# Supplementary material 1

# Supplementary data

Supplementary Table 1 Protocol deviations linked to particular patients, split by trial arm

|  | Allocated Treatment | | | | | | | | | Overall | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | | Riluzole | | Amiloride | | Placebo | | |  | | |
| N | % | N | % | N | % | N | % | N | | % |
| Out-of-time window deviation | 18 | 20.7 | 26 | 34.7 | 15 | 18.5 | 19 | 25.7 | 78 | | 24.6 |
| No |
| Yes | 69 | 79.3 | 49 | 65.3 | 66 | 81.5 | 55 | 74.3 | 239 | | 75.4 |
| Any deviation (excluding out-of-time window deviations) | 69 | 79.3 | 49 | 65.3 | 66 | 81.5 | 55 | 74.3 | 239 | | 75.4 |
| No |
| Yes | 18 | 20.7 | 26 | 34.7 | 15 | 18.5 | 19 | 25.7 | 78 | | 24.6 |
| Any protocol deviation | 87 | 100.0 | 75 | 100.0 | 81 | 100.0 | 74 | 100.0 | 317 | | 100.0 |
| Yes |

Supplementary Table 2 Summary statistics for the clinical secondary outcomes, split by trial arm, at baseline, 48 and 96 weeks

|  | | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| EDSS, score | Timepoint |  | 111 | 111 | 111 | 112 | 445 |
| Baseline | N |
| Mean | 5.901 | 5.838 | 5.878 | 5.871 | 5.872 |
| SD | 0.710 | 0.748 | 0.745 | 0.773 | 0.742 |
| 48 weeks | N | 98 | 97 | 103 | 100 | 398 |
| Mean | 5.985 | 6.036 | 6.005 | 5.905 | 5.982 |
| SD | 0.889 | 0.814 | 0.769 | 0.909 | 0.845 |
| 96 weeks | N | 95 | 92 | 100 | 96 | 383 |
| Mean | 5.932 | 5.962 | 6.030 | 5.953 | 5.970 |
| SD | 1.189 | 1.072 | 1.002 | 1.021 | 1.069 |
| MSFC, z-score | Timepoint |  | 111 | 111 | 111 | 112 | 445 |
| Baseline | N |
| Mean | -0.016 | -0.092 | -0.191 | -0.003 | -0.075 |
| SD | 0.602 | 0.952 | 1.189 | 0.906 | 0.935 |
| 48 weeks | N | 97 | 96 | 103 | 99 | 395 |
| Mean | -0.249 | -0.328 | -0.211 | -0.213 | -0.249 |
| SD | 1.089 | 1.477 | 1.255 | 1.357 | 1.297 |
| 96 weeks | N | 95 | 95 | 100 | 97 | 387 |
| Mean | -0.528 | -0.473 | -0.548 | -0.409 | -0.490 |
| SD | 1.664 | 1.687 | 1.868 | 1.776 | 1.746 |
| PASAT, no. of correct answers | Timepoint |  | 110 | 111 | 111 | 112 | 444 |
| Baseline | N |
| Mean | 36.600 | 36.910 | 39.018 | 41.464 | 38.509 |
| SD | 15.171 | 16.003 | 13.667 | 13.864 | 14.784 |
| 48 weeks | N | 97 | 94 | 103 | 98 | 392 |
| Mean | 36.361 | 39.936 | 38.049 | 41.459 | 38.936 |
| SD | 15.710 | 14.250 | 15.428 | 14.092 | 14.965 |
| 96 weeks | N | 95 | 94 | 99 | 97 | 385 |
| Mean | 36.779 | 38.394 | 41.061 | 41.907 | 39.566 |
| SD | 16.322 | 15.554 | 14.340 | 16.728 | 15.826 |
| T25FW, sec | Timepoint |  | 109 | 111 | 111 | 112 | 443 |
| Baseline | N |
| Mean | 15.699 | 19.836 | 25.136 | 18.633 | 19.842 |
| SD | 12.381 | 28.459 | 38.843 | 28.530 | 28.819 |
| 48 weeks | N | 96 | 96 | 100 | 99 | 391 |
| Mean | 23.639 | 31.248 | 25.510 | 26.498 | 26.710 |
| SD | 31.874 | 49.335 | 38.401 | 43.941 | 41.323 |
| 96 weeks | N | 94 | 93 | 99 | 96 | 382 |
| Mean | 33.899 | 33.953 | 38.988 | 32.882 | 34.976 |
| SD | 50.680 | 52.529 | 56.050 | 52.372 | 52.831 |
| 9HPT, sec-1 | Timepoint |  | 111 | 111 | 111 | 112 | 445 |
| Baseline | N |
| Mean | 0.034 | 0.034 | 0.034 | 0.033 | 0.034 |
| SD | 0.010 | 0.010 | 0.011 | 0.010 | 0.010 |
| 48 weeks | N | 97 | 96 | 103 | 99 | 395 |
| Mean | 0.032 | 0.034 | 0.034 | 0.033 | 0.034 |
| SD | 0.010 | 0.010 | 0.012 | 0.011 | 0.011 |
| 96 weeks | N | 95 | 95 | 100 | 97 | 387 |
| Mean | 0.033 | 0.034 | 0.033 | 0.033 | 0.033 |
| SD | 0.011 | 0.012 | 0.012 | 0.012 | 0.012 |
| SDMT, no. of correct answers | Timepoint |  | 111 | 109 | 109 | 112 | 441 |
| Baseline | N |
| Mean | 44.153 | 44.514 | 43.908 | 44.107 | 44.170 |
| SD | 11.410 | 13.065 | 12.400 | 12.778 | 12.386 |
| 48 weeks | N | 97 | 95 | 101 | 99 | 392 |
| Mean | 44.454 | 45.105 | 43.584 | 44.960 | 44.515 |
| SD | 12.177 | 13.075 | 14.505 | 13.093 | 13.215 |
| 96 weeks | N | 95 | 93 | 100 | 94 | 382 |
| Mean | 44.779 | 44.892 | 42.960 | 46.096 | 44.654 |
| SD | 13.743 | 14.219 | 14.906 | 14.480 | 14.339 |
| HCVA RE, no. of correct answers | Timepoint |  | 111 | 110 | 106 | 110 | 437 |
| Baseline | N |
| Mean | 52.559 | 48.655 | 48.792 | 49.845 | 49.979 |
| SD | 7.067 | 14.725 | 13.951 | 13.368 | 12.682 |
| 48 weeks | N | 97 | 95 | 99 | 99 | 390 |
| Mean | 51.443 | 49.674 | 50.434 | 50.141 | 50.426 |
| SD | 8.626 | 13.150 | 13.033 | 12.969 | 12.072 |
| 96 weeks | N | 96 | 93 | 98 | 95 | 382 |
| Mean | 51.615 | 49.065 | 48.582 | 48.968 | 49.558 |
| SD | 8.647 | 13.468 | 14.678 | 13.190 | 12.715 |
| HCVA LE, no. of correct answers | Timepoint |  | 111 | 110 | 107 | 111 | 439 |
| Baseline | N |
| Mean | 50.838 | 48.473 | 50.075 | 50.378 | 49.943 |
| SD | 10.801 | 14.836 | 11.193 | 12.668 | 12.470 |
| 48 weeks | N | 96 | 95 | 99 | 98 | 388 |
| Mean | 50.688 | 49.642 | 51.000 | 50.520 | 50.469 |
| SD | 10.805 | 14.730 | 9.876 | 11.875 | 11.902 |
| 96 weeks | N | 96 | 93 | 98 | 95 | 382 |
| Mean | 50.490 | 47.806 | 50.082 | 49.095 | 49.385 |
| SD | 11.161 | 15.812 | 10.914 | 13.696 | 13.004 |
| SLCVA 5% RE, no. of correct answers | Timepoint |  | 110 | 108 | 106 | 109 | 433 |
| Baseline | N |
| Mean | 35.155 | 30.713 | 31.660 | 34.147 | 32.938 |
| SD | 10.462 | 15.382 | 14.521 | 14.624 | 13.935 |
| 48 weeks | N | 96 | 95 | 99 | 98 | 388 |
| Mean | 32.573 | 32.768 | 32.556 | 34.000 | 32.977 |
| SD | 11.663 | 15.226 | 14.146 | 14.485 | 13.904 |
| 96 weeks | N | 95 | 93 | 98 | 94 | 380 |
| Mean | 32.621 | 30.677 | 31.888 | 31.915 | 31.782 |
| SD | 13.014 | 16.682 | 14.957 | 15.368 | 15.008 |
| SLCVA 5% LE, no. of correct answers | Timepoint |  | 110 | 108 | 107 | 110 | 435 |
| Baseline | N |
| Mean | 32.927 | 29.963 | 32.579 | 33.927 | 32.359 |
| SD | 12.820 | 16.131 | 13.401 | 14.575 | 14.311 |
| 48 weeks | N | 96 | 95 | 98 | 97 | 386 |
| Mean | 30.427 | 32.747 | 31.480 | 32.258 | 31.725 |
| SD | 12.096 | 14.824 | 13.699 | 14.264 | 13.731 |
| 96 weeks | N | 95 | 93 | 98 | 94 | 380 |
| Mean | 32.611 | 31.151 | 31.827 | 32.415 | 32.003 |
| SD | 13.072 | 15.650 | 12.906 | 13.470 | 13.759 |
| SLCVA 2.5% RE, no. of correct answers | Timepoint |  | 111 | 109 | 106 | 110 | 436 |
| Baseline | N |
| Mean | 19.865 | 19.119 | 19.896 | 20.736 | 19.906 |
| SD | 12.277 | 14.504 | 13.155 | 13.692 | 13.395 |
| 48 weeks | N | 96 | 95 | 99 | 99 | 389 |
| Mean | 17.177 | 19.137 | 19.162 | 20.505 | 19.008 |
| SD | 13.018 | 14.164 | 14.178 | 13.128 | 13.631 |
| 96 weeks | N | 96 | 93 | 98 | 95 | 382 |
| Mean | 17.021 | 18.065 | 17.857 | 19.632 | 18.139 |
| SD | 13.666 | 14.433 | 13.115 | 12.318 | 13.379 |
| SLCVA 2.5% LE, no. of correct answers | Timepoint |  | 111 | 109 | 107 | 111 | 438 |
| Baseline | N |
| Mean | 17.649 | 18.807 | 19.103 | 20.847 | 19.103 |
| SD | 12.356 | 14.164 | 12.709 | 13.978 | 13.331 |
| 48 weeks | N | 96 | 95 | 98 | 98 | 387 |
| Mean | 14.458 | 20.168 | 18.204 | 18.755 | 17.897 |
| SD | 12.115 | 14.435 | 13.376 | 13.656 | 13.532 |
| 96 weeks | N | 96 | 93 | 98 | 95 | 382 |
| Mean | 16.521 | 17.656 | 17.133 | 18.084 | 17.343 |
| SD | 13.160 | 14.228 | 14.209 | 13.378 | 13.710 |
| SLCVA 1.25% RE, no. of correct answers | Timepoint |  | 111 | 109 | 106 | 110 | 436 |
| Baseline | N |
| Mean | 8.937 | 7.688 | 9.066 | 9.845 | 8.885 |
| SD | 10.190 | 10.685 | 10.247 | 11.326 | 10.616 |
| 48 weeks | N | 96 | 94 | 99 | 99 | 388 |
| Mean | 5.792 | 7.564 | 7.697 | 9.535 | 7.662 |
| SD | 8.870 | 11.121 | 10.570 | 11.310 | 10.559 |
| 96 weeks | N | 96 | 93 | 98 | 95 | 382 |
| Mean | 5.000 | 6.430 | 6.286 | 7.600 | 6.325 |
| SD | 8.554 | 10.774 | 8.949 | 10.533 | 9.741 |
| SLCVA 1.25% LE, no. of correct answers | Timepoint |  | 111 | 109 | 107 | 111 | 438 |
| Baseline | N |
| Mean | 6.937 | 7.083 | 8.168 | 9.865 | 8.016 |
| SD | 9.592 | 10.657 | 10.670 | 11.878 | 10.759 |
| 48 weeks | N | 96 | 94 | 98 | 98 | 386 |
| Mean | 4.833 | 7.660 | 7.000 | 8.398 | 6.977 |
| SD | 8.347 | 11.074 | 10.045 | 10.845 | 10.181 |
| 96 weeks | N | 96 | 93 | 98 | 95 | 382 |
| Mean | 4.042 | 6.065 | 5.184 | 6.779 | 5.508 |
| SD | 8.173 | 10.351 | 8.836 | 9.725 | 9.316 |
| MSIS29v2, score | Timepoint |  | 111 | 111 | 111 | 112 | 445 |
| Baseline | N |
| Mean | 65.000 | 69.154 | 63.915 | 66.072 | 66.036 |
| SD | 13.828 | 15.011 | 13.374 | 14.389 | 14.251 |
| 48 weeks | N | 95 | 98 | 104 | 102 | 399 |
| Mean | 66.232 | 71.677 | 68.630 | 69.357 | 68.993 |
| SD | 14.817 | 14.873 | 15.935 | 15.749 | 15.430 |
| 96 weeks | N | 96 | 96 | 101 | 97 | 390 |
| Mean | 69.749 | 72.902 | 72.332 | 69.533 | 71.140 |
| SD | 15.117 | 15.799 | 16.335 | 17.173 | 16.137 |
| MSIS29v2 Psychological Score | Timepoint |  | 111 | 111 | 111 | 112 | 445 |
| Baseline | N |
| Mean | 16.657 | 18.163 | 15.947 | 17.103 | 16.968 |
| SD | 4.759 | 5.427 | 4.511 | 4.977 | 4.979 |
| 48 weeks | N | 95 | 98 | 104 | 102 | 399 |
| Mean | 16.737 | 19.158 | 17.721 | 18.444 | 18.024 |
| SD | 5.213 | 5.255 | 5.620 | 5.352 | 5.420 |
| 96 weeks | N | 96 | 96 | 101 | 97 | 390 |
| Mean | 17.676 | 19.333 | 19.108 | 18.256 | 18.599 |
| SD | 5.257 | 5.352 | 6.063 | 5.799 | 5.651 |
| MSIS29v2 Physical Score | Timepoint |  | 111 | 111 | 111 | 112 | 445 |
| Baseline | N |
| Mean | 48.344 | 50.991 | 47.968 | 48.969 | 49.068 |
| SD | 10.439 | 11.300 | 10.498 | 11.224 | 10.899 |
| 48 weeks | N | 96 | 98 | 104 | 102 | 400 |
| Mean | 49.517 | 52.519 | 50.909 | 50.914 | 50.971 |
| SD | 10.908 | 10.961 | 12.060 | 11.785 | 11.460 |
| 96 weeks | N | 97 | 96 | 101 | 98 | 392 |
| Mean | 52.052 | 53.569 | 53.225 | 51.273 | 52.531 |
| SD | 11.399 | 12.411 | 12.023 | 12.700 | 12.131 |
| MSWSv2 Total Score | Timepoint |  | 111 | 110 | 111 | 112 | 444 |
