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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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CONCLUSIONS

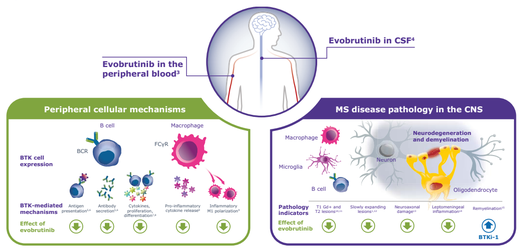
- **Evobrutinib reduces slowly expanding lesion (SEL) volume in a dose-dependent manner in relapsing MS**
  - **The greatest volume reduction was seen with evobrutinib 75 mg twice daily (BID)**
- **The effect of evobrutinib on SEL volume was especially apparent in patients with more advanced disease 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 central nervous system (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 Bruton's tyrosine kinase (BTK) inhibitor impacts brain lesions associated with chronic inflammation and tissue loss**

INTRODUCTION

SELs as a marker of clinical progression in MS

- Chronic active lesions (defined on histology and also known as smoldering 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 markers identify areas of ongoing tissue damage within chronic lesions, and may also show a subset of chronic active lesions that demonstrate expansion over time
- SEL activity and ongoing tissue damage within SELs predict long-term disability[2]

Figure 1. Evobrutinib mechanism of action



Up arrow indicates an increase; down arrow indicates a decrease

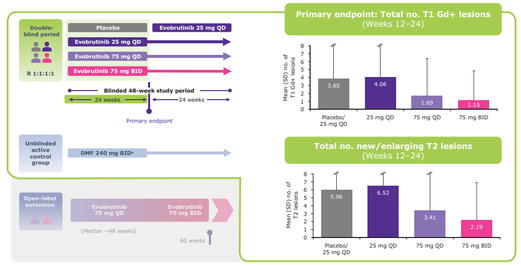
OBJECTIVE

- 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

METHODS

Study design[10] (**Figure 2**)

Figure 2. Phase II study: Investigation of evobrutinib in patients with relapsing MS



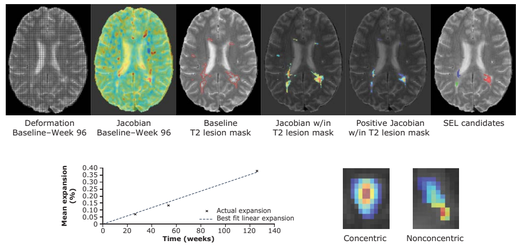
*120 mg BID for the first seven days, followed by 240 mg BID for the duration of treatment

METHODS

SEL detection on MRI

- SELs are identified as contiguous areas of existing T2 lesions (⩾10 voxels) showing positive local change, as indicated by the Jacobian determinant[16] (**Figure 3**)

Figure 3. SEL detection on MRI



Statistical analyses

- Two stratified analyses (based on the mITT analysis set) of SEL volume were conducted (**Table 1**)

Table 1. Statistical analyses of SEL volume

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[a]: • ⩽8 cc • 8–19 cc • ⩾19 cc	Stratified Hodges–Lehmann estimate of shift in SEL volume distribution and stratified Wilcoxon rank sum test
(2) Stratified analysis – completers	Baseline through **Week 48**	Treatment completers		

[a]⩽8000 mm³, 8000–19,000 mm³, ⩾19,000 mm³

- 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)

RESULTS

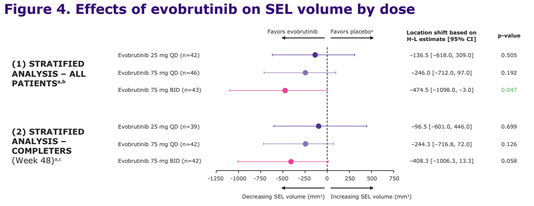
Baseline characteristics (**Table 2**)

