Effects of evobrutinib, a Bruton's tyrosine kinase inhibitor, on slowly expanding lesions: an emerging imaging marker of chronic tissue loss in multiple sclerosis

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Disclosures

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Davorka Tomic is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany and received stock or an ownership interest from Novartis.

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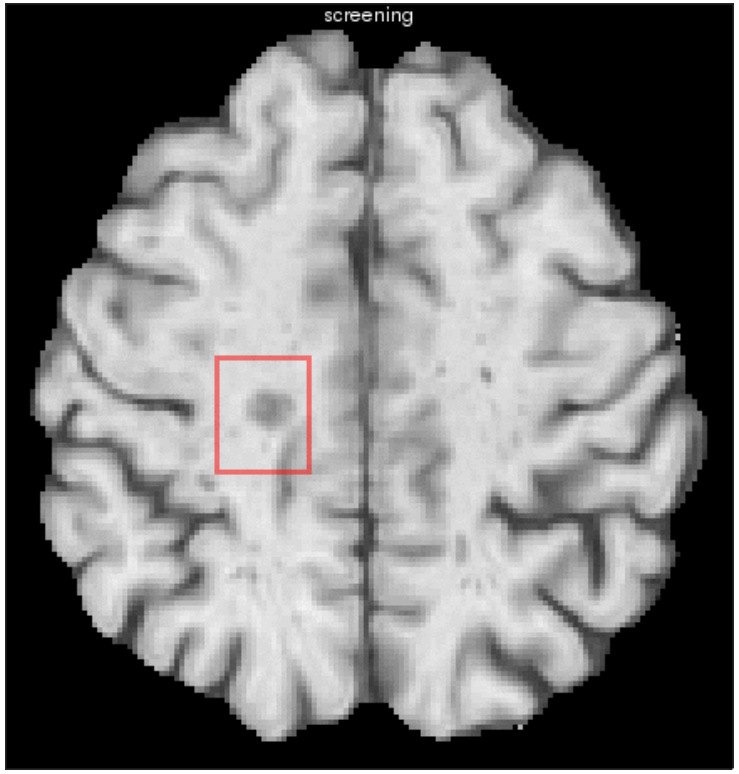
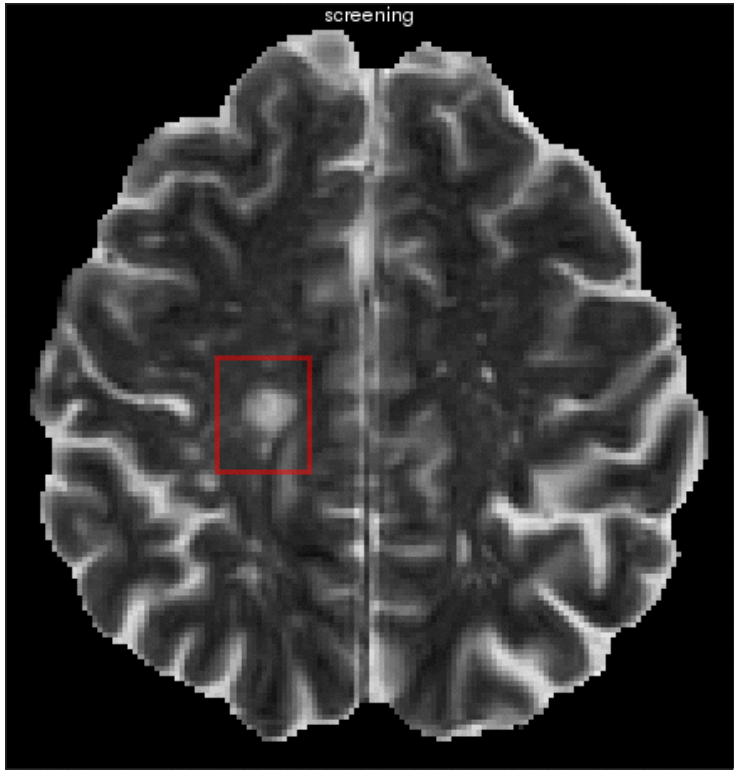
Slowly expanding lesions (SELs) as a marker of clinical progression in MS

- Chronic active lesions (defined on histology and also known as smouldering lesions, mixed active/inactive lesions or slowly expanding lesions) are chronically active, demyelinated MS lesions, likely driven by sustained microglia/macrophage activity, resulting in the progressive accumulation of irreversible neural tissue damage and axonal loss[1]
- SELs (defined on MRI) can be identified as areas within pre-existing T2 lesions that show gradual, radial expansion over time. These identify areas of ongoing tissue damage within chronic lesions and, at least, a subset of chronic active lesions that show expansion over time
- SEL activity and ongoing tissue damage within SELs predict long-term disability[2]

T1 weighted MRI



T2 weighted MRI



MRI, magnetic resonance imaging; **MS**, multiple sclerosis; **SEL**, slowly expanding lesions