| Baseline | N |
| Mean | 41.078 | 42.641 | 41.428 | 41.633 | 41.693 |
| SD | 9.773 | 9.319 | 9.182 | 9.935 | 9.544 |
| 48 weeks | N | 95 | 98 | 104 | 102 | 399 |
| Mean | 42.263 | 44.738 | 42.664 | 43.372 | 43.259 |
| SD | 9.352 | 8.053 | 10.122 | 9.919 | 9.424 |
| 96 weeks | N | 96 | 96 | 102 | 96 | 390 |
| Mean | 44.363 | 44.583 | 44.188 | 43.646 | 44.195 |
| SD | 8.804 | 9.620 | 9.445 | 10.134 | 9.481 |
| NFI Summary Interval Score | Timepoint |  | 110 | 109 | 111 | 108 | 438 |
| Baseline | N |
| Mean | 17.430 | 19.052 | 18.013 | 17.803 | 18.074 |
| SD | 3.890 | 4.799 | 4.198 | 3.856 | 4.232 |
| 48 weeks | N | 93 | 98 | 104 | 101 | 396 |
| Mean | 17.874 | 19.420 | 18.474 | 18.202 | 18.498 |
| SD | 3.693 | 4.453 | 5.250 | 4.246 | 4.486 |
| 96 weeks | N | 97 | 96 | 100 | 98 | 391 |
| Mean | 18.326 | 19.708 | 19.384 | 18.337 | 18.938 |
| SD | 3.988 | 4.828 | 5.275 | 5.451 | 4.942 |
| NFI Physical Interval Score | Timepoint |  | 111 | 109 | 111 | 110 | 441 |
| Baseline | N |
| Mean | 14.663 | 15.907 | 15.116 | 14.740 | 15.104 |
| SD | 3.869 | 4.339 | 3.780 | 3.654 | 3.935 |
| 48 weeks | N | 94 | 98 | 104 | 101 | 397 |
| Mean | 14.939 | 16.238 | 15.340 | 15.307 | 15.458 |
| SD | 3.365 | 3.799 | 4.582 | 3.984 | 3.986 |
| 96 weeks | N | 97 | 96 | 101 | 98 | 392 |
| Mean | 15.424 | 16.381 | 16.323 | 14.991 | 15.782 |
| SD | 3.801 | 4.213 | 4.535 | 4.842 | 4.392 |
| NFI Cognitive Interval Score | Timepoint |  | 110 | 109 | 111 | 109 | 439 |
| Baseline | N |
| Mean | 6.215 | 7.065 | 6.517 | 6.306 | 6.525 |
| SD | 2.243 | 2.331 | 2.207 | 2.380 | 2.307 |
| 48 weeks | N | 93 | 98 | 104 | 101 | 396 |
| Mean | 6.583 | 7.076 | 6.905 | 6.609 | 6.796 |
| SD | 2.070 | 2.163 | 2.523 | 2.334 | 2.286 |
| 96 weeks | N | 97 | 96 | 101 | 98 | 392 |
| Mean | 6.768 | 7.410 | 7.094 | 6.757 | 7.007 |
| SD | 2.059 | 2.092 | 2.544 | 2.889 | 2.429 |
| NFI Diurnal Interval Score | Timepoint |  | 111 | 110 | 111 | 110 | 442 |
| Baseline | N |
| Mean | 9.611 | 10.244 | 10.068 | 9.679 | 9.900 |
| SD | 2.932 | 3.104 | 2.780 | 2.504 | 2.841 |
| 48 weeks | N | 93 | 97 | 102 | 101 | 393 |
| Mean | 10.299 | 10.214 | 10.012 | 10.342 | 10.214 |
| SD | 2.447 | 2.479 | 2.764 | 2.457 | 2.537 |
| 96 weeks | N | 96 | 96 | 98 | 96 | 386 |
| Mean | 10.272 | 10.686 | 10.664 | 10.609 | 10.558 |
| SD | 2.851 | 2.475 | 3.240 | 2.582 | 2.799 |
| NFI Nocturnal Interval Score | Timepoint |  | 111 | 111 | 111 | 111 | 444 |
| Baseline | N |
| Mean | 7.599 | 8.243 | 7.748 | 7.961 | 7.888 |
| SD | 2.463 | 2.782 | 2.037 | 2.294 | 2.413 |
| 48 weeks | N | 94 | 98 | 104 | 102 | 398 |
| Mean | 8.077 | 8.374 | 8.109 | 8.166 | 8.181 |
| SD | 2.213 | 2.633 | 2.180 | 2.296 | 2.330 |
| 96 weeks | N | 97 | 96 | 100 | 97 | 390 |
| Mean | 8.347 | 8.413 | 8.690 | 8.171 | 8.407 |
| SD | 2.252 | 2.471 | 2.133 | 2.202 | 2.265 |
| NPRS Pain on average Score | Timepoint |  | 107 | 109 | 110 | 110 | 436 |
| Baseline | N |
| Mean | 2.505 | 3.468 | 3.109 | 2.936 | 3.007 |
| SD | 2.400 | 2.470 | 2.761 | 2.347 | 2.516 |
| 48 weeks | N | 88 | 96 | 101 | 98 | 383 |
| Mean | 2.841 | 3.760 | 3.267 | 3.378 | 3.321 |
| SD | 2.590 | 2.663 | 2.638 | 2.493 | 2.607 |
| 96 weeks | N | 93 | 92 | 98 | 97 | 380 |
| Mean | 2.968 | 3.707 | 3.633 | 3.216 | 3.382 |
| SD | 2.460 | 2.707 | 2.841 | 2.355 | 2.606 |
| BPI score | Timepoint |  | 110 | 110 | 109 | 111 | 440 |
| Baseline | N |
| Mean | 2.534 | 3.742 | 3.045 | 2.860 | 3.045 |
| SD | 2.242 | 2.498 | 2.379 | 2.306 | 2.391 |
| 48 weeks | N | 95 | 98 | 104 | 102 | 399 |
| Mean | 2.908 | 3.825 | 3.269 | 3.183 | 3.298 |
| SD | 2.227 | 2.649 | 2.507 | 2.461 | 2.481 |
| 96 weeks | N | 97 | 96 | 102 | 97 | 392 |
| Mean | 3.200 | 3.766 | 3.860 | 3.314 | 3.539 |
| SD | 2.705 | 2.653 | 2.829 | 2.510 | 2.684 |
| EQ-5D-5L index score | Timepoint |  | 111 | 110 | 111 | 111 | 443 |
| Baseline | N |
| Mean | 0.702 | 0.658 | 0.683 | 0.671 | 0.678 |
| SD | 0.156 | 0.175 | 0.170 | 0.185 | 0.172 |
| 48 weeks | N | 94 | 98 | 103 | 102 | 397 |
| Mean | 0.658 | 0.617 | 0.648 | 0.645 | 0.642 |
| SD | 0.174 | 0.207 | 0.192 | 0.186 | 0.190 |
| 96 weeks | N | 96 | 96 | 102 | 98 | 392 |
| Mean | 0.615 | 0.596 | 0.603 | 0.613 | 0.607 |
| SD | 0.206 | 0.190 | 0.227 | 0.221 | 0.211 |
| EQ-5D-5L VAS: Health State Score | Timepoint |  | 111 | 111 | 111 | 112 | 445 |
| Baseline | N |
| Mean | 67.523 | 61.730 | 66.126 | 65.241 | 65.155 |
| SD | 19.478 | 21.009 | 16.901 | 20.335 | 19.547 |
| 48 weeks | N | 93 | 97 | 103 | 102 | 395 |
| Mean | 66.140 | 58.608 | 63.563 | 62.961 | 62.797 |
| SD | 18.584 | 20.666 | 21.224 | 22.427 | 20.913 |
| 96 weeks | N | 97 | 96 | 102 | 96 | 391 |
| Mean | 61.938 | 59.625 | 61.765 | 64.281 | 61.900 |
| SD | 20.698 | 21.547 | 20.557 | 21.745 | 21.115 |
| NPS: Pain intensity score | Timepoint |  | 111 | 109 | 110 | 112 | 442 |
| Baseline | N |
| Mean | 2.387 | 3.477 | 3.291 | 3.116 | 3.066 |
| SD | 2.498 | 2.707 | 3.131 | 2.757 | 2.803 |
| 48 weeks | N | 92 | 97 | 103 | 102 | 394 |
| Mean | 2.674 | 3.722 | 3.019 | 2.873 | 3.074 |
| SD | 2.512 | 2.886 | 2.828 | 2.695 | 2.755 |
| 96 weeks | N | 93 | 94 | 98 | 97 | 382 |
| Mean | 3.140 | 3.670 | 3.765 | 3.103 | 3.421 |
| SD | 2.903 | 2.978 | 3.252 | 2.592 | 2.945 |
| NPS: Pain sharp Score | Timepoint |  | 110 | 110 | 109 | 112 | 441 |
| Baseline | N |
| Mean | 2.255 | 3.227 | 2.541 | 2.384 | 2.601 |
| SD | 2.781 | 2.936 | 3.081 | 2.788 | 2.912 |
| 48 weeks | N | 95 | 98 | 103 | 102 | 398 |
| Mean | 2.379 | 3.367 | 2.806 | 2.304 | 2.714 |
| SD | 2.852 | 3.081 | 3.172 | 2.852 | 3.013 |
| 96 weeks | N | 94 | 95 | 101 | 98 | 388 |
| Mean | 2.787 | 3.463 | 3.000 | 2.633 | 2.969 |
| SD | 3.186 | 3.158 | 3.302 | 2.916 | 3.147 |
| NPS: Pain hot Score | Timepoint |  | 110 | 110 | 110 | 112 | 442 |
| Baseline | N |
| Mean | 1.545 | 2.782 | 2.309 | 2.554 | 2.299 |
| SD | 2.403 | 2.910 | 3.025 | 2.802 | 2.824 |
| 48 weeks | N | 95 | 98 | 103 | 102 | 398 |
| Mean | 1.916 | 3.000 | 2.311 | 2.225 | 2.364 |
| SD | 2.728 | 3.179 | 2.811 | 2.911 | 2.927 |
| 96 weeks | N | 94 | 95 | 101 | 98 | 388 |
| Mean | 1.830 | 3.358 | 2.782 | 2.500 | 2.621 |
| SD | 2.703 | 3.192 | 3.342 | 2.767 | 3.055 |
| NPS: Pain dull Score | Timepoint |  | 110 | 110 | 110 | 112 | 442 |
| Baseline | N |
| Mean | 2.800 | 3.245 | 2.718 | 3.089 | 2.964 |
| SD | 2.886 | 3.054 | 2.796 | 3.027 | 2.941 |
| 48 weeks | N | 95 | 98 | 103 | 102 | 398 |
| Mean | 2.979 | 3.878 | 3.068 | 3.010 | 3.231 |
| SD | 2.957 | 3.237 | 3.033 | 3.030 | 3.077 |
| 96 weeks | N | 94 | 95 | 101 | 98 | 388 |
| Mean | 2.872 | 3.895 | 3.119 | 3.439 | 3.330 |
| SD | 2.889 | 3.211 | 2.951 | 3.033 | 3.035 |
| NPS: Pain cold score | Timepoint |  | 109 | 110 | 110 | 112 | 441 |
| Baseline | N |
| Mean | 1.615 | 1.745 | 1.773 | 1.750 | 1.721 |
| SD | 2.721 | 2.440 | 2.888 | 2.649 | 2.671 |
| 48 weeks | N | 95 | 98 | 103 | 101 | 397 |
| Mean | 1.611 | 1.878 | 1.951 | 1.941 | 1.849 |
| SD | 2.602 | 2.763 | 2.985 | 2.911 | 2.816 |
| 96 weeks | N | 94 | 95 | 101 | 98 | 388 |
| Mean | 1.745 | 2.021 | 2.178 | 2.153 | 2.028 |
| SD | 2.809 | 2.877 | 2.954 | 2.808 | 2.858 |
| NPS: Pain sensitive score | Timepoint |  | 110 | 110 | 110 | 112 | 442 |
| Baseline | N |
| Mean | 1.536 | 2.545 | 2.082 | 1.652 | 1.952 |
| SD | 2.437 | 2.926 | 2.918 | 2.308 | 2.681 |
| 48 weeks | N | 95 | 98 | 103 | 102 | 398 |
| Mean | 1.421 | 2.776 | 2.340 | 1.971 | 2.133 |
| SD | 2.267 | 3.111 | 2.999 | 2.745 | 2.837 |
| 96 weeks | N | 94 | 95 | 101 | 98 | 388 |
| Mean | 1.596 | 3.253 | 2.356 | 2.224 | 2.358 |
| SD | 2.416 | 3.169 | 3.019 | 2.538 | 2.855 |
| NPS: Pain itchy score | Timepoint |  | 110 | 110 | 110 | 112 | 442 |
| Baseline | N |
| Mean | 1.109 | 1.691 | 1.345 | 1.411 | 1.389 |
| SD | 2.181 | 2.629 | 2.379 | 2.388 | 2.400 |
| 48 weeks | N | 95 | 98 | 103 | 102 | 398 |
| Mean | 1.442 | 2.092 | 1.660 | 1.706 | 1.726 |
| SD | 2.351 | 2.667 | 2.659 | 2.627 | 2.583 |
| 96 weeks | N | 94 | 95 | 101 | 98 | 388 |
| Mean | 1.436 | 2.063 | 1.475 | 1.929 | 1.724 |
| SD | 2.504 | 2.625 | 2.248 | 2.789 | 2.552 |
| NPS: Pain unpleasant score | Timepoint |  | 108 | 110 | 109 | 112 | 439 |
| Baseline | N |
| Mean | 3.426 | 4.045 | 3.844 | 3.652 | 3.743 |
| SD | 2.799 | 2.797 | 3.028 | 2.856 | 2.871 |
| 48 weeks | N | 92 | 98 | 100 | 102 | 392 |
| Mean | 3.489 | 4.520 | 3.900 | 3.578 | 3.875 |
| SD | 2.807 | 3.130 | 3.271 | 2.748 | 3.014 |
| 96 weeks | N | 95 | 94 | 100 | 98 | 387 |
| Mean | 3.516 | 4.500 | 4.540 | 3.929 | 4.124 |
| SD | 2.909 | 3.113 | 3.122 | 2.770 | 3.001 |
| NPS: deep pain intensity score | Timepoint |  | 108 | 108 | 109 | 111 | 436 |
| Baseline | N |
| Mean | 3.435 | 3.972 | 3.624 | 3.757 | 3.697 |
| SD | 3.160 | 3.342 | 3.324 | 3.270 | 3.270 |
| 48 weeks | N | 92 | 96 | 100 | 102 | 390 |
| Mean | 3.348 | 4.313 | 3.730 | 3.500 | 3.723 |
| SD | 3.198 | 3.483 | 3.573 | 2.948 | 3.315 |
| 96 weeks | N | 95 | 93 | 101 | 98 | 387 |
| Mean | 3.589 | 4.505 | 4.386 | 3.541 | 4.005 |
| SD | 3.257 | 3.380 | 3.415 | 2.876 | 3.256 |
| NPS: surface pain intensity score | Timepoint |  | 108 | 109 | 109 | 111 | 437 |
| Baseline | N |
| Mean | 2.037 | 3.239 | 2.807 | 2.423 | 2.627 |
| SD | 2.576 | 2.883 | 2.986 | 2.765 | 2.833 |
| 48 weeks | N | 92 | 98 | 100 | 101 | 391 |
| Mean | 2.380 | 3.204 | 2.990 | 2.644 | 2.811 |
| SD | 2.471 | 2.957 | 3.053 | 2.834 | 2.850 |
| 96 weeks | N | 95 | 93 | 101 | 98 | 387 |
| Mean | 2.147 | 3.548 | 3.079 | 2.888 | 2.915 |
| SD | 2.522 | 3.275 | 2.955 | 2.643 | 2.894 |