Table 2. Baseline characteristics of the mITT analysis set

	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 Female	14 (26.4) 39 (73.6)	18 (36.0) 32 (64.0)	16 (31.4) 35 (68.6)	17 (32.1) 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 ⩾8.5 years	32 (60.4) 21 (39.6)	26 (52.0) 23 (46.0)	20 (39.2) 31 (60.8)	23 (43.4) 30 (56.6)
Type of MS				
RRMS SPMS	47 (88.7) 6 (11.3)	42 (84.0) 8 (16.0)	43 (84.3) 8 (15.7)	47 (88.7) 6 (11.3)
Number of relapses in 2 years pre-randomization, n (%)				
⩽1 relapse (non-HDA) ⩾2 relapses (HDA)	26 (49.1) 27 (50.9)	27 (54.0) 23 (46.0)	18 (35.3) 33 (64.7)	25 (47.2) 28 (52.8)
EDSS score, n (%)				
⩽3 ⩾3.5	27 (50.9) 26 (49.1)	28 (56.0) 22 (44.0)	22 (43.1) 29 (56.9)	28 (52.8) 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

Evobrutinib reduced SEL volume in a dose-dependent manner, relative to placebo (**Figure 4**)

Figure 4. Effects of evobrutinib on SEL volume by dose

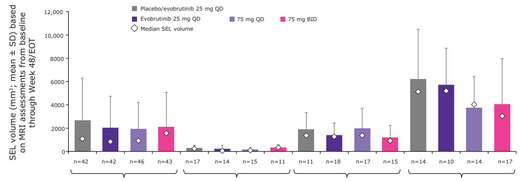


[a]Patients switched from placebo to evobrutinib 25 mg QD for the second 24-week treatment period
[b]Evobrutinib treatment groups versus placebo/evobrutinib 25 mg QD (n=42)
[c]Evobrutinib treatment groups versus placebo/evobrutinib 25 mg QD (n=38)

SEL volume by tertiles of baseline T2 lesion volume

- The effect of evobrutinib treatment on SEL volume (based on MRI assessments from baseline through Week 48/EOT) is evident within Tertiles 2 and 3 (**Figure 5**)
  - 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)

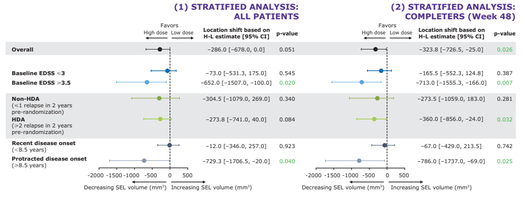
Figure 5. SEL volume by tertiles of baseline T2 lesion volume



Effect of evobrutinib on SEL volume by disease characteristics

- The effect of evobrutinib on SEL volume was also evident in patients with more advanced disease (**Figure 6**)

Figure 6. Effect of evobrutinib on SEL volume by disease characteristics, stratified by analysis



Overall (all patients: high dose/low dose, completers: high dose/low dose): n=89/n=84, n=84/n=77; EDSS ⩽3: n=40/n=47, n=37/n=42; EDSS ⩾3.5: n=49/n=37, n=47/n=35; non-HDA: n=36/n=46, n=34/n=44; HDA: n=53/n=38, n=50/n=33; Recent onset: n=33/n=51, n=30/n=46; Protracted onset: n=56/n=33, n=54/n=31. High dose: evobrutinib 75 mg QD + BID; Low dose: placebo/evobrutinib 25 mg QD + evobrutinib 25 mg QD

Abbreviations: BCR, B-cell receptor; **BID**, twice daily; **BTK**, Bruton's tyrosine kinase; **BTKi-1**, tool BTK inhibitor with similar properties to evobrutinib; **CI**, confidence interval; **CNS**, central nervous system; **CSF**, cerebrospinal fluid; **DMF**, dimethyl fumarate; **EDSS**, Expanded Disability Status Scale; **EOT**, end of treatment; **FCγR**, FC-gamma receptor; **Gd+**, gadolinium-enhancing; **HDA**, high disease activity; **H-L**, Hodges–Lehmann; **mITT**, modified intent-to-treat; **no.**, number; **QD**, once daily; **R**, randomization; **RRMS**, relapsing-remitting MS; **SD**, standard deviation; **SEL**, slowly expanding lesion; **SPMS**, secondary-progressive MS; **T1 lesion**, identified via T1-weighted MRI; **T2 lesion**, identified via T2-weighted MRI

