4.3–1.9 | 0.45 |

Abbreviations: IgG = Immunoglobulin G; FA = fractional anisotropy; NAWM = Normal appearing white matter; MTR = magnetization transfer ratio; T25FW = Timed 25-foot walk; 9HPT = 9-hole peg test; SDMT = Symbol Digit Modalities Test.

Selected secondary endpoints. All changes were calculated from screening to week 48. All baseline values are presented ad median with IQR. All differences in changes are presented as mean with standard deviation.

aMissing values were imputed with multiple imputations (see statistics).

bAnalyses were conducted by use of one-way ANCOVA with screening value as covariate and by use of multiple imputation for missing data.

cp-value was calculated from Wilcoxon signed rank test for baseline comparisons

dMean of paired thalamic nuclei was used.

**Tertiary efficacy endpoints**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **PLACEBO (N=24)** | **DIMETHYL FUMARATE (N=26)** | **Between-group difference (95% CI)a** | **p value** |
| **Clinical** |  |  |  |  |
| Change in BVMT-R | 0.8 (-1.5–3.0) | 0.4 (-2.1–2.9) | -1.0 (-3.8–1.8) | 0.48 |
| Change in CVLT-II | 1.7 (-2.6–6.0) | 1.3 (-1.5–4.2) | -0.6 (-5.2–4.1) | 0.81 |
| **MRI related** |  |  |  |  |
| New Gd-enhancing lesions at week 48b |  |  |  |  |
|    0 | 20 (90.9%) | 25 (100.0%) |  |  |
|    2 | 1 (4.5%) | 0 (0.0%) |  |  |
|    1 | 1 (4.5%) | 0 (0.0%) |  |  |
| New lesions at week 48c | 1.2 (0.3–2.1) | 1.2 (0.5–1.9) | -0.1 (-0.8–0.6) | 0.75 |
| Enlarged lesions at week 48c | 1.9 (0.9–2.8) | 1.8 (1.0–2.7) | -0.1 (-0.6–0.4) | 0.76 |
| CGM volume (ml) change | -0.9 (-5.0–3.2) | -5.6 (-9.8–-1.4) | -3.6 (-8.7–1.6) | 0.17 |
| NAWM volume (ml) change | -0.9 (-6.1–4.4) | -0.9 (-5.2–3.4) | -0.17 (-6.2–5.8) | 0.96 |
| Putamend volume (ml) change | 0.1 (0.0–0.2) | -0.1 (-0.2–0.0) | -0.17 (-0.35–0.02) | 0.08 |
| MTR in CGM change | 0.2 (-0.3–0.7) | 0.1 (-0.3–0.6) | -0.1 (-0.6–0.5) | 0.80 |
| MTR in NAWM change | 0.3 (-0.2–0.8) | 0.1 (-0.4–0.6) | -0.1 (-0.7–0.4) | 0.60 |
| MTR in thalamusd change | 0.3 (-0.2–0.8) | 0.0 (-0.5–0.5) | -0.2 (-0.8–0.4) | 0.53 |
| MTR in putamend change | 0.4 (-0.2–0.9) | 0.0 (-0.5–0.5) | -0.5 (-1.1–0.2) | 0.14 |
| MD in CGM change | 0.00 (-0.01–0.02) | -0.00 (-0.01–0.01) | 0.00 (-0.03–0.02) | 0.77 |
| MD in NAWM change | 0.001 (-0.008–0.006) | -0.004 (-0.012–0.003) | 0.002 (-0.012–0.016) | 0.77 |
| MD in thalamusd change | -0.003 (-0.020–0.014) | -0.001 (-0.016–0.014) | 0.005 (-0.022–0.031) | 0.72 |
| MD in putamend change | 0.001 (-0.012–0.014) | 0.016 (0.000–0.032) | 0.017 (-0.015–0.048) | 0.29 |
| MD in lesions change | -0.003 (-0.016–0.010) | 0.010 (-0.007–0.026) | 0.013 (-0.021–0.047) | 0.44 |
| FA in CGM change  | -0.000 (-0.004–0.003) | -0.006 (-0.008–-0.003) | 0.003 (-0.009–0.002) | 0.21 |
| FA in thalamusd change | 0.002 (-0.006–0.009) | -0.001 (-0.008–0.006) | -0.002 (-0.015–0.010) | 0.68 |
| FA in putamend change | -0.007 (-0.025–0.010) | -0.004 (-0.011–0.003) | -0.004 (-0.036–0.028) | 0.80 |
| C2 cross-sectional area (mm2) change | -0.488 (-1.758–0.782) | -1.614 (-2.880–-0.348) | -1.10 (-2.74–0.54) | 0.18 |
| **Self-reported outcomes** |  |  |  |  |
| UDI-6 change | 3.9 (-2.8–10.5) | 7.2 (-0.2–14.6) | 7.0 (-1.5–15.5) | 0.10 |
| FSMC Cognitive change | 0.6 (-2.4–3.6) | 0.5 (-3.6–4.6) | 0.0 (-3.8–3.9) | 0.99 |
| FSMC Physical change | 1.9 (-0.8–4.5) | 0.2 (-4.3–4.6) | -1.0 (-4.9–2.9) | 0.62 |
| FSMC Total change | 2.5 (-2.2–7.1) | 0.7 (-7.6–90) | -1.0 (-8.2–6.1) | 0.78 |
| MSIS-29 Physical change | -1.1 (-7.5–5.3) | -1.5 (-7.7–4.7) | 2.4 (-4.7–9.4) | 0.50 |
| MSIS-29 Psychological change | 0.3 (-7.6–8.1) | 0.8 (-7.0–8.6) | 0.95 (-12.0–10.1) | 0.86 |

Abbreviations: BVMT-R = Brief Visuospatial Memory Test Revised; CVLT-II = California Verbal Learning Test 2; Gd = Gadolinium; CGM = cortical grey matter; NAWM = normal appearing white matter; MTR = magnetisation transfer ratio; MD = mean diffusivity; FA = fractional anisotropy; C2 = cervical spinal cord level 2; UDI = Urinary Distress Inventory; FSMC = Fatigue Scale for Motor and Cognitive Functions; MSIS-29 = Multiple Sclerosis Impact Scale 29.

All changes were calculated from screening to week 48.

**a**Analyses were conducted by use of one-way ANCOVA with screening value as covariate and missing data were handled by use of multiple imputation (see statistics section).

bDue to contraindications 2 participants did not receive contrast at screening and week 48 visit.

cAnalyses were based on negative binomial regression with number of T2-lesions at screening as covariate.

dMean of the paired thalamic nuclei or paired putamen nuclei was used, respectively.