1. Elliott C, et al. *Mult Scler.* 2019;25:1915–25; 2. Elliott C, et al. *Brain.* 2019;142:2787–99

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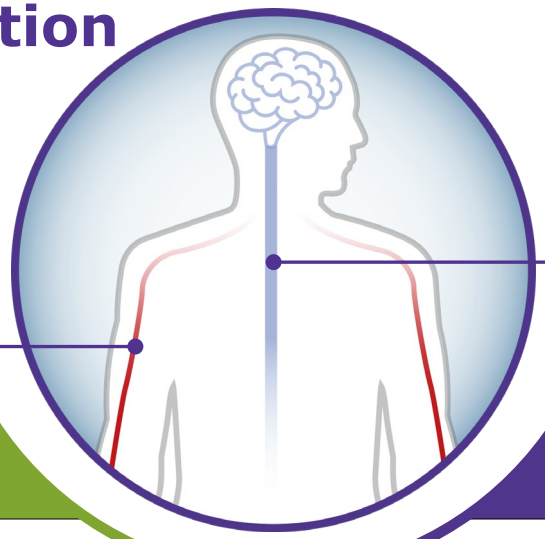
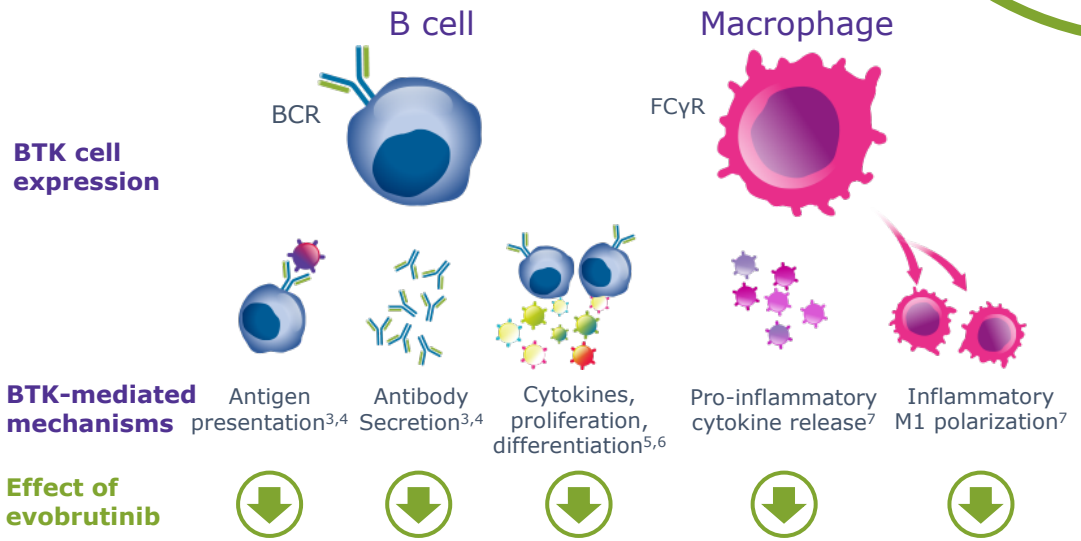
Evobrutinib mechanism of action



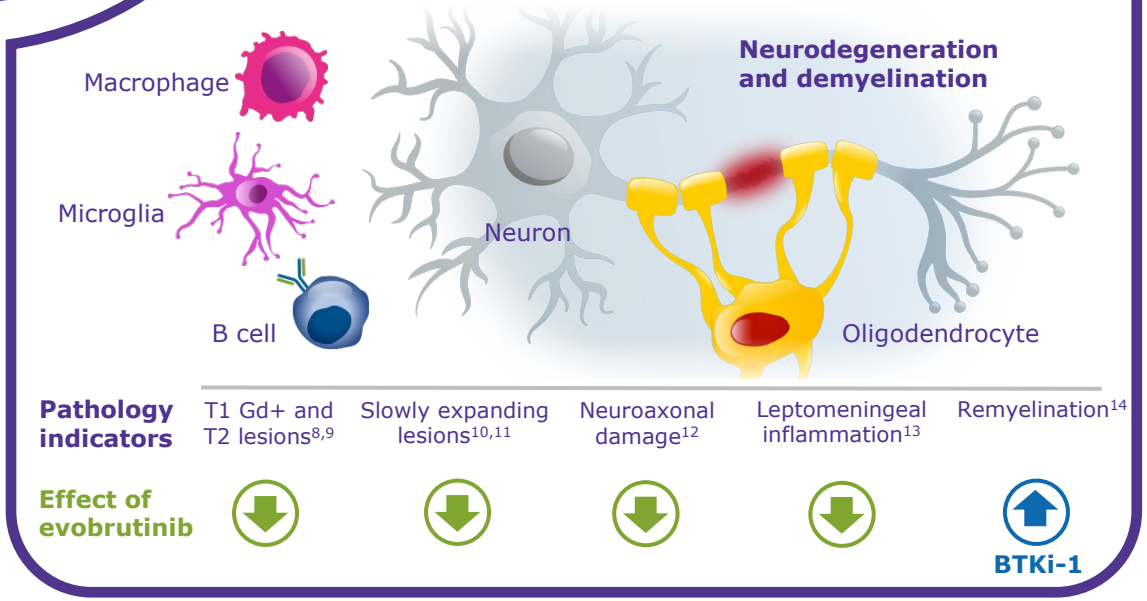
Evobrutinib in the peripheral blood[1]

Evobrutinib in CSF[2]

Peripheral cellular mechanisms



MS disease pathology in the CNS



Up arrow indicates an increase; Down arrow indicates a decrease; **BCR**, B cell receptor; **BTK**, Bruton's tyrosine kinase; **BTKi-1**, tool BTK inhibitor with similar properties to evobrutinib; **CSF**, cerebrospinal fluid; **CNS**, central nervous system; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis. 1. Becker A, et al. *Clin Trans Sci.* 2020;13:325–36; 2. Piasecka-Stryczynska K, et al. *Mult Scler Relat Disord.* 2021;51:103001; 3. Torke S, et al. *Acta Neuropathol.* 2020;140:535–48; 4. López-Herrera G, et al. *J Leukoc Biol.* 2014;95:243–50; 5. Haselmayer P, et al. *J Immunol.* 2019;202:2888–906; 6. Rijvers L, et al. *Mult Scler.* 2020;26(Suppl. 3):312 [Abstract P0403]; 7. Alankus YB, et al. *Mult Scler.* 2018;24(Suppl. 2):264 [Abstract P557]; 8. Montalban X, et al. *N Engl J Med.* 2019;380:2406–17; 9. Kuhle, J et al. *Mult Scler.* 2021;27(Suppl 2):70 [Abstract 116]; 10. Elliott C, et al. *Mult Scler.* 2019;25:1915–25; 11. Arnold D, et al. *Mult Scler.* 2021;27(Suppl 2):69 [Abstract 115]; 12. Kuhle J, et al. *Neurology.* 2021;96(22):e2783–8; 13. Kebir H, et al. *Neurology.* 2021;96(15 Suppl.):4162; 14. Martin E, et al. *Brain Plasticity.* 2020;5:123–33

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Objective

To evaluate the effect of evobrutinib treatment versus comparator on SEL volume, with SELs identified via MRI assessments (at baseline, Weeks 12, 16, 20, 24, 48 and end of treatment) in a Phase II trial

