

Supplementary Tables

Table S1: Binary logistic regression results, GROUP 1 and GROUP 2 membership as a dependent variable (Baseline – Month 12)

| | B (SE) | Odds Ratio | 95% CI | p-value |
|--|-----------------|---------------------|----------------------------|---------|
| Intercept | -21.067 (9.822) | 7.09 ⁻¹⁰ | 3.09 ⁻¹⁸ -0.163 | 0.032* |
| MS Duration | 0.033 (0.027) | 1.033 | 0.981-1.089 | 0.218 |
| Baseline EDSS | 0.336 (0.159) | 1.399 | 1.026-1.909 | 0.034* |
| Baseline BPF | 0.210 (0.115) | 1.233 | 0.984-1.545 | 0.069 |
| Baseline T1Lesion Volume (Square Root) | 0.487 (0.360) | 1.627 | 0.803-3.295 | 0.176 |
| Baseline CCF | -4.125(4.170) | 0.016 | 4.56 ⁻⁶ -57.311 | 0.323 |
| Baseline SDMT Z-score | 0.206 (0.154) | 1.229 | 0.909-1.662 | 0.181 |

Legend: BPF = Brain parenchymal fraction, CCF = corpus callosum fraction; R² = 0.022 (Cox & Snell), 0.062 (Nagelkerke), 0.051 (McFadden). Model $\chi^2= 13.8(6)$, p= 0.032.

Predictors selected from the pool of variables showing meaningful between-group differences (see Table 1), based on results of Omnibus Likelihood Ration Test (p<0.7) and on VIF statistics preventing collinearity issues.

* p < 0.05, ** p < 0.01, *** p < 0.001

Table S2: [Confirmatory Analysis, Month 12 – Month 24] Binary logistic regression results, GROUP 1 and GROUP 2 membership as a dependent variable (Month 12 – Month 24)

| | B (SE) | Odds Ratio | 95% CI | p-value |
|------------------------------------|----------------|--------------------|----------------------------|---------|
| Intercept | 26.354 (9.479) | 2.79 ¹¹ | 2383.6-3.27 ¹⁹ | 0.005** |
| MS Duration | -0.037 (0.033) | 0.964 | 0.903-1.029 | 0.274 |
| M12 EDSS | 0.208 (0.164) | 1.231 | 0.893-1.696 | 0.204 |
| M12 BPF | -0.338 (0.114) | 0.713 | 0.570-0.893 | 0.003** |
| M12 T1 Lesion Volume (Square Root) | 0.524 (0.340) | 1.690 | 0.867-3.292 | 0.123 |
| M12 CCF | -4.879 (5.226) | 0.008 | 2.71 ⁷ -213.786 | 0.351 |
| M12 SDMT Z-score | 0.456 (0.160) | 1.578 | 1.154-2.157 | 0.004** |

Legend: M12 = Month 12, BPF = Brain parenchymal fraction, CCF = corpus callosum fraction; R² = 0.055 (Cox & Snell), 0.169 (Nagelkerke), 0.143 (McFadden). Model χ²= 31.9(6), p < 0.001.

For comparability, similar predictors as in the main analysis were selected (see Supplementary Table 4).

* p < 0.05, ** p < 0.01, *** p < 0.001

Table S3: Change of basic sample characteristics over 12 months (Baseline – Month 12)