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DISCLOSURES

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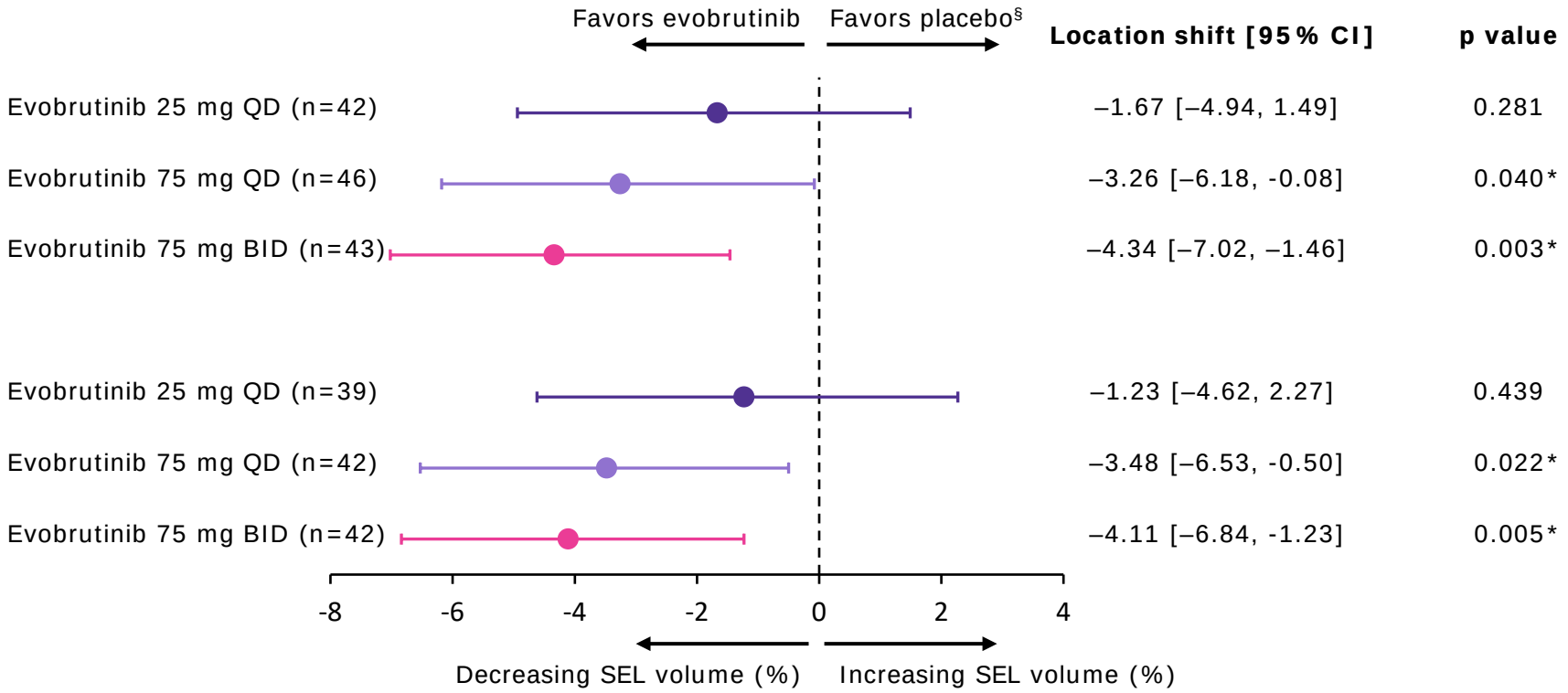
Evobrutinib reduced SEL volume (%) in a dose-dependent manner