MRI, magnetic resonance imaging; **SEL**, slowly expanding lesions

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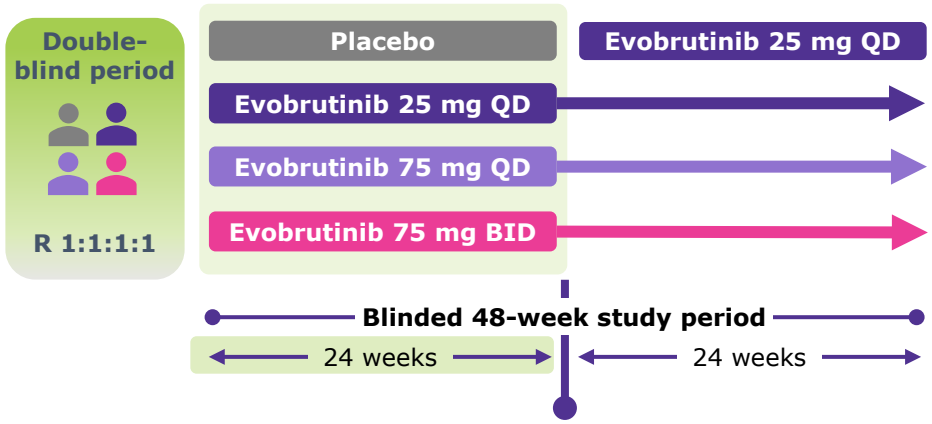
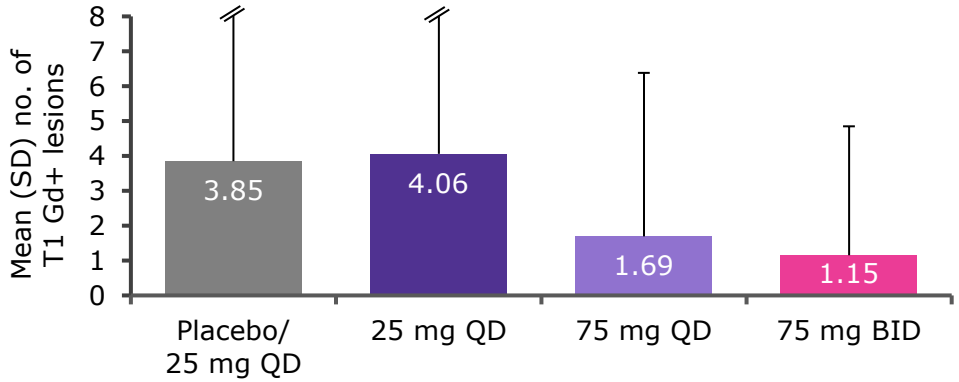
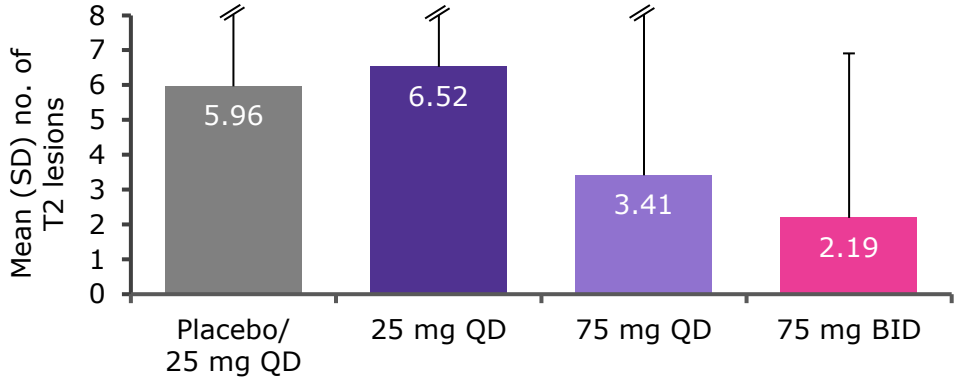
Phase II study: investigation of evobrutinib in patients with relapsing MS



Primary endpoint: Total no. T1 Gd+ lesions (Weeks 12–24)



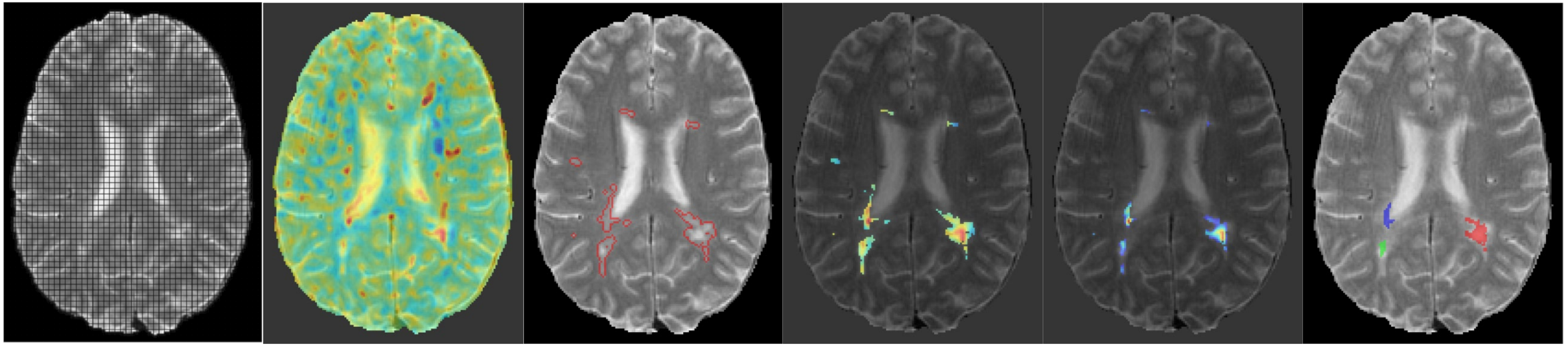
Total no. new/enlarging T2 lesions (Weeks 12–24)



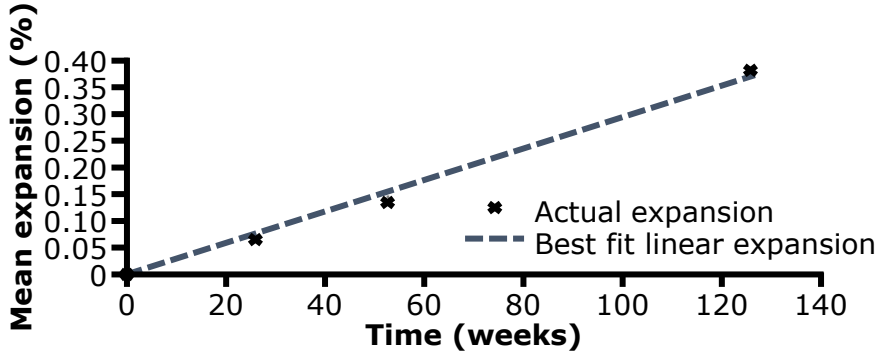
*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment
BID, twice daily; **DMF**, dimethyl fumarate; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis; **no.**, number; **QD**, once daily; **R**, randomization; **SD**, standard deviation
Montalban X, et al. *N Engl J Med.* 2019;380:2406–17