| | N Total | All Groups | GROUP 1 | GROUP 2 | GROUP 3 | GROUP 4 | Sig. | Effect Size |
|----------------------------------|---------|-------------|-------------|------------|-------------|---------------|----------------------|--------------------|
| Neurological | | | | | | | | |
| EDSS Change† | 1091 | 0 (0 – 0) | 0 (0 – 0) | 0 (0 – 0) | 0 (0 – 0.5) | 0.5 (0 – 0.5) | N/A‡ | N/A‡ |
| ≥1 Relapse Baseline-Month 12 (%) | 1091 | 266 (24.4%) | 0 (0%) | 0 (0%) | 250 (74.0%) | 16 (61.5%) | N/A‡ | N/A‡ |
| Treatment Escalation (%) | 1091 | 143 (13.1%) | 63 (9.2%) | 6 (13.6%) | 70 (20.7%) | 4 (15.4%) | < 0.001 ³ | 0.155 ⁴ |
| Neuropsychological | | | | | | | | |
| SDMT Z-Score Change | 1091 | 0.14±0.78 | 0.24±0.67 | -1.57±0.87 | 0.25±0.61 | -1.17±0.49 | N/A‡ | N/A‡ |
| BDI Total Score Change | 1091 | -0.19±5.43 | -0.34±5.01 | 0.36±6.96 | 0.07±6.00 | -0.65±5.71 | 0.396 ¹ | 0.003 ² |
| BDI Baseline – M12 Worsening (%) | 1091 | 46 (4.2%) | 20 (2.9%) | 3 (6.8%) | 22 (6.5%) | 1 (3.8%) | 0.047 ³ | 0.085 ⁴ |
| BDI Baseline – M12 Depressed (%) | 1091 | 431 (39.5%) | 232 (34.0%) | 24 (54.5%) | 163 (48.2%) | 12 (46.2%) | < 0.001 ³ | 0.149 ⁴ |
| Radiological | | | | | | | | |
| BPF Change (%) | 763 | -0.07±0.77 | -0.01±0.63 | -0.29±0.65 | -0.11±0.98 | -0.60±1.03 | 0.002 ¹ | 0.019 ² |
| CC Change (%) | 762 | -1.65±2.37 | -1.61±2.26 | -1.92±2.68 | -1.70±2.54 | -1.70±2.74 | 0.690 ¹ | 0.002 ² |
| T1 LV Change (ml) | 749 | 0.05±0.45 | 0.05±0.41 | 0.01±0.27 | 0.06±0.48 | 0.18±1.06 | 0.973 ¹ | 0.000 ² |
| T2 LV Change (ml) | 749 | 0.15±1.23 | 0.08±0.97 | -0.01±1.17 | 0.21±1.37 | 1.42±3.44 | 0.398 ¹ | 0.004 ² |

Legend: Group 1 = Neurologically & Cognitively Stable, Group 2 = Neurologically Stable but Cognitively Worsening, Group 3 = Neurologically Worsening but Cognitively Stable, Group 4 = Neurologically and Cognitively Worsening, BPF = Brain parenchymal fraction, CC = corpus callosum, T1 LV = T1 Lesion Volume, T2 LV = T2 Lesion Volume, M12 = Month 12; ¹Kruskal-Wallis H test, ² χ^2 -test, ³ χ^2 -test, ⁴Cramer's-V; Differences losing significance after BH procedure are not highlighted. Unless otherwise indicated, mean±SD reported.

† The difference was not statistically tested because it stems from the group definition per se

‡ Reported median and interquartile range

Table S4: [Confirmatory Analysis, Month 12 – Month 24] Basic sample characteristics at Month 12