9HPT: Nine Hole Peg Test. EDSS: Expanded Disability Status Scale. EuroQol-5 dimensions-5 level. HCVA: high contrast visual acuity. LE: left eye. MSFC: Multiple Sclerosis Functional Composite. MSIS29v2: multiple sclerosis impact scale 29 items version 2. MSWSv2: multiple sclerosis walking scale version 2. NFI: Neurological Fatigue Index. NPRS: numeric pain rating scale. NPS: neuropathic pain scale. PASAT: Paced Auditory Serial Addition Test. RE: right eye. SD: standard deviation. SDMT: Symbol Digit Modalities Test. SLCVA: Sloan Low Contrast Visual Acuity. T25FW: timed-25-foot walk. VAS: visual analogue scale.

Supplementary Table 3 Multiple regression analyses for the clinical secondary outcomes at 48 weeks

| **Outcome variable** | **N** | **AMD**  **(Amiloride – Placebo)** | **95% Confidence Limits\* for AMD** | | **P-value** | **AMD (Fluoxetine – Placebo)** | **95% Confidence Limits\* for AMD** | | **P-value** | **AMD**  **(Riluzole – Placebo)** | **95% Confidence Limits\* for AMD** | | **P-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| EDSS score | 398 | 0.145 | 0.016 | 0.277 | 0.042 | 0.060 | -0.090 | 0.209 | 0.406 | 0.198 | 0.068 | 0.343 | 0.007 |
| 9HPT, sec-1 | 395 | 0.000000756 | -0.00147 | 0.00148 | 0.999 | -0.000893 | -0.00239 | 0.000605 | 0.242 | 0.000465 | -0.00104 | 0.00197 | 0.544 |
| MSFC§, z-score | 395 | 0.062 | -0.113 | 0.236 | 0.488 | -0.092 | -0.269 | 0.085 | 0.308 | 0.010 | -0.168 | 0.188 | 0.913 |
| PASAT, no. of correct answers | 392 | -0.689 | -3.112 | 1.734 | 0.577 | -0.632 | -3.106 | 1.842 | 0.616 | 2.051 | -0.437 | 4.540 | 0.106 |
| SDMT, no. of correct answers | 390 | -0.580 | -2.441 | 1.281 | 0.541 | -1.011 | -2.887 | 0.865 | 0.290 | -0.277 | -2.169 | 1.616 | 0.774 |
| HCVA RE, no. of correct answers | 385 | 1.012 | -1.236 | 3.260 | 0.377 | -1.079 | -3.340 | 1.183 | 0.349 | -0.292 | -2.562 | 1.979 | 0.801 |
| HCVA LE, no. of correct answers | 385 | 0.707 | -1.548 | 2.961 | 0.538 | -0.294 | -2.559 | 1.972 | 0.799 | 1.059 | -1.228 | 3.345 | 0.363 |
| SLCVA 5% RE, no. of correct answers | 380 | -0.276 | -3.185 | 2.633 | 0.852 | -2.822 | -5.740 | 0.096 | 0.058 | -0.215 | -3.159 | 2.729 | 0.886 |
| SLCVA 5% LE, no. of correct answers | 380 | -0.597 | -3.228 | 2.034 | 0.656 | -1.345 | -3.983 | 1.293 | 0.317 | 2.597 | -0.071 | 5.264 | 0.056 |
| SLCVA 2.5% RE, no. of correct answers | 383 | -0.327 | -3.070 | 2.417 | 0.815 | -2.622 | -5.372 | 0.129 | 0.062 | -0.402 | -3.180 | 2.376 | 0.776 |
| SLCVA 2.5% LE, no. of correct answers | 383 | 0.591 | -1.913 | 3.096 | 0.643 | -1.830 | -4.348 | 0.689 | 0.154 | 2.549 | 0.015 | 5.083 | 0.049 |
| SLCVA 1.25% RE, no. of correct answers | 382 | -1.218 | -3.589 | 1.153 | 0.313 | -2.708 | -5.087 | -0.329 | 0.026 | -0.889 | -3.298 | 1.520 | 0.469 |
| SLCVA 1.25% LE, no. of correct answers | 382 | -0.689 | -3.034 | 1.657 | 0.564 | -1.699 | -4.064 | 0.666 | 0.159 | 0.180 | -2.201 | 2.560 | 0.882 |
| MSIS29v2 Total score | 399 | 0.425 | -2.779 | 3.628 | 0.795 | -2.221 | -5.497 | 1.055 | 0.183 | 0.536 | -2.728 | 3.799 | 0.747 |
| MSIS29v2 Physical Impact score | 400 | 0.461 | -1.849 | 2.771 | 0.695 | -1.015 | -3.372 | 1.342 | 0.398 | 0.527 | -1.827 | 2.881 | 0.660 |
| MSIS 29 – Psychological Impact | 399 | -0.097 | -1.303 | 1.108 | 0.874 | -1.261 | -2.491 | -0.030 | 0.045 | 0.083 | -1.141 | 1.308 | 0.894 |
| MSWSv2 score | 398 | -0.715 | -2.599 | 1.169 | 0.456 | -0.866 | -2.796 | 1.063 | 0.378 | 1.013 | -0.910 | 2.937 | 0.301 |
| NPRS Pain on Average score | 377 | -0.287 | -0.875 | 0.302 | 0.339 | -0.394 | -1.010 | 0.222 | 0.209 | -0.044 | -0.643 | 0.556 | 0.886 |
| BPI score | 395 | -0.012 | -0.552 | 0.527 | 0.964 | -0.011 | -0.562 | 0.541 | 0.970 | 0.129 | -0.421 | 0.679 | 0.645 |
| EQ-5D-L5 index score | 395 | 0.003 | -0.039 | 0.046 | 0.874 | 0.002 | -0.041 | 0.046 | 0.916 | -0.016 | -0.059 | 0.028 | 0.482 |
| EQ-5D-L5 VAS score | 395 | 0.681 | -4.490 | 5.853 | 0.796 | 2.641 | -2.671 | 7.953 | 0.329 | -2.696 | -7.963 | 2.572 | 0.315 |
| NFI summary interval score | 390 | 0.189 | -0.799 | 1.178 | 0.707 | 0.304 | -0.716 | 1.324 | 0.558 | 0.575 | -0.439 | 1.589 | 0.266 |
| NFI physical interval score | 393 | -0.039 | -0.961 | 0.884 | 0.934 | -0.050 | -0.998 | 0.897 | 0.917 | 0.508 | -0.438 | 1.454 | 0.292 |
| NFI cognitive score | 391 | 0.124 | -0.321 | 0.569 | 0.584 | 0.226 | -0.232 | 0.684 | 0.333 | -0.056 | -0.514 | 0.401 | 0.809 |
| NFI diurnal interval score | 390 | -0.600 | -1.148 | -0.052 | 0.032 | 0.015 | -0.544 | 0.575 | 0.957 | -0.423 | -0.981 | 0.135 | 0.137 |
| NFI nocturnal interval score | 397 | 0.094 | -0.384 | 0.572 | 0.700 | 0.315 | -0.177 | 0.806 | 0.209 | 0.093 | -0.393 | 0.579 | 0.706 |
| NPS Q1 Pain Intensity score | 392 | -0.006 | -0.632 | 0.620 | 0.985 | 0.167 | -0.477 | 0.812 | 0.610 | 0.567 | -0.071 | 1.204 | 0.081 |
| NPS Q2 Sharp Pain score | 395 | 0.378 | -0.293 | 1.049 | 0.269 | 0.165 | -0.518 | 0.848 | 0.635 | 0.470 | -0.211 | 1.152 | 0.176 |
| NPS Q3 Hot pain score | 396 | 0.153 | -0.485 | 0.790 | 0.638 | 0.429 | -0.229 | 1.086 | 0.201 | 0.559 | -0.086 | 1.205 | 0.089 |
| NPS Q4 Dull pain score | 396 | 0.193 | -0.531 | 0.916 | 0.601 | 0.137 | -0.602 | 0.876 | 0.716 | 0.696 | -0.037 | 1.428 | 0.063 |
| NPS Q5 Cold pain score | 394 | -0.043 | -0.725 | 0.638 | 0.901 | -0.222 | -0.920 | 0.476 | 0.532 | -0.091 | -0.781 | 0.598 | 0.794 |
| NPS Q6 Sensitive pain score | 396 | 0.046 | -0.598 | 0.690 | 0.888 | -0.398 | -1.054 | 0.259 | 0.234 | 0.254 | -0.400 | 0.909 | 0.445 |
| NPS Q7 Itchy pain score | 396 | -0.072 | -0.679 | 0.534 | 0.815 | -0.122 | -0.742 | 0.498 | 0.700 | 0.177 | -0.438 | 0.792 | 0.571 |
| NPS Q9 Unpleasant pain score | 387 | 0.112 | -0.542 | 0.767 | 0.736 | 0.022 | -0.646 | 0.691 | 0.948 | 0.660 | 0.002 | 1.317 | 0.049 |
| NPS Q10a Deep pain intensity | 382 | 0.271 | -0.485 | 1.027 | 0.481 | 0.008 | -0.765 | 0.780 | 0.984 | 0.643 | -0.125 | 1.412 | 0.101 |
| NPS Q10b Surface pain intensity score | 384 | 0.158 | -0.497 | 0.814 | 0.635 | 0.024 | -0.646 | 0.694 | 0.944 | 0.045 | -0.618 | 0.707 | 0.895 |

\*The confidence interval for EDSS is a 95% bootstrap percentile confidence interval based on 1000 resamples.

§Signed square root transformed. Wilcoxon-Mann-Whitney test p-value=0.178

AMD: Adjusted mean difference. 9HPT: Nine Hole Peg Test. BPI: brief pain inventory. EDSS: Expanded Disability Status Scale. EuroQol-5 dimensions-5 level. HCVA: high contrast visual acuity. LE: left eye. MSFC: Multiple Sclerosis Functional Composite. MSIS29v2: multiple sclerosis impact scale 29 items version 2. MSWSv2: multiple sclerosis walking scale version 2. NFI: Neurological Fatigue Index. NPRS: numeric pain rating scale. NPS: neuropathic pain scale. PASAT: Paced Auditory Serial Addition Test. RE: right eye. SDMT: Symbol Digit Modalities Test. SLCVA: Sloan Low Contrast Visual Acuity. T25FW: timed-25-foot walk. VAS: visual analogue scale.