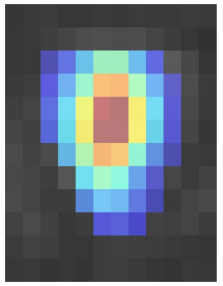
SEL detection on MRI

SELs are identified as contiguous areas of existing T2 lesion (≥10 voxels) showing positive local change as indicated by the Jacobian determinant

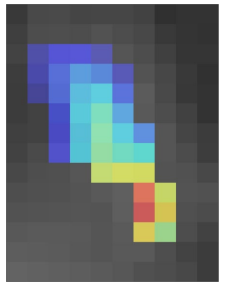


Deformation Baseline–Week 96 | Jacobian Baseline–Week 96 | Baseline T2 lesion mask | Jacobian w/in T2 lesion mask | Positive Jacobian w/in T2 lesion mask | SEL candidates





Concentric



Nonconcentric

MRI, magnetic resonance imaging; **SEL**, slowly expanding lesions; **T2 lesions**, identified via T2-weighted MRI; **w/in**, within

Elliott C, et al. *Mult Scler.* 2017;23 (Suppl. 3):52–3 (Abstract/OP 186; Detection and characterisation of slowly evolving lesions in.... ECTRIMS Online Library. Elliott C. Oct 27 2017; 202544 (ectrims-congress.eu)

Statistical analyses

- Two stratified analyses* of SEL volume (absolute) and SEL volume as a percentage of baseline T2 lesion volume were conducted:

Analysis name	Time period	Patients	Strata	Treatment effect analysis
(1) Stratified analysis – all patients	Baseline through **Week 48/EOT**	Treatment completers and early discontinuers	Baseline T2 lesion volume tertiles†: • ≤8 cc • 8–19 cc • ≥19 cc	Stratified Hodges–Lehmann estimate of shift in SEL volume distribution (absolute or percent) and stratified Wilcoxon rank sum test
(2) Stratified analysis – completers	Baseline through **Week 48**	Treatment completers		

- Subgroup analyses:
  - **Evobrutinib high dose**: Evobrutinib 75 mg QD ✚ Evobrutinib 75 mg BID

VERSUS

  - **Evobrutinib low dose**: Placebo / Evobrutinib 25 mg QD ✚ Evobrutinib 25 mg QD

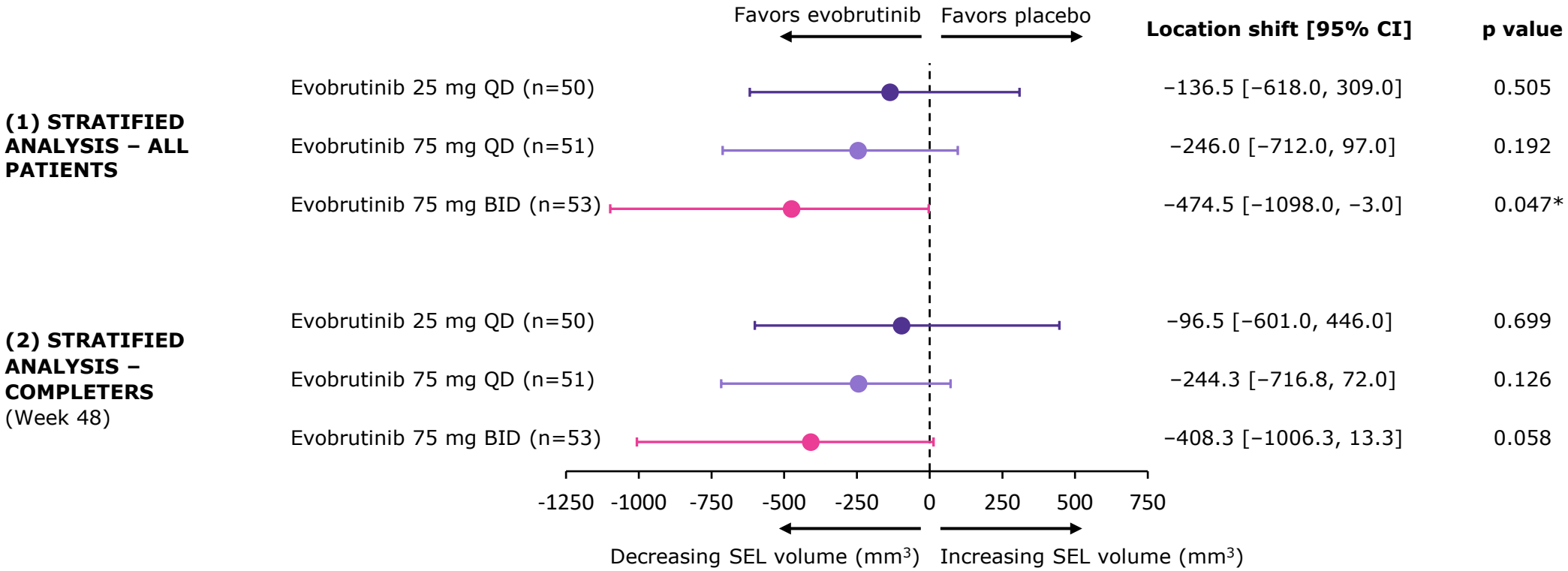
*Based on the modified intention-to-treat analysis set; †≤8000 mm^3, 8000–19,000 mm^3, ≥19,000 mm^3
BID, twice daily; **EOT,** end of treatment; **QD**, once daily; **SEL**, slowly expanding lesions

Baseline characteristics

	Placebo/evobrutinib 25 mg QD (n=53)	Evobrutinib 25 mg QD (n=50)	Evobrutinib 75 mg QD (n=51)	Evobrutinib 75 mg BID (n=53)
Sex, n (%)				
Male	14 (26.4)	18 (36.0)	16 (31.4)	17 (32.1)
Female	39 (73.6)	32 (64.0)	35 (68.6)	36 (67.9)
Age, years (mean ±SD)	41.6 ±10.8	42.4 ±9.4	42.9 ±10.1	42.2 ±11.5
Time since MS onset, years, n (%)				
<8.5 years	32 (60.4)	26 (52.0)	20 (39.2)	23 (43.4)
≥8.5 years	21 (39.6)	23 (46.0)	31 (60.8)	30 (56.6)
Type of MS				
RRMS	47 (88.7)	42 (84.0)	43 (84.3)	47 (88.7)
SPMS	6 (11.3)	8 (16.0)	8 (15.7)	6 (11.3)
Number of relapses in 2 years pre-randomization, n (%)				
≤1 relapse (non-HDA)	26 (49.1)	27 (54.0)	18 (35.3)	25 (47.2)
≥2 relapses (HDA)	27 (50.9)	23 (46.0)	33 (64.7)	28 (52.8)
EDSS score, n (%)				
≤3	27 (50.9)	28 (56.0)	22 (43.1)	28 (52.8)
≥3.5	26 (49.1)	22 (44.0)	29 (56.9)	25 (47.2)
T2 lesion volume, cc (mean ±SD)	15.9 ±12.6	13.8 ±11.7	14.0 ±12.2	19.0 ±13.5