| Characteristics | N Total | All Groups | GROUP 1 | GROUP 2 | GROUP 3 | GROUP 4 | Sig. | Effect Size |
|---------------------------|---------|-----------------|-----------------|------------------|-----------------|-----------------|-------------------------------|--------------------|
| Demographic | | | | | | | | |
| Number of patients (%) | 1060 | 1060 (100%) | 692 (65.3%) | 50 (4.7%) | 291 (27.5%) | 27 (2.6%) | N/A | N/A |
| Females (%) | 1060 | 733 (69.2%) | 459 (66.3%) | 38 (76.0%) | 215 (73.9%) | 21 (77.8%) | 0.053 ¹ | 0.085 ² |
| Age | 1060 | 38.5±9.1 | 38.4±9.1 | 42.1±10.0 | 37.8±8.7 | 40.3±7.6 | 0.017³ | 0.010 ⁴ |
| Education | 1060 | 14.7±3.0 | 14.7±3.0 | 15.0±3.1 | 14.6±3.0 | 14.3±3.1 | 0.757 ³ | 0.001 ⁴ |
| Neurological | | | | | | | | |
| Disease Duration | 1060 | 10.0±7.3 | 9.5±7.2 | 12.8±8.1 | 10.3±7.2 | 12.7±7.6 | 0.002³ | 0.014 ⁴ |
| EDSS† | 1060 | 2.0 (1.5 – 3.5) | 2.0 (1.5 – 3.5) | 3.25 (2.0 – 4.0) | 2.5 (1.5 – 4.0) | 3.5 (2.0 – 4.0) | < 0.001³ | 0.027 ⁴ |
| DMT (%) | 1060 | | | | | | 0.585 ¹ | 0.047 ² |
| High Efficacy | | 276 (26.0%) | 171 (24.7%) | 14 (28.0%) | 80 (27.5%) | 11 (40.7%) | | |
| Low Efficacy | | 657 (62.0%) | 439 (63.4%) | 29 (58.0%) | 175 (60.1%) | 14 (51.9%) | | |
| Neuropsychological | | | | | | | | |
| Cogn. Impaired ‡ (%) | 1060 | 325 (30.7%) | 187 (27.0%) | 20 (40.0%) | 105 (36.1%) | 13 (48.1%) | 0.003¹ | 0.116 ² |
| SDMT Z-Score | 1060 | -0.87±1.41 | -0.79±1.33 | -0.90±1.98 | -1.06±1.43 | -0.90±1.93 | 0.058 ³ | 0.007 ⁴ |
| BDI Total Score | 1060 | 7.4±7.4 | 6.8±7.1 | 7.6±7.1 | 9.0±7.7 | 6.9±8.4 | < 0.001³ | 0.020 ⁴ |
| Radiological | | | | | | | | |
| BPF (%) | 796 | 85.1±2.3 | 85.2±2.19 | 83.2±2.56 | 85.0±2.45 | 84.5±2.50 | < 0.001³ | 0.023 ⁴ |
| CCF (%) | 794 | 0.30±0.05 | 0.30±0.05 | 0.26±0.05 | 0.30±0.05 | 0.29±0.05 | 0.003⁵ | 0.015 ⁶ |
| T1 Lesion Volume (ml) | 796 | 1.62±2.09 | 1.46±1.93 | 3.18±3.40 | 1.79±2.19 | 2.06±1.89 | 0.002³ | 0.019 ⁴ |
| T2 Lesion Volume (ml) | 796 | 4.84±7.65 | 4.25±6.99 | 12.6±15.2 | 5.27±7.35 | 5.20±6.36 | < 0.001³ | 0.021 ⁴ |

Legend: Group 1 = Neurologically & Cognitively Stable, Group 2 = Neurologically Stable but Cognitively Worsening, Group 3 = Neurologically Worsening but Cognitively Stable, Group 4 = Neurologically and Cognitively Worsening, DMT = Disease modifying treatment, Cogn. Impaired = Cognitively Impaired
BPF = Brain parenchymal fraction, CCF = corpus callosum fraction; ¹χ²-test, ²Cramer's-V, ³Kruskal-Wallis H test, ⁴ε², ⁵Fischer's One-Way ANOVA, ⁶η²; Differences losing significance after BH procedure are not highlighted. Unless otherwise indicated, mean±SD reported.

‡ Cognitive impairment defined as SDMT below the benchmark of -1.5 SD, using norms adjusted for age and education.

† Reported median and interquartile range

Table S5: [Confirmatory Analysis, Month 12 – Month 24] Change of basic sample characteristics over 12 months (Month 12 – Month 24)

| | N Total | All Groups | GROUP 1 | GROUP 2 | GROUP 3 | GROUP 4 | Sig. | Effect Size |
|---------------------------------|------------|-------------|-------------|------------|-------------|---------------|----------------------|--------------------|
| Neurological | | | | | | | | |
| EDSS Change† | 1060 | 0 (0 – 0) | 0 (0 – 0) | 0 (0 – 0) | 0 (0 – 0.5) | 0.5 (0 – 0.5) | N/A‡ | N/A‡ |
| ≥1 Relapse M12 – M24 (%) | 1060 | 247 (23.3%) | 0 (0%) | 0 (0%) | 227 (78.0%) | 20 (74.1%) | N/A‡ | N/A‡ |
| Treatment Escalation (%) | 1060 | 80 (7.5%) | 31 (4.5%) | 2 (4.0%) | 44 (15.1%) | 3 (11.1%) | < 0.001 ³ | 0.181 ⁴ |
| Neuropsychological | | | | | | | | |
| SDMT Z-Score Change | 1060 | 0.05±0.77 | 0.17±0.64 | -1.40±0.70 | 0.14±0.65 | -1.51±0.51 | N/A‡ | N/A‡ |
| BDI Total Score Change | 1057 | -0.06±5.33 | -0.10±4.95 | -0.80±5.54 | -0.06±6.12 | 2.30±5.18 | 0.081 ¹ | 0.006 ² |
| BDI M12 – M24 Worsening (%) | 1057 | 42 (4.0%) | 24 (3.5%) | 2 (4.1%) | 13 (4.5%) | 3 (11.1%) | 0.235 ³ | 0.064 ⁴ |
| BDI M12 – M24 Depressed (%) | 1050 | 405 (38.2%) | 231 (33.4%) | 19 (38.0%) | 144 (49.5%) | 11 (40.7%) | < 0.001 ³ | 0.146 ⁴ |
| Radiological | | | | | | | | |
| BPF Change (%) | 635 | -0.24±0.60 | -0.20±0.60 | -0.22±0.47 | -0.31±0.60 | -0.37±0.61 | 0.455 ¹ | 0.004 ² |
| CC Change (%) | 623 | -0.67±1.92 | -0.55±1.90 | -1.48±2.10 | -0.80±1.97 | -1.14±1.22 | 0.050 ¹ | 0.013 ² |
| T1 Lesion Volume Change (ml) | 635 | 0.18±0.37 | 0.15±0.28 | 0.42±0.48 | 0.21±0.48 | 0.34±0.65 | 0.060 ¹ | 0.012 ² |
| T2 Lesion Volume Change (ml) | 635 | 0.42±1.43 | 0.29±1.05 | 1.68±2.79 | 0.55±1.86 | 0.67±1.37 | 0.006 ¹ | 0.019 ² |