Supplementary Table 4 Results from patient reported pain outcome analyses at 96 weeks

| **Outcome variable** | **N** | **AMD**  **(Amiloride– Placebo)** | **95% Confidence Limits\* for AMD** | | **P-value** | **AMD**  **(Fluoxetine– Placebo)** | **95% Confidence Limits for AMD** | | **P-value** | **AMD**  **(Riluzole – Placebo)** | **95% Confidence Limits for AMD** | | **P-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| NPRS Pain Average score | 374 | 0.156 | -0.422 | 0.734 | 0.596 | 0.018 | -0.577 | 0.612 | 0.954 | 0.144 | -0.446 | 0.734 | 0.631 |
| BPI score | 388 | 0.416 | -0.191 | 1.024 | 0.179 | 0.178 | -0.439 | 0.795 | 0.571 | -0.030 | -0.653 | 0.592 | 0.924 |
| NPS Q1 Pain Intensity score | 379 | 0.384 | -0.303 | 1.071 | 0.273 | 0.524 | -0.173 | 1.222 | 0.140 | 0.398 | -0.300 | 1.096 | 0.263 |
| NPS Q2 Sharp Pain score | 384 | 0.186 | -0.541 | 0.913 | 0.615 | 0.277 | -0.462 | 1.015 | 0.462 | 0.389 | -0.352 | 1.130 | 0.302 |
| NPS Q3 Hot pain score | 385 | 0.333 | -0.357 | 1.024 | 0.343 | 0.008 | -0.701 | 0.718 | 0.982 | 0.669 | -0.034 | 1.372 | 0.062 |
| NPS Q4 Dull pain score | 385 | -0.193 | -0.944 | 0.559 | 0.615 | -0.352 | -1.118 | 0.414 | 0.367 | 0.316 | -0.449 | 1.081 | 0.417 |
| NPS Q5 Cold pain score | 384 | -0.081 | -0.769 | 0.607 | 0.817 | -0.373 | -1.076 | 0.330 | 0.298 | -0.190 | -0.890 | 0.511 | 0.595 |
| NPS Q6 Sensitive pain score | 385 | -0.143 | -0.812 | 0.526 | 0.675 | -0.482 | -1.162 | 0.198 | 0.164 | 0.504 | -0.181 | 1.189 | 0.149 |
| NPS Q7 Itchy pain score | 385 | -0.469 | -1.119 | 0.182 | 0.157 | -0.355 | -1.020 | 0.309 | 0.293 | -0.048 | -0.712 | 0.615 | 0.886 |
| NPS Q9 Unpleasant pain score | 381 | 0.361 | -0.335 | 1.057 | 0.308 | -0.259 | -0.966 | 0.448 | 0.472 | 0.374 | -0.333 | 1.080 | 0.299 |
| NPS Q10a Deep pain intensity score | 378 | **0.876** | **0.092** | **1.661** | **0.029** | 0.176 | -0.623 | 0.975 | 0.666 | **0.851** | **0.046** | **1.656** | **0.038** |
| NPS Q10b Surface pain intensity score | 379 | -0.053 | -0.717 | 0.611 | 0.876 | -0.454 | -1.129 | 0.222 | 0.187 | 0.119 | -0.563 | 0.801 | 0.731 |

AMD: Adjusted mean difference. BPI: brief pain inventory. NPRS: numeric pain rating scale. NPS: neuropathic pain scale. Q: question

Supplementary Table 5 Logistic regression results for NPS Q8 at 96 weeks

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| N=318 | **Adjusted Odds Ratio**  **Amiloride vs placebo** | **95% CI** | | **P-value** | **Adjusted Odds Ratio**  **Fluoxetine vs placebo** | **95% CI** | | **P-value** | **Adjusted Odds Ratio**  **Riluzole vs placebo** | **95% CI** | | **P-value** |
| **Lower** | **Upper** |  | **Lower** | **Upper** |  | **Lower** | **Upper** |  |
| I feel a background pain all of the time and occasional flare ups (breakthrough pain) some of the time (score) | 1.299 | 0.677 | 2.504 | 0.431 | 0.846 | 0.426 | 1.668 | 0.630 | 1.638 | 0.860 | 3.146 | 0.135 |
| I feel a single type of pain all the time | 1.828 | 0.769 | 4.523 | 0.178 | 1.300 | 0.506 | 3.375 | 0.584 | 1.936 | 0.816 | 4.785 | 0.140 |
| I feel a single type of pain only sometimes. Other times, I am pain free (score) | 0.564 | 0.295 | 1.068 | 0.080 | 1.030 | 0.541 | 1.964 | 0.928 | 0.423 | 0.218 | 0.808 | **0.010** |

CI: confidence interval. NPS: neuropathic pain scale.

Supplementary Table 6 Summary statistics for the Advanced MRI outcomes at baseline and 96 weeks: All patients recording baseline and 96 weeks

|  | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| DGMV at baseline (ml) | N | 94 | 94 | 96 | 96 | 380 |
| Mean | 44.34 | 44.34 | 44.76 | 45.34 | 44.7 |
| SD | 3.9 | 3.95 | 3.88 | 4.36 | 4.03 |
| CGMV at baseline (ml) | N | 94 | 94 | 96 | 96 | 380 |
| Mean | 787.46 | 788.87 | 791.26 | 790.23 | 789.47 |
| SD | 47.73 | 37.35 | 40.66 | 48.94 | 43.8 |
| DGMV at 96 weeks (ml) | N | 94 | 94 | 96 | 96 | 380 |
| Mean | 44.22 | 44.03 | 44.41 | 45.16 | 44.46 |
| SD | 3.95 | 3.94 | 3864.385 | 4397.350 | 4052.447 |
| CGMV at 96 weeks (ml) | N | 94 | 94 | 96 | 96 | 380 |
| Mean | 776.94 | 780.3 | 783.66 | 783.2 | 781.05 |
| SD | 47.93 | 37.74 | 43.52 | 48.81 | 44.64 |
| Percentage DGMV change at 96 weeks (ml) | N | 94 | 94 | 96 | 96 | 380 |
| Mean | -0.287 | -0.693 | -0.762 | -0.388 | -0.533 |
| SD | 1.578 | 1.556 | 1.498 | 1.718 | 1.596 |
| Percentage CGMV change at 96 weeks (ml) | N | 94 | 94 | 96 | 96 | 380 |
| Mean | -1.331 | -1.081 | -0.975 | -0.882 | -1.066 |
| SD | 1.261 | 1.443 | 1.283 | 1.263 | 1.320 |
| MUCCA at baseline (mm2) | N | 29 | 32 | 34 | 27 | 122 |
| Mean | 70.634 | 70.253 | 68.088 | 68.637 | 69.383 |
| SD | 9.844 | 9.399 | 7.678 | 10.458 | 9.263 |
| MUCCA at 96 weeks (mm2) | N | 29 | 32 | 34 | 27 | 122 |
| Mean | 69.790 | 69.159 | 67.200 | 68.178 | 68.546 |
| SD | 9.778 | 9.200 | 8.017 | 10.495 | 9.275 |
| Mean NAA at baseline (millimolar units) (London) | N | 27 | 32 | 34 | 28 | 121 |
| Mean | 8.823 | 8.584 | 8.637 | 8.433 | 8.617 |
| SD | 0.948 | 0.969 | 0.861 | 0.891 | 0.915 |
| Mean myo-inositol at baseline (millimolar units) (London) | N | 27 | 32 | 34 | 28 | 121 |
| Mean | 4.946 | 4.842 | 4.893 | 5.010 | 4.918 |
| SD | 0.800 | 0.583 | 0.790 | 0.628 | 0.700 |
| Mean Glx at baseline (millimolar units) (London) | N | 27 | 32 | 34 | 28 | 121 |
| Mean | 10.738 | 10.527 | 10.660 | 10.841 | 10.684 |
| SD | 0.941 | 0.857 | 0.997 | 0.798 | 0.901 |
| Mean NAA at 96 weeks (millimolar units) (London) | N | 27 | 32 | 34 | 28 | 121 |
| Mean | 8.359 | 7.924 | 8.190 | 8.081 | 8.132 |
| SD | 0.817 | 0.742 | 0.698 | 0.722 | 0.750 |
| Mean myo-inositol at 96 weeks (millimolar units) (London) | N | 27 | 32 | 34 | 28 | 121 |
| Mean | 4.444 | 4.608 | 4.556 | 4.776 | 4.595 |
| SD | 0.832 | 0.654 | 0.809 | 0.683 | 0.747 |
| Mean Glx at 96 weeks (millimolar units) (London) | N | 27 | 32 | 34 | 28 | 121 |
| Mean | 9.990 | 9.832 | 9.904 | 10.144 | 9.960 |
| SD | 0.765 | 1.085 | 0.864 | 0.924 | 0.917 |
| Mean NAA at baseline (millimolar units) (Edinburgh) | N | 11 | 8 | 7 | 10 | 36 |
| Mean | 1517.000 | 1529.000 | 1568.286 | 1523.400 | 1531.417 |
| SD | 155.818 | 78.365 | 206.797 | 200.012 | 161.679 |
| Mean NAA at 96 weeks (millimolar units) (Edinburgh) | N | 11 | 8 | 7 | 10 | 36 |
| Mean | 1560.909 | 1576.125 | 1681.286 | 1480.200 | 1565.278 |
| SD | 213.504 | 221.759 | 247.237 | 156.343 | 210.751 |
| Mean myo-inositol at baseline (millimolar units) (Edinburgh) | N | 11 | 8 | 7 | 10 | 36 |
| Mean | 471.818 | 447.625 | 437.286 | 488.300 | 464.306 |
| SD | 50.372 | 68.889 | 84.019 | 82.563 | 70.915 |
| Mean myo-inositol at 96 weeks (millimolar units) (Edinburgh) | N | 11 | 8 | 7 | 10 | 36 |
| Mean | 483.545 | 456.000 | 439.286 | 484.800 | 469.167 |
|  | SD | 67.419 | 81.668 | 59.013 | 95.125 | 76.873 |
| Mean Glx at baseline (millimolar units) (Edinburgh) | N | 11 | 8 | 7 | 10 | 36 |
| Mean | 1223.818 | 1183.500 | 1206.143 | 1170.200 | 1196.528 |
| SD | 166.709 | 115.693 | 205.346 | 126.638 | 149.865 |
| Mean Glx at 96 weeks (millimolar units) (Edinburgh) | N | 11 | 8 | 7 | 10 | 36 |
| Mean | 1142.818 | 1176.375 | 1171.000 | 1148.300 | 1157.278 |
| SD | 152.887 | 112.401 | 164.827 | 178.583 | 149.242 |
| WBV MTR at baseline (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 33.355 | 33.026 | 33.996 | 33.311 | 33.421 |
| SD | 7.013 | 4.149 | 5.856 | 4.829 | 5.375 |
| GM MTR at baseline (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 32.246 | 31.686 | 32.737 | 32.017 | 32.160 |
| SD | 6.926 | 4.090 | 5.816 | 4.926 | 5.357 |
| NAWM MTR at baseline (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 39.285 | 38.865 | 39.456 | 38.983 | 39.133 |
| SD | 6.922 | 4.438 | 5.881 | 5.251 | 5.518 |
| T2L MTR at baseline (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 27.361 | 27.221 | 28.012 | 27.616 | 27.563 |
| SD | 7.935 | 5.571 | 7.435 | 5.741 | 6.555 |
| WBV MTR at 96 weeks (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 33.274 | 33.196 | 33.071 | 32.939 | 33.108 |
| SD | 4.648 | 4.383 | 4.701 | 4.180 | 4.407 |
| GM MTR at 96 weeks (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 32.323 | 31.977 | 31.844 | 31.767 | 31.952 |
| SD | 4.538 | 4.434 | 4.525 | 4.276 | 4.379 |
| NAWM MTR at 96 weeks (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 39.286 | 39.109 | 38.684 | 38.708 | 38.923 |
| SD | 4.841 | 4.649 | 4.835 | 4.670 | 4.684 |
| T2L MTR at 96 weeks (mean) | N | 22 | 30 | 29 | 31 | 112 |
| Mean | 27.459 | 27.911 | 26.945 | 27.193 | 27.373 |
| SD | 5.326 | 6.076 | 6.232 | 5.030 | 5.638 |
| *PWSAD at baseline* (mm2/s) | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 7.673 | 7.565 | 6.956 | 7.671 | 7.525 |
|  | *SD* | 0.957 | 0.594 | 0.326 | 0.744 | 0.758 |
| *PWSFA at baseline* (scaled between 0 and 1) | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 0.443 | 0.439 | 0.457 | 0.436 | 0.442 |
|  | *SD* | 0.030 | 0.023 | 0.008 | 0.015 | 0.022 |
| *PWSMD at baseline* (mm2/s) | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 4.092 | 3.677 | 3.268 | 4.064 | 3.848 |
|  | *SD* | 1.433 | 0.835 | 0.347 | 1.146 | 1.101 |
| *PWSRD at baseline* (mm2/s) | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 4.707 | 4.270 | 4.158 | 4.551 | 4.469 |
|  | *SD* | 1.198 | 0.581 | 0.184 | 0.943 | 0.883 |
| *PWSAD at 96 weeks follow-up* (mm2/s) | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 8.821 | 8.945 | 7.975 | 9.055 | 8.771 |
|  | *SD* | 1.362 | 1.017 | 0.417 | 1.137 | 1.127 |
| *PWSFA at 96 weeks follow-up* (scaled between 0 and 1) | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 0.445 | 0.452 | 0.452 | 0.449 | 0.449 |
|  | *SD* | 0.019 | 0.016 | 0.014 | 0.024 | 0.019 |
| *PWSMD at 96 weeks follow-up* (mm2/s) | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 4.428 | 4.269 | 3.466 | 4.526 | 4.255 |
|  | *SD* | 1.875 | 1.249 | 0.391 | 1.462 | 1.444 |
| *PWSRD at 96 weeks follow-up* | *N* | 11 | 8 | 6 | 10 | 35 |
|  | *Mean* | 4.826 | 4.577 | 4.149 | 4.801 | 4.646 |
|  | *SD* | 1.636 | 0.859 | 0.188 | 1.220 | 1.183 |

Spectroscopy metabolites were measured with water reference scaling.

AMD: adjusted mean difference. CGM: cortical grey matter. CGMV: cortical grey matter volume. DGM: deep grey matter. DGMV: deep grey matter volume. Glx: combined glutamate and glutamine concentration. GM: grey matter. MTR: magnetisation transfer ration. MUCCA= mean upper cervical cross-sectional area. NAA: N-acetyl aspartate. NAWM: normal-appearing white matter. PWSAD: peak width of skeletonised axial diffusivity. PWSFA: peak width of skeletonised fractional anisotropy. PWSMD: peak width of skeletonised mean diffusivity. PWSRD: peak width of skeletonised radial diffusivity. SD: standard deviation. T2L: T2 lesion. WBV: whole brain volume.