mITT analysis set. **BID**, twice daily; **EDSS**, Expanded Disability Status Scale; **HDA**, high disease activity; **mITT**, modified intention-to-treat; **MS**, multiple sclerosis; **QD**, once daily; **RRMS**, relapsing-remitting MS; **SD**, standard deviation; **SPMS**, secondary-progressive MS

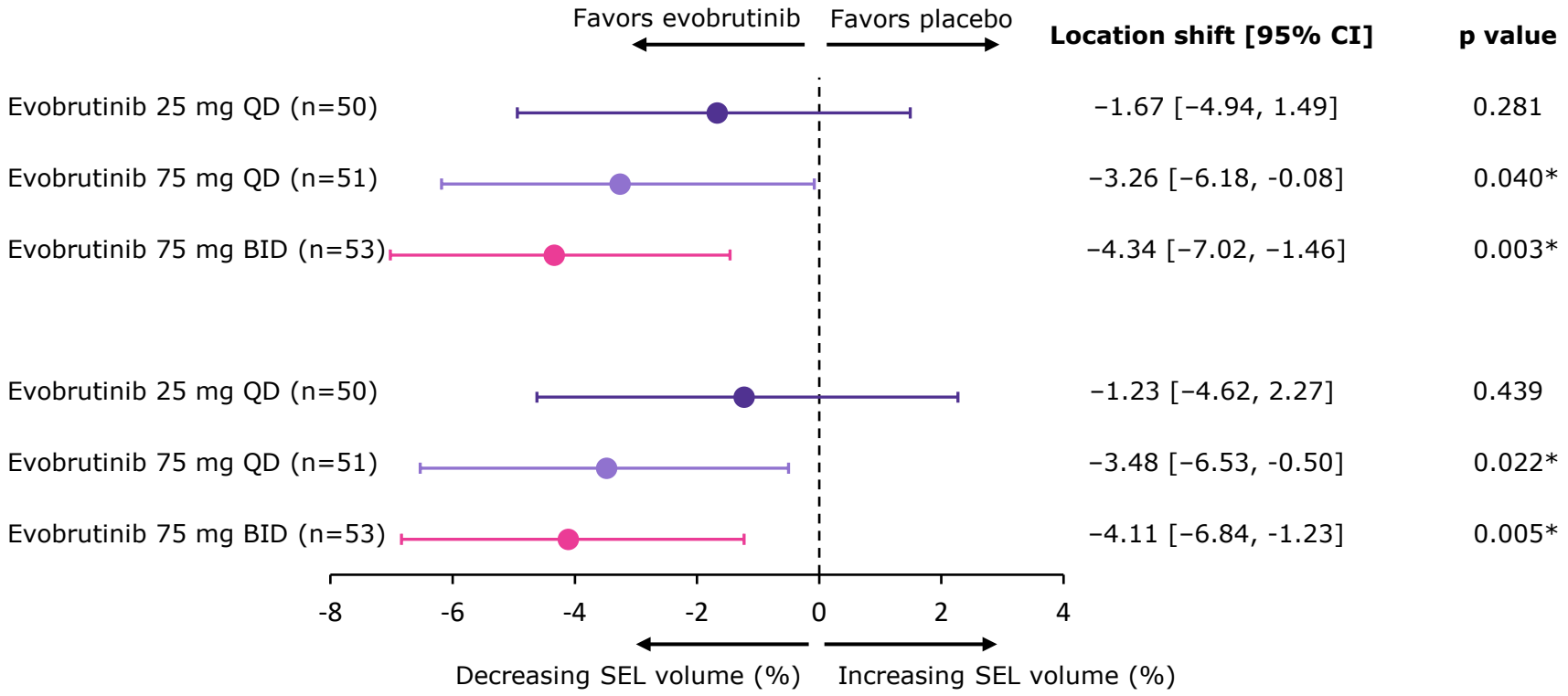
Evobrutinib reduced SEL volume in a dose-dependent manner



SEL volume decreased with increasing evobrutinib dose relative to the placebo

*p value <0.05
BID, twice daily; **CI**, confidence interval; **QD**, once daily; **SEL**, slowly expanding lesions

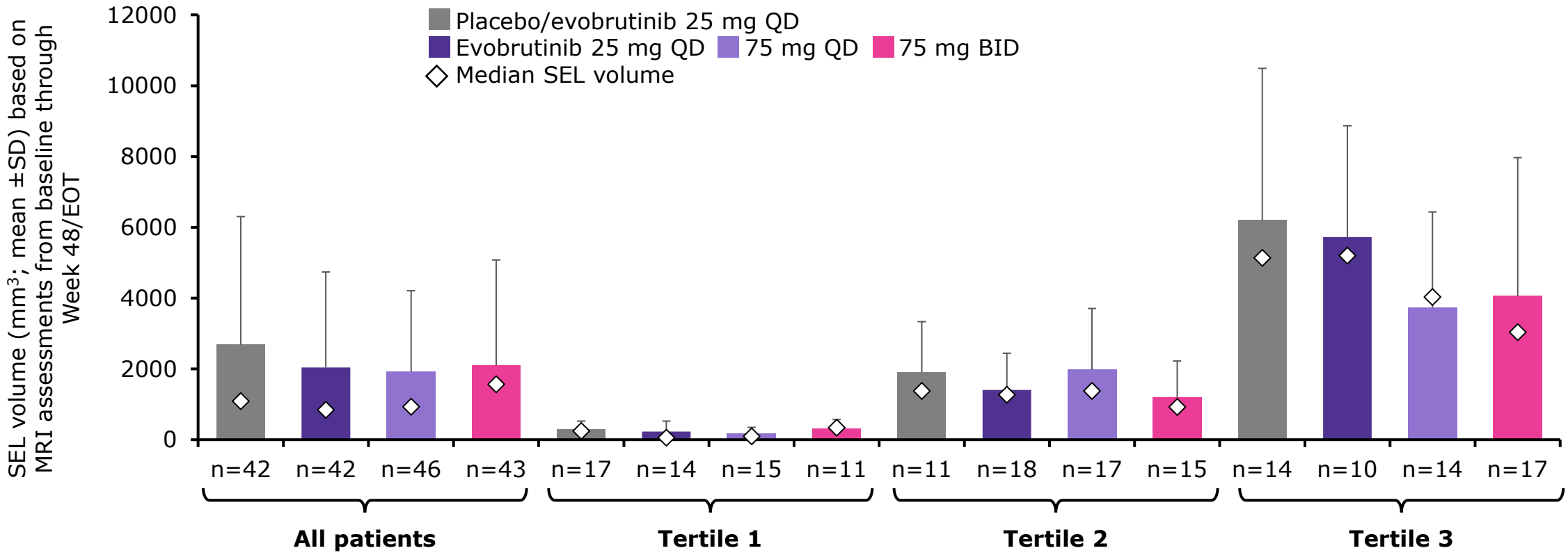
Evobrutinib reduced SEL volume (%) in a dose-dependent manner