Legend: Group 1 = Neurologically & Cognitively Stable, Group 2 = Neurologically Stable but Cognitively Worsening, Group 3 = Neurologically Worsening but Cognitively Stable, Group 4 = Neurologically and Cognitively Worsening, BPF = Brain parenchymal fraction, CC = corpus callosum, M12 = Month 12, M24 = Month 24; ¹Kruskal-Wallis H test, ² χ^2 , ³ χ^2 -test, ⁴Cramer's-V; Differences losing significance after BH procedure are not highlighted. Unless otherwise indicated, mean±SD reported.

† The difference was not statistically tested because it stems from the group definition per se

‡ Reported median and interquartile range

Table S6: [Confirmatory Analysis, Month 12 – Month 24] Post-Hoc pairwise comparison of selected subgroups at Month 12

| | GROUP 1 vs. GROUP 2 | | GROUP 1 vs. GROUP 4 | | GROUP 2 vs. GROUP 4 | | GROUP 3 vs. GROUP 4 | |
|-------------------------|---------------------|-------------------|---------------------|-------|---------------------|-------|---------------------|-------|
| | Mean Difference / W | Sig. | Mean Difference / W | Sig. | Mean Difference / W | Sig. | Mean Difference / W | Sig. |
| Age | 3.79 | 0.037 | 1.74 | 0.609 | -1.34 | 0.781 | 2.18 | 0.414 |
| Disease Duration | 4.02 | 0.023 | 3.34 | 0.085 | -0.14 | 1.000 | 2.284 | 0.370 |
| EDSS | 4.85 | 0.003 | 3.26 | 0.097 | -0.48 | 0.987 | 1.07 | 0.874 |
| BDI Total Score | 1.56 | 0.688 | -0.31 | 0.996 | -1.23 | 0.821 | -2.47 | 0.299 |
| BPF | -5.77 | < 0.001 | -2.05 | 0.467 | 1.90 | 0.535 | -1.62 | 0.662 |
| CCF | 0.03 | 0.005 | 0.02 | 0.521 | -0.01 | 0.766 | 0.01 | 0.890 |
| T1 Lesion Volume | 4.69 | 0.005 | 2.43 | 0.315 | -1.43 | 0.745 | 1.40 | 0.757 |
| T2 Lesion Volume | 5.21 | 0.001 | 2.09 | 0.452 | -2.35 | 0.346 | 1.03 | 0.886 |
| T2 Lesion Volume Change | 4.09 | 0.020 | 0.78 | 0.947 | -1.87 | 0.548 | -0.23 | 0.999 |

Legend: Group 1 = Neurologically & Cognitively Stable, Group 2 = Neurologically Stable but Cognitively Worsening, Group 3 = Neurologically Worsening but Cognitively Stable, Group 4 = Neurologically and Cognitively Worsening, BPF = Brain parenchymal fraction, CCF = corpus callosum fraction; ¹Dwass-Steel-Critchlow-Fligner, ²Tukey