

Supplementary materials

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

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

^aAnalyses 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^a (Baseline to Year 2)

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

^aAnalyses 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; T_{2w}, T₂-weighted.