Supplementary materials

Table S1 Time to disability worsening confirmed for 12 weeks at all time points up to Year 7 in BVL groups\textsuperscript{a} (Baseline to Year 2)

| Year | Group 1 vs Group 3 | Group 2 vs Group 3 |
|------|--------------------|--------------------|
|      | Hazard ratio (95% CI); \( p \)-value | Hazard ratio (95% CI); \( p \)-value |
| 3    | 0.57 (0.39, 0.83); \( p \)=0.0033 | 0.64 (0.46, 0.90); \( p \)=0.0091 |
| 4    | 0.54 (0.38, 0.77); \( p \)=0.0006 | 0.63 (0.46, 0.85); \( p \)=0.0030 |
| 5    | 0.55 (0.39, 0.77); \( p \)=0.0006 | 0.66 (0.49, 0.90); \( p \)=0.0079 |
| 6    | 0.59 (0.42, 0.82); \( p \)=0.0017 | 0.68 (0.51, 0.92); \( p \)=0.0117 |
| 7    | 0.58 (0.42, 0.81); \( p \)=0.0012 | 0.68 (0.51, 0.91); \( p \)=0.0085 |

\textsuperscript{a}Analyses based on pooled data from placebo and active treatment groups (total population); Group 1 (least BVL): ≤0.52% reduction; Group 2 (intermediate BVL): >0.52 to 2.18% reduction; Group 3 (most BVL): >2.18% reduction.

BVL, brain volume loss; CI, confidence Interval.
Table S2 Time to disability worsening confirmed for 24 weeks at all time points (years 3–7) in BVL groups\textsuperscript{a} (Baseline to Year 2)

| Year | Group 1 vs Group 3 | Group 2 vs Group 3 |
|------|-------------------|-------------------|
|      | Hazard ratio (95% CI); \(p\)-value | Hazard ratio (95% CI); \(p\)-value |
| 3    | 0.52 (0.34, 0.80); \(p\)=0.0027     | 0.68 (0.47, 0.98); \(p\)=0.0400 |
| 4    | 0.53 (0.36, 0.78); \(p\)=0.0014     | 0.67 (0.48, 0.94); \(p\)=0.0215 |
| 5    | 0.53 (0.36, 0.77); \(p\)=0.0009     | 0.72 (0.51, 0.99); \(p\)=0.0449 |
| 6    | 0.57 (0.39, 0.82); \(p\)=0.0024     | 0.73 (0.53, 1.01); \(p\)=0.0534 |
| 7    | 0.57 (0.40, 0.81); \(p\)=0.0019     | 0.71 (0.52, 0.97); \(p\)=0.0318 |

\textsuperscript{a}Analyses based on pooled data from placebo and active treatment groups (total population); Group 1 (least BVL): ≤0.52% reduction; Group 2 (intermediate BVL): >0.52 to 2.18% reduction; Group 3 (most BVL): >2.18% reduction.

BVL, brain volume loss; CI, confidence Interval.
Table S3 Combined surrogate analysis

| Potential surrogates                                      | PTE mediated through the potential surrogates |
|-----------------------------------------------------------|-----------------------------------------------|
| BVL at Year 2 + Relapses over 2 years                     | 82.1%                                         |
| BVL at Year 2 + New or enlarging T2w lesions over 2 years | 61.5%                                         |
| Relapses over 2 years+ New or enlarging T2w lesions over 2 years | 48.7%                                         |
| BVL at Year 2 + Relapses over 2 years + New or enlarging T2w lesions over 2 years | 76.9%                                         |

BVL, brain volume loss; PTE, proportion of treatment effect; T2w, T2-weighted.