SEL volume, as a percentage of baseline T2 lesion volume, decreased with increasing evobrutinib dose relative to placebo

*p value <0.05
Unstratified test results show that most of the adjustment for baseline T2 lesion volume is accomplished by using the percent volume endpoint with additional adjustment accomplished by using stratification
BID, twice daily; **CI**, confidence interval; **QD**, once daily; **SEL**, slowly expanding lesions

SEL volume by tertiles of baseline T2 lesion volume

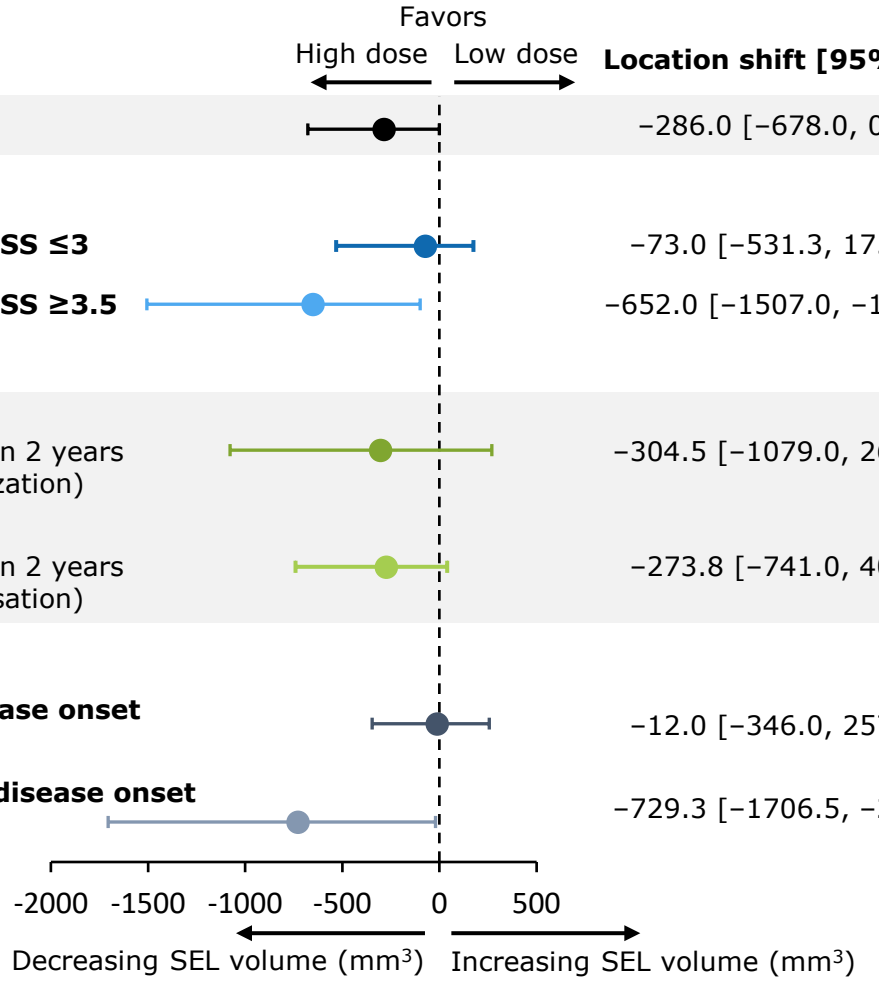


Effect of evobrutinib treatment on SEL volume is evident within tertiles 2 and 3

Tertiles of baseline T2 lesion volume (cc) in overall population – Tertile 1: ≤8 cc (≤8000 mm³); Tertile 2: 8–19 cc (8000–19,000 mm³); Tertile 3: ≥19 cc (≥19,000 mm³)
SEL volume based on MRI assessments from baseline through Week 48/EOT
BID, twice daily; **EOT**, end of treatment; **MRI**, magnetic resonance imaging; **QD**, once daily; **SD**, standard deviation; **SEL**, slowly expanding lesions