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

*p value <0.05; §Patients switched from placebo to evobrutinib 25 mg QD for the second 24-week treatment period; †Evobrutinib treatment groups versus placebo/evobrutinib 25 mg QD (n=42); ‡Evobrutinib treatment groups versus placebo/evobrutinib 25 mg QD (n=38)
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

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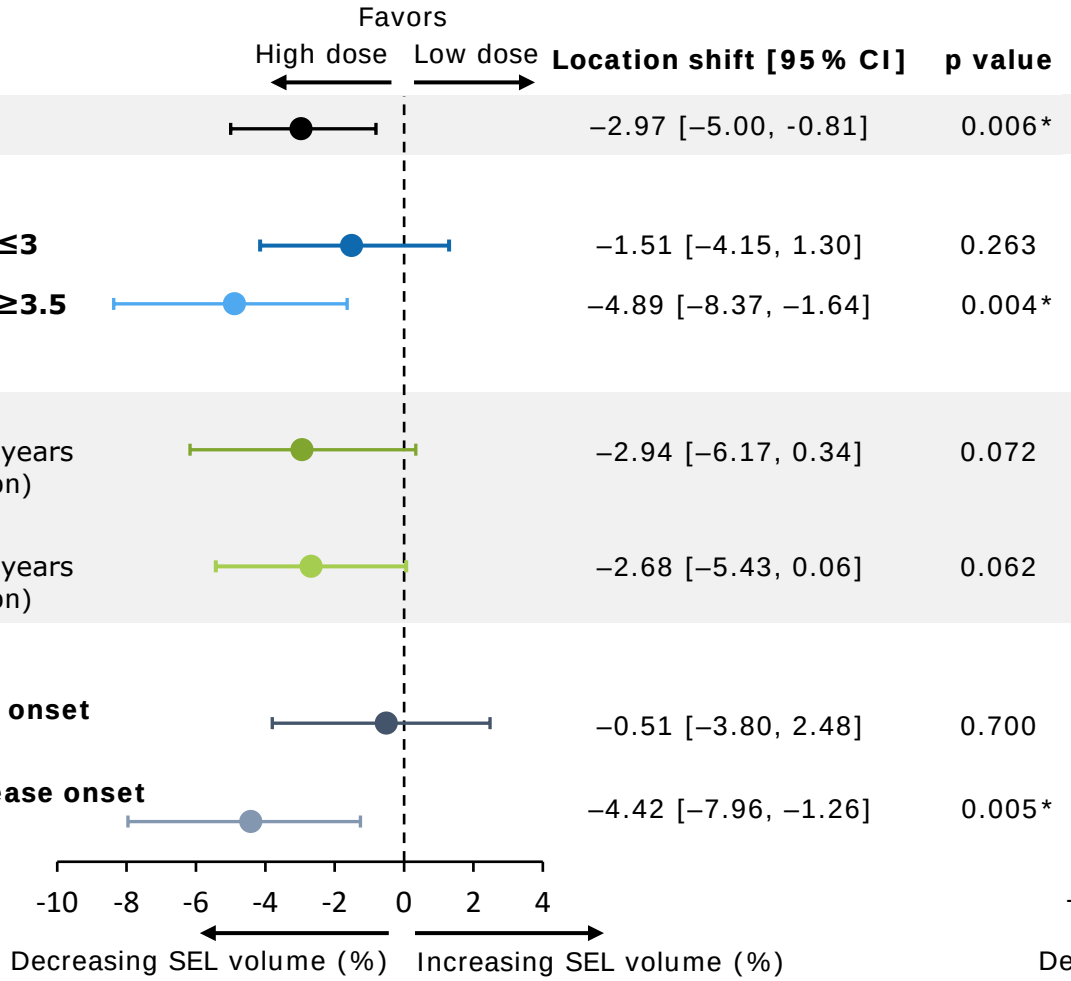
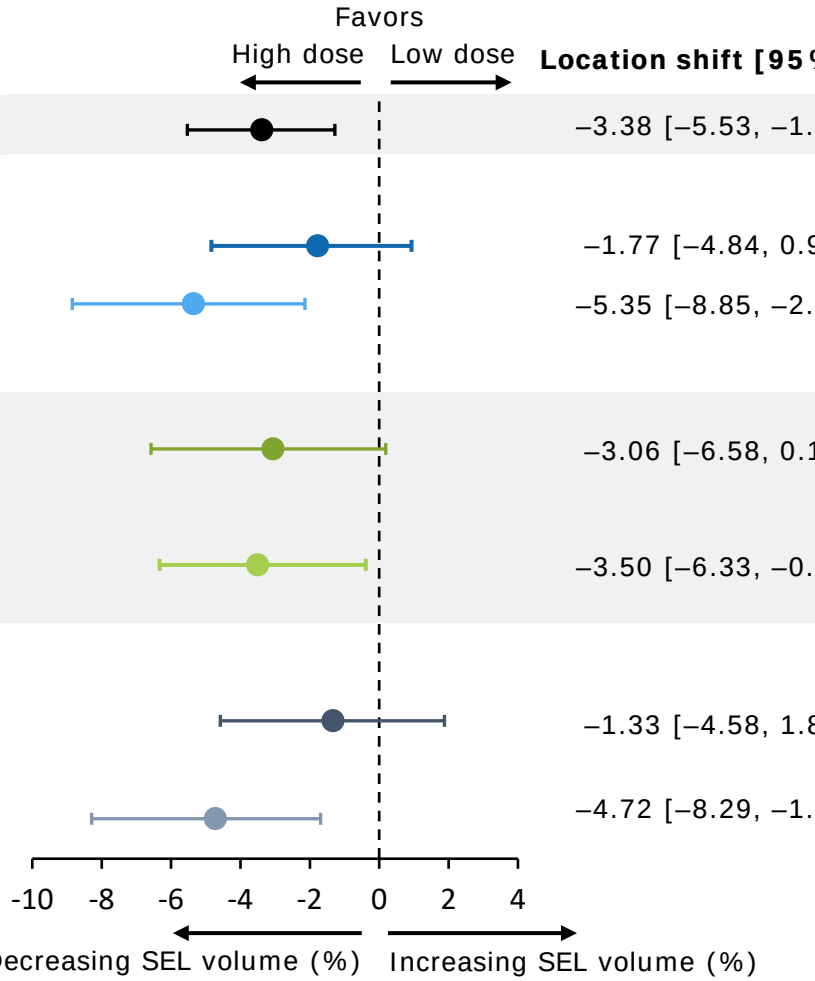
The effect of evobrutinib on SEL volume (%) was also evident in patients with more advanced disease

