Supplementary Material

**eTable 1.** Baseline characteristics stratified by baseline CSF NfL levels.

2. Correlation between CSF NfL levels and clinical and MRI measures.

**eTable 3.** Correlation between serum NfL levels and clinical and MRI measures.
**eTable 1.** Baseline characteristics stratified by baseline CSF NfL levels.

| Variable                        | Lowest tertile of CSF NfL (N = 57) | Mid tertile of CSF NfL (N = 57) | Upper tertile of CSF NfL (N = 58) |
|---------------------------------|------------------------------------|----------------------------------|-----------------------------------|
| NFL range, pg/mL                | 0-1142                             | 1143-4302                        | 4359-80313                        |
| Age, mean (SD), years           | 38.9 (6.5)                         | 37.1 (8.1)                       | 34.8 (7.6)                        |
| Female, n (%)                   | 44 (77)                            | 37 (65)                          | 39 (67)                           |
| Disease duration, mean (SD), years | 8.5 (6.6)                         | 6.9 (6.1)                        | 5.4 (5.7)                         |
| EDSS score, mean (SD)           | 2.3 (0.8)                          | 2.5 (0.8)                        | 2.4 (0.8)                         |
| MSFC score, mean (SD) [n]a       | -0.03 (0.72) [26]                  | 0.04 (0.66) [28]                 | 0.12 (0.57) [23]                  |
| Gd+ lesions, mean (SD) [n]a      | 0.9 (2.2) [55]                     | 3.4 (5.5) [56]                   | 5.2 (9.1) [58]                    |
| Patients with Gd+ lesions at Year 0, n (%) | 16/55 (29)                        | 33/56 (59)                       | 47/58 (81)                        |
| T2 lesion volume, mean (SD) [n], mm³ | 8,841 (11,048) [48]              | 13,931 (15,571) [45]            | 15,586 (11,227) [49]             |
| BPF, mean (SD) [n]              | 0.830 (0.019) [24]                 | 0.833 (0.015) [24]               | 0.832 (0.014) [20]               |
BPF: brain parenchymal fraction; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; IM: intramuscular; MSFC: Multiple Sclerosis Functional Composite; NfL: neurofilament light chain.

*If different from the total $n$ in the group.*
**eTable 2.** Correlation between CSF NfL levels and clinical and MRI measures.

| Time variable | Measure                        | CSF NfL Baseline | CSF NfL Year 2 All | CSF NfL Year 2 Placebo | CSF NfL Year 2 IFNβ-1a |
|---------------|--------------------------------|------------------|--------------------|------------------------|------------------------|
|               |                                | r    | n   | r    | n   | r    | n   | r    | n   |
| Cross-sectional analyses<sup>a</sup> | EDSS                           | 0.08 | 172 | 0.27** | 105 | 0.2 | 50 | 0.27* | 55 |
|               | MSFC                           | 0.03 | 77  | −0.25** | 94 | −0.22 | 43 | −0.25 | 51 |
|               | Gd+ lesion number              | 0.46**** | 169 | 0.38**** | 104 | 0.26 | 48 | 0.47*** | 56 |
|               | Gd+ lesion volume              | 0.47**** | 169 | 0.39**** | 104 | 0.30* | 48 | 0.46*** | 56 |
|               | T2 lesion volume               | 0.36**** | 142 | 0.28**  | 97 | 0.26 | 46 | 0.27  | 51 |
|               | BPF                            | 0.04 | 68  | −0.19 | 85 | −0.15 | 42 | −0.2  | 43 |
| Year 2<sup>b</sup> | Gd+ lesion number Year 1 + Year 2 | 0.44**** | 80  | 0.45**** | 103 | 0.38** | 47 | 0.50**** | 56 |
|               | New T2 lesions                 | 0.34** | 75  | 0.53**** | 103 | 0.41** | 48 | 0.55**** | 55 |
|               | Relapses                       | 0.18* | 172 | 0.41**** | 107 | 0.21 | 50 | 0.54**** | 57 |
|               | BPF change                     | −0.27* | 68  | −0.31** | 85 | −0.27* | 42 | −0.32* | 43 |
|               | EDSS change                    | 0.06 | 82  | 0.19*  | 105 | 0.06 | 50 | 0.21  | 55 |
|               | MSFC change                    | −0.15 | 60  | −0.36*** | 93 | −0.24 | 42 | −0.48*** | 51 |
| Year 8<sup>b</sup> | BPF change                     | −0.15 | 45  | −0.46**** | 67 | −0.34* | 32 | −0.56*** | 35 |
|               | EDSS change                    | −0.01 | 70  | 0.27**  | 99 | 0.14 | 47 | 0.32*  | 52 |
| Year 15<sup>b</sup> | EDSS change                   | 0.1  | 58  | 0.15  | 84 | 0.05  | 40 | 0.2   | 44 |

BPF: brain parenchymal fraction; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; MSFC: Multiple Sclerosis Functional Composite; *r*; Spearman's rank correlation coefficient.

* *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.
For cross-sectional analyses, the association between NfL and clinical/radiological measurements at the time of NfL sample collections are reported.
Statistically significant correlations are in bold.
Compared with baseline.
**eTable 3. Correlation between serum NfL levels and clinical and MRI measures.**

| Time variable       | Measure          | Serum NfL at Year 3 | Serum NfL at Year 4 | Serum NfL mean of Year 3 and Year 4 |
|---------------------|------------------|--------------------|--------------------|-----------------------------------|
|                     |                  | r  | n    | r  | n    | r  | n    |
| 8 year (Year 0–Year 8) | BPF change       | -0.36* | 38   | -0.18 | 62   | -0.211, NS | 71   |
|                     | EDSS change      | 0.27* | 55   | 0.26* | 76   | 0.25* | 92   |
| 15 year (Year 0–Year 15) | EDSS change     | 0.24  | 45   | 0.30* | 63   | 0.24* | 77   |

BPF: brain parenchymal fraction; EDSS: Expanded Disability Status Scale; NS: not significant; r: Spearman’s rank correlation coefficient. Statistically significant correlations are shown in bold. *p < 0.05.