Supplementary Table 7 Summary statistics for the OCT left eye RNFL outcomes at baseline and 96 weeks: All patients recording baseline and 96 weeks

|  | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| Global average pRNFL thickness at baseline (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 81.349 | 83.744 | 84.528 | 83.585 | 83.233 |
| SD | 11.337 | 13.926 | 16.452 | 12.958 | 13.591 |
| Temporal sector average pRNFL thickness at baseline (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 48.419 | 50.051 | 51.361 | 52.317 | 50.491 |
| SD | 14.053 | 13.755 | 16.294 | 12.388 | 14.068 |
| Nasal sector average pRNFL thickness at baseline (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 66.767 | 72.795 | 70.917 | 68.244 | 69.566 |
| SD | 16.102 | 18.631 | 15.498 | 15.458 | 16.483 |
| Nasal inferior sector average pRNFL thickness at baseline (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 102.558 | 100.282 | 95.361 | 97.683 | 99.113 |
| SD | 23.371 | 22.348 | 23.850 | 19.976 | 22.352 |
| Temporal inferior sector average pRNFL thickness at baseline (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 112.674 | 115.205 | 118.583 | 116.927 | 115.730 |
| SD | 24.495 | 26.258 | 31.063 | 24.849 | 26.462 |
| Temporal superior sector average pRNFL thickness at baseline(µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 109.953 | 112.487 | 117.528 | 116.049 | 113.862 |
| SD | 22.473 | 18.664 | 26.548 | 18.920 | 21.765 |
| Nasal superior sector average pRNFL thickness at baseline (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 95.186 | 95.923 | 100.278 | 97.902 | 97.220 |
| SD | 21.928 | 21.822 | 18.085 | 20.884 | 20.712 |
| Papillomacular bundle average pRNFL thickness at baseline(µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 37.674 | 38.667 | 39.917 | 40.293 | 39.101 |
| SD | 10.122 | 10.491 | 12.858 | 9.103 | 10.603 |
| Global average pRNFL thickness at 96 weeks(µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 79.488 | 80.103 | 81.056 | 81.707 | 80.566 |
| SD | 10.802 | 13.659 | 16.195 | 12.329 | 13.162 |
| Temporal sector pRNFL average thickness at 96 weeks (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 49.837 | 50.359 | 51.667 | 52.634 | 51.101 |
| SD | 14.420 | 14.383 | 17.537 | 12.577 | 14.644 |
| Nasal sector average pRNFL thickness at 96 weeks (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 59.558 | 63.282 | 62.333 | 63.220 | 62.044 |
| SD | 12.888 | 15.219 | 12.972 | 12.591 | 13.406 |
| Nasal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 94.767 | 94.205 | 87.750 | 93.415 | 92.692 |
| SD | 18.330 | 20.890 | 20.102 | 19.721 | 19.740 |
| Temporal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 117.512 | 115.462 | 118.972 | 117.366 | 117.302 |
| SD | 23.565 | 25.399 | 31.274 | 25.414 | 26.162 |
| Temporal superior sector average pRNFL thickness at 96 weeks(µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 113.674 | 112.744 | 118.417 | 116.122 | 115.151 |
| SD | 20.233 | 19.858 | 25.615 | 19.580 | 21.231 |
| Nasal superior sector average pRNFL thickness at 96 weeks(µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 91.628 | 91.179 | 94.806 | 94.707 | 93.031 |
| SD | 20.315 | 19.152 | 18.493 | 20.373 | 19.534 |
| Papillomacular bundle average pRNFL thickness at 96 weeks(µm) | N | 43 | 39 | 36 | 41 | 159 |
| Mean | 37.837 | 38.128 | 39.556 | 39.610 | 38.755 |
| SD | 10.670 | 10.778 | 13.239 | 9.005 | 10.873 |

pRNFL: peripapillary retinal nerve fibre layer. SD: standard deviation.

Supplementary Table 8 Summary statistics for the OCT right eye RNFL outcomes at baseline and 96 weeks: All patients recording baseline and 96 weeks

|  | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| Global average pRNFL thickness at baseline (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 80.244 | 81.071 | 86.472 | 81.250 | 82.080 |
| SD | 12.240 | 16.408 | 15.476 | 14.127 | 14.638 |
| Temporal sector average pRNFL thickness at baseline (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 55.289 | 57.024 | 63.972 | 57.925 | 58.301 |
| SD | 16.327 | 19.395 | 20.012 | 18.957 | 18.729 |
| Nasal sector average pRNFL thickness at baseline (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 60.022 | 63.310 | 66.611 | 61.175 | 62.607 |
| SD | 11.663 | 14.932 | 14.843 | 13.961 | 13.926 |
| Nasal inferior sector average pRNFL thickness at baseline (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 93.133 | 93.667 | 90.083 | 91.150 | 92.110 |
| SD | 19.236 | 24.569 | 23.528 | 19.059 | 21.503 |
| Temporal inferior sector average pRNFL thickness at baseline (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 119.622 | 115.619 | 128.417 | 121.600 | 121.018 |
| SD | 26.050 | 28.166 | 26.899 | 26.562 | 27.048 |
| Temporal superior sector average pRNFL thickness at baseline(µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 116.067 | 115.119 | 123.111 | 116.125 | 117.393 |
| SD | 19.460 | 23.334 | 22.769 | 21.342 | 21.721 |
| Nasal superior sector average pRNFL thickness at baseline(µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 82.667 | 84.310 | 89.944 | 83.175 | 84.822 |
| SD | 18.428 | 21.283 | 18.714 | 19.171 | 19.465 |
| Papillomacular bundle average pRNFL thickness at baseline(µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 42.400 | 41.905 | 48.722 | 43.525 | 43.945 |
| SD | 11.063 | 13.310 | 14.987 | 14.317 | 13.521 |
| Global average pRNFL thickness at 96 weeks(µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 80.556 | 79.905 | 85.528 | 80.600 | 81.497 |
| SD | 12.549 | 16.385 | 15.272 | 14.232 | 14.649 |
| Temporal sector pRNFL average thickness at 96 weeks (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 53.067 | 53.833 | 59.639 | 55.675 | 55.356 |
| SD | 15.153 | 17.483 | 17.694 | 17.725 | 17.005 |
| Nasal sector average pRNFL thickness at 96 weeks (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 62.222 | 63.667 | 68.278 | 61.700 | 63.804 |
| SD | 12.822 | 14.858 | 14.587 | 14.394 | 14.234 |
| Nasal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 96.356 | 95.048 | 92.972 | 92.050 | 94.215 |
| SD | 20.527 | 26.381 | 23.603 | 19.682 | 22.520 |
| Temporal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 116.400 | 110.976 | 123.306 | 118.950 | 117.153 |
| SD | 26.112 | 27.655 | 25.449 | 26.275 | 26.535 |
| Temporal superior sector average pRNFL thickness at 96 weeks(µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 115.267 | 112.548 | 120.833 | 114.700 | 115.656 |
| SD | 20.059 | 23.500 | 24.322 | 22.123 | 22.437 |
| Nasal superior sector average pRNFL thickness at 96 weeks(µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 85.600 | 85.405 | 91.194 | 83.475 | 86.264 |
| SD | 18.896 | 24.102 | 18.527 | 18.235 | 20.146 |
| Papillomacular bundle average pRNFL thickness at 96 weeks(µm) | N | 45 | 42 | 36 | 40 | 163 |
| Mean | 42.067 | 40.905 | 47.583 | 43.425 | 43.319 |
| SD | 11.335 | 12.380 | 14.280 | 14.588 | 13.227 |

pRNFL: peripapillary retinal nerve fibre layer. SD: standard deviation.

Supplementary Table 9 Summary statistics for the OCT left eye RNFL outcomes at baseline and 96 weeks in patients without optic neuritis: All patients with no optic neuritis recording baseline and 96 weeks

|  | | Allocated Treatment | | | | Overall | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |  |
| Global average pRNFL thickness at baseline (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 83.714 | 86.630 | 91.192 | 86.419 | 86.714 |
| SD | 10.217 | 12.774 | 12.986 | 10.987 | 11.814 |
| Temporal sector average pRNFL thickness at baseline (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 51.600 | 52.370 | 57.500 | 54.452 | 53.807 |
| SD | 13.353 | 11.318 | 14.012 | 10.331 | 12.384 |
| Nasal sector average pRNFL thickness at baseline (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 68.400 | 75.556 | 75.077 | 70.806 | 72.109 |
| SD | 15.986 | 17.432 | 14.585 | 15.890 | 16.094 |
| Nasal inferior sector average pRNFL thickness at baseline (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 102.971 | 103.296 | 101.615 | 100.613 | 102.134 |
| SD | 24.048 | 23.180 | 21.307 | 20.493 | 22.117 |
| Temporal inferior sector average pRNFL thickness at baseline (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 119.314 | 117.963 | 131.000 | 124.032 | 122.790 |
| SD | 18.708 | 19.615 | 24.567 | 20.750 | 21.145 |
| Temporal superior sector average pRNFL thickness at baseline(µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 115.114 | 115.815 | 127.154 | 118.742 | 118.849 |
| SD | 18.311 | 17.352 | 22.276 | 15.994 | 18.830 |
| Nasal superior sector average pRNFL thickness at baseline(µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 92.429 | 99.593 | 104.654 | 98.871 | 98.403 |
| SD | 20.816 | 22.435 | 18.013 | 21.433 | 20.997 |
| Papillomacular bundle average pRNFL thickness at baseline(µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 39.686 | 40.259 | 44.192 | 41.871 | 41.370 |
| SD | 9.970 | 8.994 | 12.185 | 8.330 | 9.925 |
| Global average pRNFL thickness at 96 weeks(µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 81.600 | 82.963 | 87.769 | 84.290 | 83.958 |
| SD | 9.732 | 12.430 | 12.904 | 10.127 | 11.304 |
| Temporal sector pRNFL average thickness at 96 weeks (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 53.086 | 52.704 | 58.308 | 54.806 | 54.588 |
| SD | 13.661 | 12.143 | 15.043 | 10.474 | 12.909 |
| Nasal sector average pRNFL thickness at 96 weeks (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 60.914 | 65.630 | 65.885 | 65.097 | 64.160 |
| SD | 12.669 | 13.904 | 12.533 | 12.713 | 12.950 |
| Nasal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 95.600 | 96.852 | 93.692 | 96.000 | 95.571 |
| SD | 19.220 | 21.290 | 17.654 | 20.290 | 19.448 |
| Temporal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 123.400 | 118.741 | 131.846 | 124.129 | 124.378 |
| SD | 17.515 | 18.300 | 24.398 | 21.907 | 20.741 |
| Temporal superior sector average pRNFL thickness at 96 weeks(µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 117.514 | 115.926 | 128.000 | 118.871 | 119.798 |
| SD | 17.125 | 18.068 | 22.147 | 16.885 | 18.784 |
| Nasal superior sector average pRNFL thickness at 96 weeks(µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 88.629 | 95.407 | 100.154 | 94.903 | 94.319 |
| SD | 19.441 | 19.755 | 17.966 | 20.687 | 19.737 |
| Papillomacular bundle average pRNFL thickness at 96 weeks(µm) | N | 35 | 27 | 26 | 31 | 119 |
| Mean | 39.829 | 39.667 | 44.077 | 41.097 | 41.050 |
| SD | 10.612 | 9.215 | 12.224 | 8.223 | 10.145 |

pRNFL: peripapillary retinal nerve fibre layer. SD: standard deviation.

Supplementary Table 10 Summary statistics for the OCT right eye RNFL outcomes at baseline and 96 weeks in patients without optic neuritis: All patients with no optic neuritis recording baseline and 96 weeks

|  | | Allocated Treatment | | | | | Overall | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |  | |
| Global average pRNFL thickness at baseline (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 81.000 | 84.241 | 90.963 | 85.583 | 85.186 | |
| SD | 12.407 | 15.804 | 14.108 | 13.561 | 14.278 | |
| Temporal sector average pRNFL thickness at baseline (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 56.697 | 59.345 | 68.000 | 63.208 | 61.460 | |
| SD | 17.133 | 18.580 | 18.464 | 16.694 | 18.038 | |
| Nasal sector average pRNFL thickness at baseline (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 59.485 | 65.862 | 69.370 | 64.583 | 64.566 | |
| SD | 12.135 | 15.137 | 15.492 | 14.711 | 14.599 | |
| Nasal inferior sector average pRNFL thickness at baseline (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 93.303 | 96.586 | 95.148 | 92.875 | 94.496 | |
| SD | 18.068 | 22.248 | 23.945 | 18.986 | 20.648 | |
| Temporal inferior sector average pRNFL thickness at baseline (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 124.667 | 120.724 | 136.000 | 127.708 | 127.009 | |
| SD | 22.434 | 27.981 | 23.278 | 26.509 | 25.319 | |
| Temporal superior sector average pRNFL thickness at baseline(µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 115.364 | 120.517 | 128.667 | 124.000 | 121.699 | |
| SD | 18.733 | 21.394 | 21.026 | 19.810 | 20.565 | |
| Nasal superior sector average pRNFL thickness at baseline(µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 82.848 | 86.621 | 93.778 | 84.917 | 86.867 | |
| SD | 19.938 | 18.335 | 18.842 | 19.567 | 19.385 | |
| Papillomacular bundle average pRNFL thickness at baseline(µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 42.727 | 43.207 | 51.815 | 47.500 | 46.035 | |
| SD | 11.435 | 13.502 | 14.502 | 13.355 | 13.498 | |
| Global average pRNFL thickness at 96 weeks(µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 81.364 | 82.828 | 90.074 | 85.042 | 84.602 | |
| SD | 12.691 | 15.951 | 13.837 | 13.716 | 14.278 | |
| Temporal sector pRNFL average thickness at 96 weeks (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 54.030 | 56.345 | 63.222 | 61.167 | 58.336 | |
| SD | 15.755 | 17.613 | 16.178 | 15.307 | 16.472 | |
| Nasal sector average pRNFL thickness at 96 weeks (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 61.576 | 65.655 | 71.222 | 64.875 | 65.628 | |
| SD | 13.014 | 15.041 | 15.129 | 15.078 | 14.740 | |
| Nasal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 97.424 | 97.724 | 98.630 | 94.000 | 97.062 | |
| SD | 19.289 | 23.982 | 23.456 | 19.569 | 21.429 | |
| Temporal inferior sector average pRNFL thickness at 96 weeks (µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 121.394 | 116.069 | 130.889 | 125.708 | 123.212 | |
| SD | 21.833 | 27.351 | 21.929 | 26.018 | 24.568 | |
| Temporal superior sector average pRNFL thickness at 96 weeks(µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 115.000 | 118.172 | 127.000 | 122.833 | 120.345 | |
| SD | 19.750 | 22.163 | 22.299 | 20.574 | 21.407 | |
| Nasal superior sector average pRNFL thickness at 96 weeks(µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 85.364 | 86.517 | 95.222 | 84.500 | 87.832 | |
| SD | 19.808 | 20.014 | 18.234 | 19.267 | 19.582 | |
| Papillomacular bundle average pRNFL thickness at 96 weeks(µm) | N | 33 | 29 | 27 | 24 | 113 | |
| Mean | 42.515 | 42.103 | 50.333 | 47.042 | 45.239 | |
| SD | 11.657 | 12.737 | 13.739 | 12.936 | 13.010 | |

pRNFL: peripapillary retinal nerve fibre layer. SD: standard deviation.