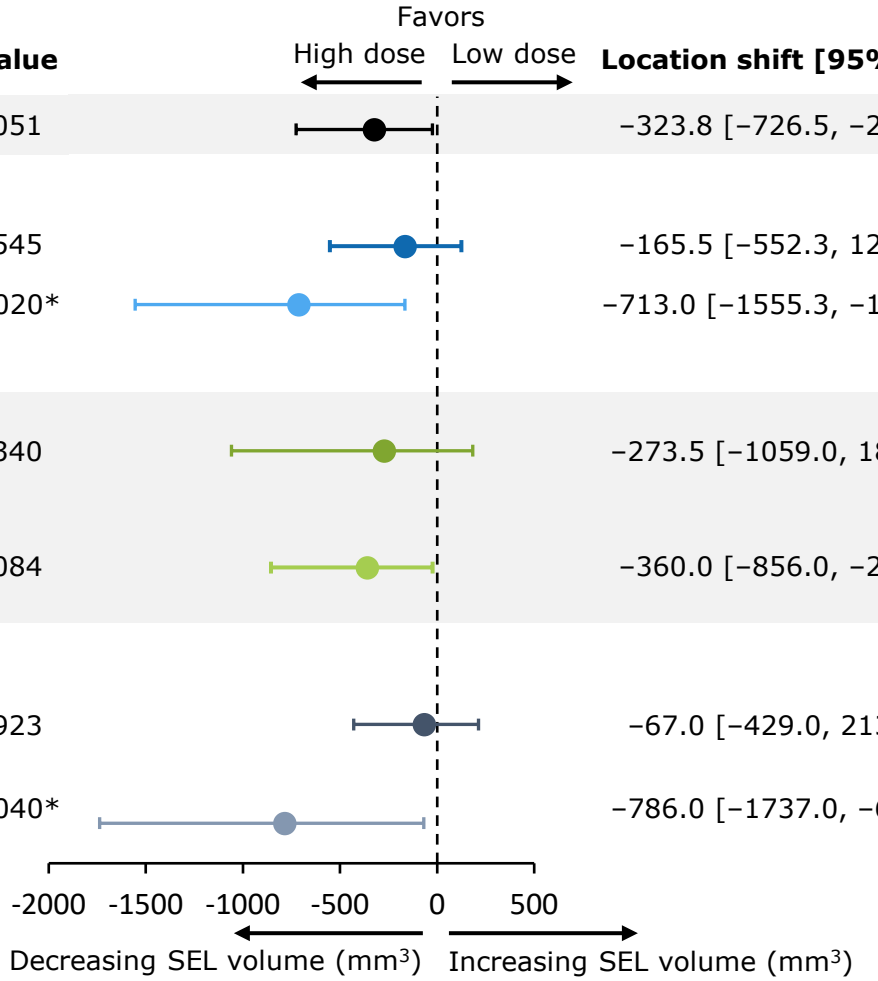
The effect of evobrutinib on SEL volume was also evident in patients with more advanced disease

(1) STRATIFIED ANALYSIS: ALL PATIENTS



	Location shift [95% CI]	p value
Overall	−286.0 [−678.0, 0.0]	0.051
Baseline EDSS ≤3	−73.0 [−531.3, 175.0]	0.545
Baseline EDSS ≥3.5	−652.0 [−1507.0, −100.0]	0.020*
Non-HDA (≤1 relapse in 2 years pre-randomization)	−304.5 [−1079.0, 269.0]	0.340
HDA (≥2 relapse in 2 years pre-randomisation)	−273.8 [−741.0, 40.0]	0.084
Recent disease onset (<8.5 years)	−12.0 [−346.0, 257.0]	0.923
Protracted disease onset (≥8.5 years)	−729.3 [−1706.5, −20.0]	0.040*

(2) STRATIFIED ANALYSIS: COMPLETERS (Week 48)

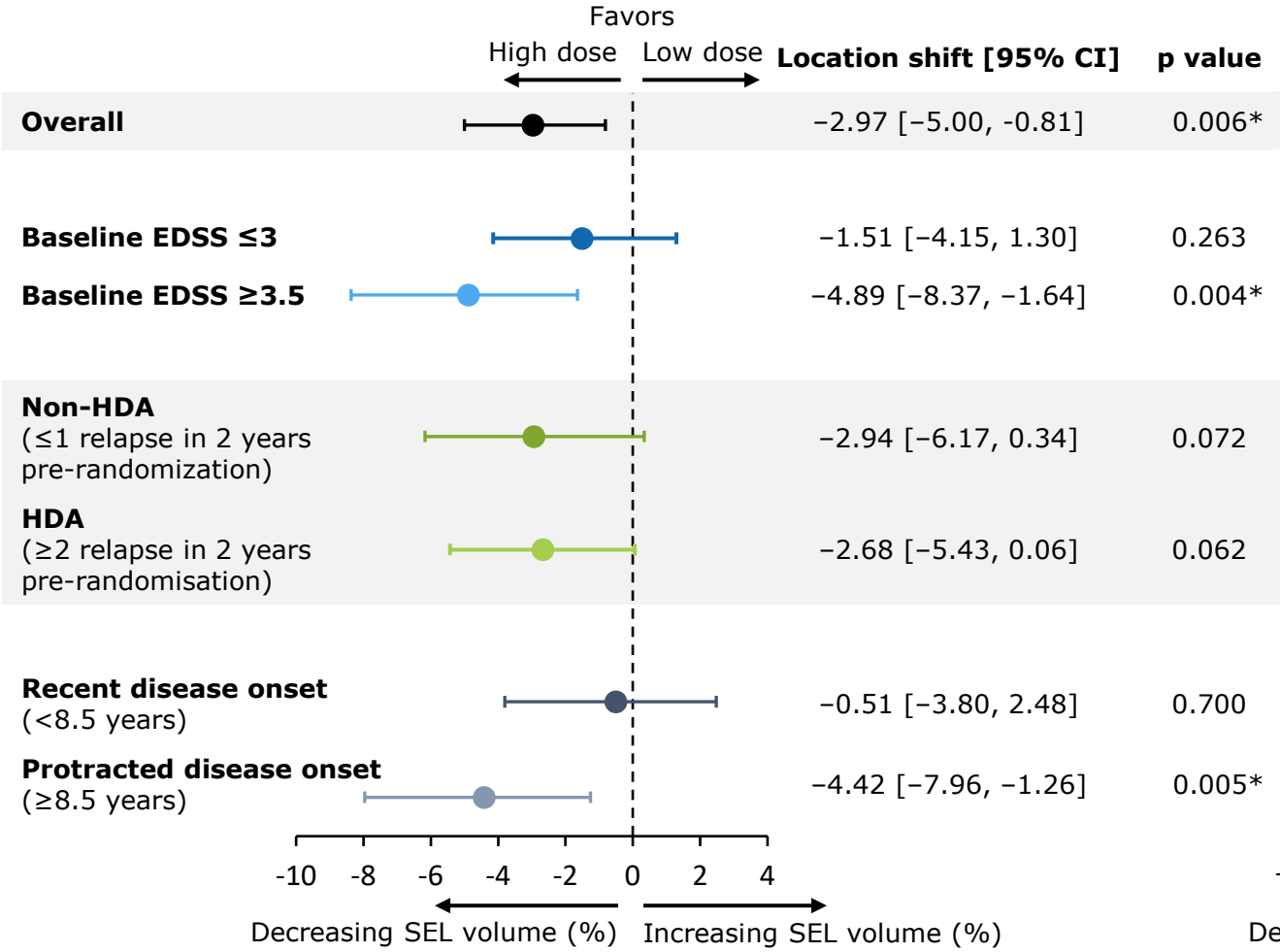


	Location shift [95% CI]	p value
Overall	−323.8 [−726.5, −25.0]	0.026*
Baseline EDSS ≤3	−165.5 [−552.3, 124.8]	0.387
Baseline EDSS ≥3.5	−713.0 [−1555.3, −166.0]	0.007*
Non-HDA (≤1 relapse in 2 years pre-randomization)	−273.5 [−1059.0, 183.0]	0.281
HDA (≥2 relapse in 2 years pre-randomisation)	−360.0 [−856.0, −24.0]	0.032*
Recent disease onset (<8.5 years)	−67.0 [−429.0, 213.5]	0.742
Protracted disease onset (≥8.5 years)	−786.0 [−1737.0, −69.0]	0.025*