Supplementary Table 11 Summary statistics for the OCT left eye Macular OCT outcomes at baseline and 96 weeks: All patients recording baseline and 96 weeks

|  | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| Average thickness 4 inner ETDRS sectors of GCL+IPL at baseline (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 74.872 | 74.994 | 75.311 | 77.360 | 75.637 |
| SD | 13.418 | 14.665 | 16.889 | 13.118 | 14.420 |
| Average thickness 4 inner + 4 outer ETDRS sectors of GCL+IPL at baseline (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 64.608 | 65.228 | 65.253 | 66.878 | 65.488 |
| SD | 9.663 | 10.307 | 12.465 | 9.965 | 10.532 |
| Average MV at baseline (mm3) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 8.173 | 8.291 | 8.203 | 8.207 | 8.218 |
| SD | 0.417 | 0.441 | 0.534 | 0.451 | 0.458 |
| Average thickness 4 inner sectors ETDRS of whole macula layers at baseline (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 321.343 | 326.063 | 323.243 | 322.695 | 323.297 |
| SD | 18.154 | 18.484 | 21.870 | 18.186 | 19.056 |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at baseline (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 300.776 | 305.159 | 302.223 | 302.134 | 302.543 |
| SD | 15.879 | 16.364 | 19.934 | 16.637 | 17.108 |
| Average thickness from the 4 inner ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 74.145 | 74.169 | 74.601 | 76.317 | 74.809 |
| SD | 13.507 | 14.842 | 16.582 | 13.127 | 14.399 |
| Average thickness from the 4 inner and 4 outer ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 64.003 | 64.472 | 64.588 | 65.997 | 64.762 |
| SD | 9.692 | 10.357 | 12.433 | 9.950 | 10.531 |
| Average MV at 96 weeks (mm3) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 8.149 | 8.228 | 8.164 | 8.174 | 8.178 |
| SD | 0.419 | 0.436 | 0.522 | 0.471 | 0.458 |
| Average thickness from the 4 inner sectors ETDRS of whole macula layers at 96 weeks (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 320.163 | 323.313 | 321.574 | 321.488 | 321.607 |
| SD | 18.148 | 18.006 | 21.183 | 19.122 | 18.951 |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at 96 weeks (µm) | N | 43 | 40 | 37 | 41 | 161 |
| Mean | 299.837 | 302.728 | 300.713 | 300.939 | 301.037 |
| SD | 15.957 | 16.101 | 19.503 | 17.474 | 17.120 |

ETDRS: early treatment diabetic retinopathy study. SD: standard deviation. GCL+IPL: ganglion cell layer and inner plexiform layer. MV: macular volume.

Supplementary Table 12 Summary statistics for the OCT right eye Macular OCT outcomes at baseline and 96 weeks: All patients recording baseline and 96 weeks

|  | | Allocated Treatment | | | | | Overall | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |  | |
| Average thickness 4 inner ETDRS sectors of GCL+IPL at baseline (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 73.762 | 69.110 | 76.384 | 76.750 | 73.889 | |
| SD | 14.735 | 18.165 | 14.209 | 14.369 | 15.664 | |
| Average thickness 4 inner + 4 outer ETDRS sectors of GCL+IPL at baseline (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 63.849 | 61.125 | 66.058 | 66.365 | 64.267 | |
| SD | 10.480 | 12.673 | 10.559 | 10.622 | 11.241 | |
| Average MV at baseline (mm3) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 8.183 | 8.163 | 8.242 | 8.200 | 8.196 | |
| SD | 0.448 | 0.543 | 0.440 | 0.454 | 0.471 | |
| Average thickness 4 inner ETDRS sectors of whole macula layers at baseline (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 321.762 | 320.494 | 324.555 | 322.197 | 322.226 | |
| SD | 19.346 | 21.920 | 17.705 | 18.681 | 19.398 | |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at baseline (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 301.061 | 300.224 | 303.543 | 301.822 | 301.635 | |
| SD | 17.087 | 20.011 | 16.323 | 16.913 | 17.561 | |
| Average thickness from the 4 inner ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 73.488 | 68.767 | 75.695 | 75.520 | 73.274 | |
| SD | 14.869 | 18.188 | 14.243 | 14.479 | 15.687 | |
| Average thickness from the 4 inner and 4 outer ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 63.576 | 60.692 | 65.299 | 65.352 | 63.661 | |
| SD | 10.585 | 12.683 | 10.621 | 10.659 | 11.255 | |
| Average MV at 96 weeks (mm3) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 8.160 | 8.095 | 8.174 | 8.156 | 8.145 | |
| SD | 0.437 | 0.539 | 0.431 | 0.467 | 0.467 | |
| Average thickness from the 4 inner ETDRS sectors of whole macula layers at 96 weeks (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 321.105 | 318.424 | 322.652 | 320.651 | 320.686 | |
| SD | 18.923 | 21.953 | 17.471 | 19.672 | 19.474 | |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at 96 weeks (µm) | N | 43 | 43 | 41 | 38 | 165 | |
| Mean | 300.360 | 297.945 | 301.366 | 300.201 | 299.944 | |
| SD | 16.680 | 19.948 | 16.014 | 17.544 | 17.515 | |

ETDRS: early treatment diabetic retinopathy study. GCL+IPL: ganglion cell layer and inner plexiform layer. MV: macular volume.

Supplementary Table 13 Summary statistics for the OCT left eye Macular OCT outcomes at baseline and 96 weeks in patients without optic neuritis: All patients with no optic neuritis recording baseline and 96 weeks

|  | | Allocated Treatment | | | | | Overall | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |  | |
| Average thickness 4 inner ETDRS sectors of GCL+IPL at baseline (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 78.914 | 77.647 | 82.426 | 79.617 | 79.568 | |
| SD | 10.657 | 11.985 | 12.327 | 11.226 | 11.486 | |
| Average thickness 4 inner + 4 outer ETDRS sectors of GCL+IPL at baseline (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 67.600 | 67.220 | 70.417 | 68.563 | 68.376 | |
| SD | 7.340 | 8.403 | 9.475 | 8.690 | 8.420 | |
| Average MV at baseline (mm3) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 8.283 | 8.347 | 8.395 | 8.266 | 8.319 | |
| SD | 0.350 | 0.379 | 0.453 | 0.446 | 0.404 | |
| Average thickness 4 inner ETDRS sectors of whole macula layers at baseline (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 325.729 | 328.129 | 331.111 | 324.142 | 327.112 | |
| SD | 15.617 | 15.341 | 18.789 | 17.158 | 16.681 | |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at baseline (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 304.889 | 307.194 | 309.472 | 304.050 | 306.256 | |
| SD | 13.326 | 13.848 | 16.861 | 16.156 | 14.968 | |
| Average thickness from the 4 inner ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 78.229 | 76.707 | 81.528 | 78.625 | 78.698 | |
| SD | 10.740 | 12.565 | 12.386 | 11.032 | 11.619 | |
| Average thickness from the 4 inner and 4 outer ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 67.011 | 66.366 | 69.741 | 67.717 | 67.640 | |
| SD | 7.404 | 8.635 | 9.612 | 8.457 | 8.470 | |
| Average MV at 96 weeks (mm3) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 8.249 | 8.280 | 8.359 | 8.243 | 8.279 | |
| SD | 0.369 | 0.372 | 0.439 | 0.457 | 0.406 | |
| Average thickness from the 4 inner ETDRS sectors of whole macula layers at 96 weeks (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 324.257 | 325.371 | 329.231 | 323.408 | 325.424 | |
| SD | 16.116 | 15.022 | 18.403 | 17.877 | 16.779 | |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at 96 weeks (µm) | N | 35 | 29 | 27 | 30 | 121 | |
| Mean | 303.625 | 304.659 | 308.005 | 303.250 | 304.757 | |
| SD | 13.989 | 13.610 | 16.462 | 16.691 | 15.101 | |

ETDRS: early treatment diabetic retinopathy study. SD: standard deviation. GCL+IPL: ganglion cell layer and inner plexiform layer. MV: macular volume.

Supplementary Table 14 Summary statistics for the OCT right eye Macular OCT outcomes at baseline and 96 weeks in patients without optic neuritis: All patients with no optic neuritis recording baseline and 96 weeks

|  | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| Average thickness 4 inner ETDRS sectors of GCL+IPL at baseline (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 75.402 | 71.750 | 80.266 | 81.927 | 77.124 |
| SD | 14.759 | 18.610 | 12.409 | 11.373 | 14.988 |
| Average thickness 4 inner + 4 outer ETDRS sectors of GCL+IPL at baseline (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 64.814 | 63.060 | 68.903 | 70.167 | 66.561 |
| SD | 10.583 | 12.852 | 9.311 | 8.969 | 10.827 |
| Average MV at baseline (mm3) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 8.194 | 8.234 | 8.343 | 8.296 | 8.264 |
| SD | 0.449 | 0.581 | 0.399 | 0.432 | 0.468 |
| Average thickness 4 inner ETDRS sectors of whole macula layers at baseline (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 321.886 | 323.250 | 328.798 | 326.302 | 324.962 |
| SD | 18.987 | 23.208 | 15.930 | 16.338 | 18.861 |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at baseline (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 301.379 | 302.866 | 307.379 | 305.542 | 304.191 |
| SD | 17.024 | 21.296 | 14.716 | 15.577 | 17.301 |
| Average thickness from the 4 inner ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 75.091 | 71.112 | 79.460 | 81.188 | 76.513 |
| SD | 14.917 | 18.681 | 12.585 | 11.162 | 15.033 |
| Average thickness from the 4 inner and 4 outer ETDRS sectors of GCL+IPL at 96 weeks (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 64.511 | 62.474 | 68.081 | 69.417 | 65.958 |
| SD | 10.661 | 13.006 | 9.483 | 8.867 | 10.879 |
| Average MV at 96 weeks (mm3) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 8.166 | 8.156 | 8.273 | 8.257 | 8.211 |
| SD | 0.440 | 0.587 | 0.400 | 0.440 | 0.468 |
| Average thickness from the 4 inner ETDRS sectors of whole macula layers at 96 weeks (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 321.144 | 320.681 | 326.629 | 325.583 | 323.393 |
| SD | 18.752 | 23.632 | 16.345 | 16.526 | 19.029 |
| Average thickness from the 4 inner + 4 outer ETDRS sectors of whole macular layers at 96 weeks (µm) | N | 33 | 29 | 31 | 24 | 117 |
| Mean | 300.542 | 300.194 | 305.052 | 304.354 | 302.433 |
| SD | 16.746 | 21.636 | 14.861 | 15.833 | 17.379 |

ETDRS: early treatment diabetic retinopathy study. SD: standard deviation. GCL+IPL: ganglion cell layer and inner plexiform layer. MV: macular volume.

Supplementary Table 15 Multiple regression analyses for the OCT outcomes at 96 weeks.

| Outcome variable | N | AMD  (Amiloride – Placebo) | 95% Confidence Limits for AMD | | P-value | AMD  (Fluoxetine – Placebo) | 95% Confidence Limits for AMD | | P-value | AMD  (Riluzole – Placebo) | 95% Confidence Limits for AMD | | P-value |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Global average pRNFL thickness (µm), eyes with no optic neuritis only: LEFT eyes  [Primary OCT analysis] | 119 | -0.819 | -2.245 | 0.607 | 0.258 | 0.210 | -1.126 | 1.547 | 0.756 | -0.982 | -2.387 | 0.422 | 0.169 |
| Global average pRNFL thickness (µm), eyes with no optic neuritis only: RIGHT eyes  [Primary OCT analysis] | 113 | -0.260 | -1.334 | 0.814 | 0.632 | 0.961 | -0.072 | 1.993 | 0.068 | -0.868 | -1.922 | 0.187 | 0.106 |
| Global average pRNFL thickness (µm), all patients, adjusted for optic neuritis: LEFT eyes | 159 | -0.870 | -2.080 | 0.339 | 0.157 | 0.429 | -0.731 | 1.589 | 0.466 | -1.053 | -2.240 | 0.133 | 0.082 |
| Global average pRNFL thickness (µm), all patients, adjusted for optic neuritis: RIGHT eyes | 163 | -0.037 | -0.901 | 0.827 | 0.933 | 1.033 | 0.236 | 1.829 | 0.011 | -0.408 | -1.221 | 0.404 | 0.323 |
| GCL+IPL overall average thickness (µm), eyes with no optic neuritis only: LEFT eyes | 121 | 0.157 | -0.525 | 0.839 | 0.649 | 0.223 | -0.424 | 0.869 | 0.497 | -0.102 | -0.776 | 0.572 | 0.765 |
| GCL+IPL overall average thickness (µm), eyes with no optic neuritis only: RIGHT eyes | 117 | -0.062 | -0.628 | 0.503 | 0.828 | 0.452 | -0.119 | 1.023 | 0.120 | 0.200 | -0.397 | 0.796 | 0.508 |
| GCL+IPL overall average thickness (µm), all patients, adjusted for optic neuritis: LEFT eyes | 161 | 0.196 | -0.403 | 0.796 | 0.518 | 0.237 | -0.343 | 0.817 | 0.420 | 0.058 | -0.528 | 0.643 | 0.846 |
| GCL+IPL overall average thickness (µm), all patients, adjusted for optic neuritis: RIGHT eyes | 165 | 0.331 | -0.242 | 0.903 | 0.256 | 0.813 | 0.246 | 1.380 | 0.005 | 0.573 | 0.003 | 1.144 | 0.049 |
| Total MV (mm³), eyes with no optic neuritis only: LEFT eyes | 121 | -0.012 | -0.047 | 0.024 | 0.516 | -0.008 | -0.042 | 0.025 | 0.631 | -0.044 | -0.079 | -0.009 | 0.013 |
| Total MV (mm³), eyes with no optic neuritis only: RIGHT eyes | 117 | -0.028 | -0.065 | 0.009 | 0.133 | 0.015 | -0.022 | 0.052 | 0.411 | -0.040 | -0.078 | -0.002 | 0.039 |
| Total MV (mm³), all patients, adjusted for optic neuritis: LEFT eyes | 161 | -0.006 | -0.037 | 0.024 | 0.680 | 0.010 | -0.020 | 0.039 | 0.521 | -0.028 | -0.058 | 0.002 | 0.063 |
| Total MV (mm³), all patients, adjusted for optic neuritis: RIGHT eyes | 165 | -0.023 | -0.056 | 0.010 | 0.177 | 0.020 | -0.013 | 0.053 | 0.223 | -0.025 | -0.057 | 0.008 | 0.138 |
| Whole macula layers ETDRS INNER sector thickness (µm), eyes with no optic neuritis only: LEFT eyes | 121 | -1.087 | -2.641 | 0.468 | 0.169 | -0.664 | -2.128 | 0.800 | 0.371 | -2.020 | -3.545 | -0.495 | 0.010 |
| Whole macula layers ETDRS INNER sector thickness (µm), eyes with no optic neuritis only: RIGHT eyes | 117 | -1.373 | -3.045 | 0.298 | 0.106 | 0.052 | -1.619 | 1.723 | 0.951 | -1.952 | -3.674 | -0.229 | 0.027 |
| Whole macula layers ETDRS INNER sector thickness (µm), all patients, adjusted for optic neuritis: LEFT eyes | 161 | -0.470 | -1.786 | 0.845 | 0.481 | -0.012 | -1.282 | 1.258 | 0.985 | -1.481 | -2.771 | -0.192 | 0.025 |
| Whole macula layers ETDRS INNER sector thickness (µm), all patients, adjusted for optic neuritis: RIGHT eyes | 165 | -0.556 | -2.138 | 1.026 | 0.488 | 0.768 | -0.793 | 2.328 | 0.333 | -0.692 | -2.244 | 0.860 | 0.380 |
| Whole macula layers ETDRS ALL sector thickness (µm), eyes with no optic neuritis only: LEFT eyes | 121 | -0.640 | -1.961 | 0.681 | 0.339 | -0.410 | -1.656 | 0.836 | 0.516 | -1.755 | -3.053 | -0.457 | 0.009 |
| Whole macula layers ETDRS ALL sector thickness (µm), eyes with no optic neuritis only: RIGHT eyes | 117 | -1.048 | -2.452 | 0.357 | 0.142 | 0.463 | -0.941 | 1.868 | 0.515 | -1.555 | -3.001 | -0.108 | 0.035 |
| Whole macula layers ETDRS ALL sector thickness (µm), all patients, adjusted for optic neuritis: LEFT eyes | 161 | -0.320 | -1.449 | 0.809 | 0.576 | 0.253 | -0.837 | 1.343 | 0.647 | -1.198 | -2.305 | -0.091 | 0.034 |
| Whole macula layers ETDRS ALL sector thickness (µm), all patients, adjusted for optic neuritis: RIGHT eyes | 165 | -0.627 | -1.883 | 0.629 | 0.326 | 0.846 | -0.393 | 2.085 | 0.180 | -0.734 | -1.966 | 0.497 | 0.241 |
| Temporal sector pRNFL thickness (µm), eyes with no optic neuritis only: LEFT eyes | 119 | 0.290 | -1.015 | 1.595 | 0.661 | 0.746 | -0.484 | 1.976 | 0.232 | -0.338 | -1.635 | 0.959 | 0.607 |
| Temporal sector pRNFL thickness (µm), eyes with no optic neuritis only: RIGHT eyes | 113 | -1.983 | -3.848 | -0.118 | 0.037 | -1.012 | -2.823 | 0.798 | 0.270 | -1.326 | -3.173 | 0.520 | 0.157 |
| Temporal sector pRNFL thickness (µm), all patients, adjusted for optic neuritis: LEFT eyes | 159 | -0.213 | -1.339 | 0.914 | 0.710 | 0.928 | -0.157 | 2.012 | 0.093 | -0.047 | -1.152 | 1.059 | 0.934 |
| Temporal sector pRNFL thickness (µm), all patients, adjusted for optic neuritis: RIGHT eyes | 163 | -0.978 | -2.508 | 0.553 | 0.209 | -0.181 | -1.600 | 1.239 | 0.802 | -0.845 | -2.291 | 0.602 | 0.250 |

ETDRS: early treatment diabetic retinopathy study. GCL+IPL: ganglion cell layer and inner plexiform layer. MV: macular volume. pRNFL: peripapillary retinal nerve fibre layer.

Supplementary Table 16 Summary statistics for the CSF outcomes at baseline and 48 weeks: All patients recording baseline and 48 weeks

|  | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| CSF NfL at baseline (pg/mL) | N | 11 | 9 | 10 | 9 | 39 |
| Mean | 867.37 | 1078.78 | 829.24 | 907.16 | 915.56 |
| SD | 521.17 | 633.96 | 326.79 | 357.72 | 466.14 |
| CSF NfH at baseline (pg/mL) | N | 11 | 9 | 10 | 9 | 39 |
| Mean | 464.81 | 462.24 | 478.93 | 452.01 | 464.88 |
| SD | 203.41 | 185.39 | 123.28 | 133.31 | 159.87 |
| CSF NfL at 48 weeks (pg/mL) | N | 11 | 9 | 10 | 9 | 39 |
| Mean | 905.51 | 1002.77 | 812.81 | 794.92 | 878.66 |
| SD | 469.15 | 513.54 | 345.68 | 221.79 | 398.44 |
| CSF NfH at 48 weeks (pg/mL) | N | 11 | 9 | 10 | 9 | 39 |
| Mean | 500.51 | 488.47 | 443.54 | 437.83 | 468.66 |
| SD | 145.35 | 176.03 | 119.60 | 74.54 | 131.98 |

CSF: cerebrospinal fluid. SD: standard deviation. NfL: neurofilament light chain. NfH: neurofilament heavy chain.

Supplementary Table 17 Summary statistics for the CSF outcomes at baseline and 96 weeks: All patients recording baseline and 96 weeks

|  | | Allocated Treatment | | | | Overall |
| --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |
| CSF NfL 96 baseline (pg/mL) | N | 10 | 8 | 11 | 6 | 35 |
| Mean | 796.62 | 1015.66 | 818.78 | 974.84 | 884.20 |
| SD | 490.52 | 678.94 | 311.96 | 306.25 | 458.44 |
| CSF NfH 96 baseline (pg/mL) | N | 10 | 8 | 11 | 6 | 35 |
| Mean | 433.88 | 412.71 | 470.72 | 465.66 | 446.07 |
| SD | 185.13 | 103.37 | 120.08 | 158.78 | 140.68 |
| CSF NfL at 96 weeks (pg/mL) | N | 10 | 8 | 11 | 6 | 35 |
| Mean | 955.27 | 967.60 | 829.02 | 1315.98 | 980.25 |
| SD | 735.97 | 616.43 | 380.78 | 1198.28 | 709.17 |
| CSF NfH at 96 weeks (pg/mL) | N | 10 | 8 | 11 | 6 | 35 |
| Mean | 466.75 | 449.19 | 464.45 | 653.46 | 494.02 |
| SD | 133.58 | 118.08 | 131.82 | 684.68 | 295.13 |

CSF: cerebrospinal fluid. SD: standard deviation. NfL: neurofilament light chain. NfH: neurofilament heavy chain.

Supplementary Table 18 Summary statistics for the CSF Panel of Additional Biomarker outcomes at baseline and 48 weeks: All patients recording baseline and 48 weeks\*

|  | | Allocated Treatment | | | | | Overall | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |  | |
| Soluble CD14 at baseline (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 164.16 | 132.55 | 165.47 | 172.69 | 159.17 | |
| SD | 35.22 | 45.96 | 39.67 | 40.40 | 41.43 | |
| Ferritin at baseline  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 5.18 | 3.66 | 3.87 | 4.03 | 4.23 | |
| SD | 4.19 | 3.13 | 3.15 | 1.68 | 3.16 | |
| GFAP at baseline  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 0.04 | 0.45 | 0.04 | 0.02 | 0.13 | |
| SD | 0.06 | 1.21 | 0.06 | 0.02 | 0.58 | |
| Neopterin at baseline  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 1.95 | 2.07 | 2.12 | 2.08 | 2.05 | |
| SD | 1.04 | 1.67 | 0.72 | 1.29 | 1.16 | |
| NCAM at baseline  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 265.08 | 288.47 | 321.99 | 269.72 | 286.14 | |
| SD | 50.11 | 65.19 | 91.96 | 19.01 | 64.54 | |
| MMP9 at baseline  (pg/mL) | N | 11 | 9 | 10 | 8 | 38 | |
| Mean | 0.39 | 0.54 | 0.19 | 0.15 | 0.32 | |
| SD | 0.70 | 0.68 | 0.23 | 0.12 | 0.52 | |
| Soluble CD14 at 48wks  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 154.32 | 146.23 | 158.59 | 164.06 | 155.79 | |
| SD | 30.73 | 44.33 | 34.91 | 53.39 | 39.89 | |
| Ferritin at 48wks  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 4.44 | 4.01 | 3.83 | 3.57 | 3.98 | |
| SD | 4.20 | 3.20 | 2.35 | 1.61 | 2.96 | |
| GFAP at 48wks  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 0.04 | 0.40 | 0.04 | 0.02 | 0.12 | |
| SD | 0.06 | 0.90 | 0.07 | 0.02 | 0.44 | |
| Neopterin at 48wks  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 1.85 | 2.23 | 2.01 | 2.20 | 2.06 | |
| SD | 0.64 | 1.16 | 0.98 | 1.02 | 0.93 | |
| NCAM at 48wks  (pg/mL) | N | 11 | 9 | 10 | 9 | 39 | |
| Mean | 260.55 | 292.86 | 285.99 | 255.02 | 273.25 | |
| SD | 66.01 | 71.18 | 81.54 | 35.51 | 65.67 | |
| MMP9 at 48wks  (pg/mL) | N | 11 | 9 | 10 | 8 | 38 | |
| Mean | 0.42 | 0.20 | 0.12 | 0.35 | 0.27 | |
| SD | 0.49 | 0.24 | 0.15 | 0.68 | 0.43 | |

\*Growth-associated protein 43 (GAP43) could not be assessed for technical reasons.

SD: standard deviation. GFAP: glial fibrillary acidic protein. MMP-9: matrix metalloproteinase-9. NCAM: neural cell adhesion molecule. NfH: neurofilament high.

Supplementary Table 19 Summary statistics for the CSF Panel of Additional Biomarker outcomes at baseline and 96 weeks: All patients recording baseline and 96 weeks\*

|  | | Allocated Treatment | | | | | Overall | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fluoxetine | Riluzole | Amiloride | Placebo |  | |
| Soluble CD14 at baseline  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 163.23 | 140.85 | 158.24 | 191.97 | 161.47 | |
| SD | 36.99 | 62.31 | 44.62 | 23.75 | 45.81 | |
| Ferritin at baseline  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 5.17 | 3.17 | 3.68 | 3.25 | 3.92 | |
| SD | 4.41 | 2.41 | 3.05 | 1.94 | 3.22 | |
| GFAP at baseline  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 0.04 | 0.51 | 0.04 | 0.10 | 0.16 | |
| SD | 0.06 | 1.27 | 0.05 | 0.18 | 0.62 | |
| Neopterin at baseline  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 1.83 | 1.61 | 2.15 | 2.37 | 1.97 | |
| SD | 1.01 | 1.17 | 0.69 | 1.28 | 1.00 | |
| NCAM at baseline  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 263.57 | 288.94 | 309.62 | 270.98 | 285.11 | |
| SD | 52.56 | 63.41 | 96.41 | 25.58 | 68.98 | |
| MMP9 at baseline  (pg/mL) | N | 10 | 8 | 11 | 5 | 34 | |
| Mean | 0.38 | 0.52 | 0.19 | 0.23 | 0.33 | |
| SD | 0.73 | 0.62 | 0.21 | 0.12 | 0.51 | |
| Soluble CD14 at 96wks  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 151.20 | 138.46 | 160.14 | 151.06 | 151.07 | |
| SD | 41.48 | 62.58 | 30.37 | 40.73 | 42.91 | |
| Ferritin at 96wks  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 4.82 | 5.34 | 4.15 | 4.15 | 4.62 | |
| SD | 4.52 | 5.28 | 3.09 | 1.80 | 3.83 | |
| GFAP at 96wks  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 0.03 | 0.44 | 0.04 | 0.07 | 0.13 | |
| SD | 0.05 | 0.93 | 0.07 | 0.11 | 0.46 | |
| Neopterin at 96wks  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 2.08 | 1.50 | 1.89 | 1.57 | 1.80 | |
| SD | 0.92 | 0.49 | 1.06 | 0.85 | 0.87 | |
| NCAM at 96wks  (pg/mL) | N | 10 | 8 | 11 | 6 | 35 | |
| Mean | 276.72 | 275.21 | 267.73 | 250.13 | 268.99 | |
| SD | 74.93 | 69.48 | 100.52 | 47.02 | 76.60 | |
| MMP9 at 96wks  (pg/mL) | N | 10 | 8 | 11 | 5 | 34 | |
| Mean | 0.32 | 1.17 | 0.10 | 0.47 | 0.47 | |
| SD | 0.46 | 1.87 | 0.09 | 0.64 | 1.01 | |

\*Growth-associated protein 43 (GAP43) could not be assessed for technical reasons.