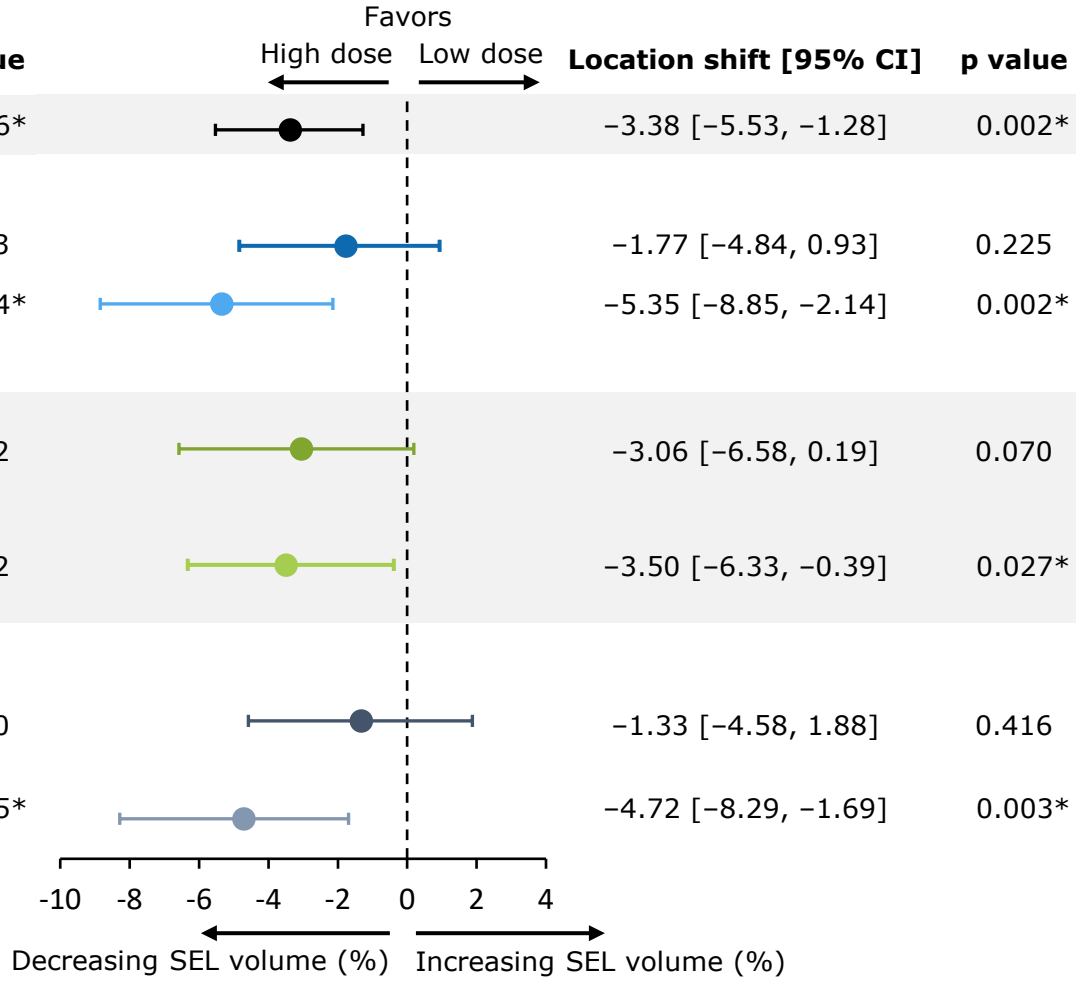
Overall: (high dose/low dose) n=104/n=103; **EDSS ≤3:** n=50/n=55; **EDSS ≥3.5:** n=54/n=48; **non-HDA:** n=43/n=53; **HDA:** n=61/n=50; **Recent onset:** n=43/n=58; **Protracted onset:** n=61/n=44
High dose: evobrutinib 75 mg QD + BID; **Low dose:** placebo/evobrutinib 25 mg QD + evobrutinib 25 mg QD; *p value <0.05
BID, twice daily; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **HDA**, high disease activity; **QD**, once daily; **SEL**, slowly expanding lesions

The effect of evobrutinib on SEL volume (%) was also evident in patients with more advanced disease

(1) STRATIFIED ANALYSIS: ALL PATIENTS



(2) STRATIFIED ANALYSIS: COMPLETERS (Week 48)



Overall: (high dose/low dose) n=104/n=103; **EDSS ≤3:** n=50/n=55; **EDSS ≥3.5:** n=54/n=48; **non-HDA:** n=43/n=53; **HDA:** n=61/n=50; **Recent onset:** n=43/n=58; **Protracted onset:** n=61/n=44
High dose: evobrutinib 75 mg QD + BID; **Low dose:** placebo/evobrutinib 25 mg QD + evobrutinib 25 mg QD; *p value <0.05
BID, twice daily; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **HDA**, high disease activity; **QD**, once daily; **SEL**, slowly expanding lesions

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Conclusions

- Evobrutinib reduces SEL volume (absolute or percent) in a dose-dependent manner in relapsing MS
  - Greatest volume reduction with evobrutinib 75 mg BID
- The effect of evobrutinib on SEL volume was also especially apparent in patients with more advanced disease and greater T2 lesion volume (subgroup analysis)

- The suppression of SEL volume in the evobrutinib treatment groups relative to the placebo treatment group suggests that evobrutinib has an effect on myeloid cells (including microglia and macrophages) within the CNS
- Progressive accumulation of irreversible neural tissue damage and axonal loss as measured by SELs may be predictive of long-term clinical progression[1,2]

This is the first evidence that a BTK inhibitor impacts brain lesions associated with chronic inflammation and tissue loss

BID, twice daily; **BTK**, Bruton's tyrosine kinase; **CNS**, central nervous system; **MS**, multiple sclerosis; **SEL**, slowly expanding lesions

1. Elliott C, et al. *Mult Scler.* 2019;25:1915–25; 2. Elliott C, et al. *Brain.* 2019;142:2787–99