SD: standard deviation. GFAP: glial fibrillary acidic protein. MMP-9: matrix metalloproteinase-9. NCAM: neural cell adhesion molecule. NfH: neurofilament high.

Supplementary Table 20 Multiple regression analyses for the CSF Panel of Additional Biomarkers\*

| **Outcome variable** | **N** | **Adjusted Mean difference**  **(Amiloride Treatment – Placebo)** | **95% Confidence Limits for adjusted mean difference** | | **P-value** | **Adjusted Mean difference**  **(Fluoxetine Treatment – Placebo)** | **95% Confidence Limits for adjusted mean difference** | | **P-value** | **Adjusted Mean difference**  **(Riluzole Treatment – Placebo)** | **95% Confidence Limits for adjusted mean difference** | | **P-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Soluble CD14 at 48 weeks | 39 | 1.390 | -28.722 | 31.503 | 0.926 | -3.633 | -33.049 | 25.783 | 0.803 | 11.030 | -21.475 | 43.535 | 0.494 |
| Ferritin at 48 weeks | 39 | 0.522 | -0.894 | 1.938 | 0.458 | -0.130 | -1.521 | 1.262 | 0.851 | 0.710 | -0.740 | 2.160 | 0.326 |
| GFAP at 48 weeks | 39 | 0.017 | -0.051 | 0.085 | 0.616 | 0.010 | -0.057 | 0.076 | 0.769 | 0.065 | -0.008 | 0.138 | 0.078 |
| Neopterin at 48 weeks | 39 | -0.196 | -0.840 | 0.447 | 0.538 | -0.274 | -0.903 | 0.354 | 0.380 | 0.049 | -0.609 | 0.707 | 0.881 |
| NCAM at 48 weeks | 39 | -8.787 | -52.832 | 35.259 | 0.687 | 11.072 | -30.022 | 52.165 | 0.587 | 24.092 | -19.126 | 67.310 | 0.264 |
| MMP9 at 48 weeks | 38 | -0.218 | -0.620 | 0.183 | 0.276 | 0.002 | -0.398 | 0.402 | 0.991 | -0.262 | -0.686 | 0.163 | 0.218 |
| Soluble CD14 at 96 weeks | 35 | 32.636 | -2.790 | 68.063 | 0.070 | 22.812 | -12.894 | 58.518 | 0.201 | 27.880 | -11.506 | 67.266 | 0.158 |
| Ferritin at 96 weeks | 35 | -0.584 | -4.091 | 2.923 | 0.735 | -0.973 | -4.586 | 2.640 | 0.585 | 0.690 | -3.076 | 4.456 | 0.710 |
| GFAP at 96 weeks | 35 | 0.008 | -0.078 | 0.094 | 0.843 | 0.005 | -0.082 | 0.092 | 0.909 | 0.065 | -0.030 | 0.160 | 0.171 |
| Neopterin at 96 weeks | 35 | 0.391 | -0.434 | 1.216 | 0.339 | 0.616 | -0.232 | 1.463 | 0.148 | 0.264 | -0.637 | 1.165 | 0.553 |
| NCAM at 96 weeks | 35 | -17.899 | -69.917 | 34.118 | 0.486 | 37.704 | -13.796 | 89.203 | 0.145 | 13.018 | -41.270 | 67.306 | 0.627 |
| MMP9 at 96 weeks | 34 | -0.376 | -1.473 | 0.722 | 0.488 | -0.202 | -1.317 | 0.914 | 0.713 | 0.596 | -0.596 | 1.788 | 0.314 |
| PER PROTOCOL: Soluble CD14 at 48 weeks | 23 | -10.367 | -56.953 | 36.218 | 0.642 | -9.354 | -60.320 | 41.613 | 0.701 | 11.028 | -38.991 | 61.048 | 0.645 |
| PER PROTOCOL: Ferritin at 48 weeks | 23 | 0.694 | -1.510 | 2.899 | 0.512 | 0.472 | -2.052 | 2.996 | 0.696 | 0.750 | -1.405 | 2.905 | 0.470 |
| PER PROTOCOL: GFAP at 48 weeks | 23 | 0.012 | -0.115 | 0.139 | 0.842 | 0.011 | -0.134 | 0.157 | 0.869 | 0.084 | -0.048 | 0.216 | 0.194 |
| PER PROTOCOL: Neopterin at 48 weeks | 23 | -0.085 | -0.998 | 0.828 | 0.846 | -0.526 | -1.582 | 0.529 | 0.305 | 0.247 | -0.661 | 1.155 | 0.571 |
| PER PROTOCOL: NCAM at 48 weeks | 23 | -26.557 | -88.278 | 35.165 | 0.374 | -14.073 | -78.603 | 50.456 | 0.649 | 31.060 | -25.117 | 87.236 | 0.257 |
| PER PROTOCOL: MMP9 at 48 weeks | 22 | 0.054 | -0.235 | 0.343 | 0.693 | 0.039 | -0.291 | 0.369 | 0.804 | 0.122 | -0.184 | 0.429 | 0.407 |
| PER PROTOCOL: Soluble CD14 at 96 weeks | 22 | 41.924 | -5.175 | 89.023 | 0.077 | 39.987 | -11.132 | 91.106 | 0.116 | 35.430 | -17.833 | 88.693 | 0.176 |
| PER PROTOCOL: Ferritin at 96 weeks | 22 | -1.168 | -6.169 | 3.833 | 0.624 | -0.888 | -6.575 | 4.799 | 0.743 | 0.514 | -4.441 | 5.469 | 0.827 |
| PER PROTOCOL: GFAP at 96 weeks | 22 | 0.000 | -0.133 | 0.133 | 0.997 | 0.010 | -0.142 | 0.161 | 0.894 | 0.093 | -0.051 | 0.237 | 0.187 |
| PER PROTOCOL: Neopterin at 96 weeks | 22 | 0.208 | -0.915 | 1.331 | 0.697 | 0.592 | -0.692 | 1.876 | 0.339 | 0.195 | -0.978 | 1.368 | 0.727 |
| PER PROTOCOL: NCAM at 96 weeks | 22 | -37.034 | -120.183 | 46.114 | 0.356 | 15.484 | -71.093 | 102.062 | 0.707 | 16.004 | -63.485 | 95.494 | 0.672 |
| PER PROTOCOL: MMP9 at 96 weeks | 21 | -0.116 | -1.568 | 1.337 | 0.866 | -0.189 | -1.846 | 1.468 | 0.809 | 1.410 | -0.185 | 3.006 | 0.079 |

\*Growth-associated protein 43 (GAP43) could not be assessed for technical reasons.

SD: standard deviation. GFAP: glial fibrillary acidic protein. MMP-9: matrix metalloproteinase-9. NCAM: neural cell adhesion molecule. NfH: neurofilament high.

Supplementary Table 21 Examination of the additional effect of including CSF neurofilament variables

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Baseline Variables** | **N** | **No CSF Nf variables** | **Plus CSF NfH** | **Plus CSF NfL** | **Plus both CSF NfH and NfL** |
| 1 | SLCVA 2.5% RE, SLCVA 5% RE, SDMT, Mean myo-inositol (London), HCVA RE, LCVA 2.5% LE, SLCVA 1.25% RE, HCVA LE, Mean T2L MTR, SLCVA 5% LE, SLCVA 1.25% LE, T2LV, PASAT and MSFC | 39 | RSD=1.501  R²=0.363  Adj R²=  -0.152 | RSD=1.375  R²=0.492  Adj R²=  0.034 | RSD=1.482  R²=0.410  Adj R²=  -0.122 | RSD=1.399  R²=0.500  Adj R²=  -0.0007 |
| 2 | SLCVA 2.5% RE, SDMT, HCVA RE, SLCVA 2.5% LE, HCVA LE, SLCVA 1.25% LE, T2LV, PASAT and MSFC | 49 | RSD=1.411  R²=0.211  Adj R²=  -0.052 | RSD=1.336  R²=0.312  Adj R²=  0.056 | RSD=1.399  R²=0.245  Adj R²=  -0.035 | RSD=1.349  R²=0.318  Adj R²=  0.037 |

RSD: Residual Standard Deviation, R²: R-squared, Adj R²: Adjusted R-squared. Nf: neurofilament. NfL: neurofilament light chain. NfH: neurofilament heavy chain. SLCVA: Sloan low contrast visual acuity. SDMT: symbol digit modalities test. HCVA: high contrast visual acuity. RE: right eye. LE: left eye. T2L: T2 lesion. MTR: magnetisation transfer ratio. T2LV: T2 lesion volume. PASAT: paced auditory serial addition test and MSFC: multiple sclerosis functional composite.

Supplementary Table 22 Coefficient effect and statistical significance of CSF Neurofilaments to predict PBVC at 96 weeks after adjusting for other variables

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model** | **N** | **CSF Neurofilament variables included** | **Unstandardized Coefficients** | **95% Confidence Intervals** | **Standardized coefficients** | **P-values** |
| 1 | 39 | NfH | NfH: -0.0034 | -0.0065 to -0.00024 | -0.427 | 0.036 |
| 1 | 39 | NfL | NfL: -0.0007 | -0.0018 to 0.00046 | -0.274 | 0.225 |
| 1 | 39 | Both NfH and NfL | NfH: -0.0044 | -0.0094 to 0.00058 | -0.554 | 0.080 |
| NfL: 0.0004 | -0.0012 to 0.0021 | 0.178 | 0.585 |
| 2 | 49 | NfH | NfH: -0.0031 | -0.0059 to -0.00032 | -0.362 | 0.030 |
| 2 | 49 | NfL | NfL: -0.0006 | -0.0015 to 0.00035 | -0.221 | 0.216 |
| 2 | 49 | Both NfH and Nf) | NfH: -0.0040 | -0.0083 to 0.00027 | -0.465 | 0.065 |
| NfL: 0.0004 | -0.00098 to 0.0017 | 0.143 | 0.578 |

NfL: neurofilament light chain. NfH: neurofilament heavy chain. CSF: cerebrospinal fluid.

Supplementary Table 23 Multiple linear regression analysis to investigate the effect of SLCVA Low contrast 1.25% OD on PBVC at 96 weeks: with interaction terms included.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Parameter**  **Estimate** | **Standard**  **Error** | **t Value** | **P-value** | **Standardized**  **Estimate** | **95% Confidence Limits** | |
| Intercept | -1.6343 | 0.17064 | -9.58 | <0.000001 | 0 | -1.9698 | -1.2988 |
| SLCVA 1.25% RE | 0.03256 | 0.01109 | 2.94 | 0.00352 | 0.27101 | 0.01076 | 0.05437 |
| Fluoxetine | 0.04444 | 0.24364 | 0.18 | 0.85537 | 0.015 | -0.4346 | 0.5235 |
| Riluzole | 0.05232 | 0.23335 | 0.22 | 0.8227 | 0.01772 | -0.4065 | 0.51114 |
| Amiloride | 0.41912 | 0.24505 | 1.71 | 0.08802 | 0.14096 | -0.0627 | 0.90095 |
| Interaction term:  SLCVA 1.25% RE in Fluoxetine arm | -0.0133 | 0.01727 | -0.77 | 0.4427 | -0.064 | -0.0472 | 0.02069 |
| SLCVA 1.25% RE in Riluzole arm | -0.0135 | 0.01654 | -0.82 | 0.41434 | -0.0656 | -0.046 | 0.019 |
| SLCVA 1.25% RE in Amiloride arm | -0.0347 | 0.01667 | -2.08 | 0.03833 | -0.1789 | -0.0674 | -0.0019 |

SLCVA: Sloan low contrast visual acuity. RE: right eye.

Supplementary Table 24 Multiple linear regression analysis to investigate the effect of MSFC score on PBVC at 96 weeks: with interaction terms included.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Parameter**  **Estimate** | **Standard**  **Error** | **t Value** | **P-value** | **Standardized**  **Estimate** | **95% Confidence Limits** | |
| Intercept | -1.29843 | 0.12803 | -10.14 | <0.00001 | 0 | -1.55016 | -1.04669 |
| MSFC | 0.34908 | 0.14346 | 2.43 | 0.01542 | 0.25369 | 0.06702 | 0.63114 |
| Fluoxetine | -0.12294 | 0.18245 | -0.67 | 0.50082 | -0.04134 | -0.48167 | 0.23579 |
| Riluzole | -0.11723 | 0.18138 | -0.65 | 0.51847 | -0.03983 | -0.47384 | 0.23939 |
| Amiloride | 0.03896 | 0.18209 | 0.21 | 0.83071 | 0.01324 | -0.31907 | 0.39698 |
| Interaction term: MSFC in Fluoxetine arm | -0.26321 | 0.26195 | -1 | 0.31562 | -0.06038 | -0.77824 | 0.25182 |
| Interaction term: MSFC in Riluzole arm | -0.13209 | 0.19341 | -0.68 | 0.49506 | -0.05134 | -0.51236 | 0.24819 |
| Interaction term: MSFC in Amiloride arm | -0.39324 | 0.18248 | -2.15 | 0.03178 | -0.17684 | -0.75203 | -0.03445 |

MSFC: multiple sclerosis functional composite.