(1) STRATIFIED ANALYSIS: ALL PATIENTS



	Location shift [95% CI]	p value
Overall	–2.97 [–5.00, -0.81]	0.006*
Baseline EDSS ≤3	–1.51 [–4.15, 1.30]	0.263
Baseline EDSS ≥3.5	–4.89 [–8.37, –1.64]	0.004*
Non-HDA (≤1 relapse in 2 years pre-randomization)	–2.94 [–6.17, 0.34]	0.072
HDA (≥2 relapse in 2 years pre-randomisation)	–2.68 [–5.43, 0.06]	0.062
Recent disease onset (<8.5 years)	–0.51 [–3.80, 2.48]	0.700
Protracted disease onset (≥8.5 years)	–4.42 [–7.96, –1.26]	0.005*

(2) STRATIFIED ANALYSIS: COMPLETERS (Week 48)



	Location shift [95% CI]	p value
Overall	–3.38 [–5.53, –1.28]	0.002*
Baseline EDSS ≤3	–1.77 [–4.84, 0.93]	0.225
Baseline EDSS ≥3.5	–5.35 [–8.85, –2.14]	0.002*
Non-HDA (≤1 relapse in 2 years pre-randomization)	–3.06 [–6.58, 0.19]	0.070
HDA (≥2 relapse in 2 years pre-randomisation)	–3.50 [–6.33, –0.39]	0.027*
Recent disease onset (<8.5 years)	–1.33 [–4.58, 1.88]	0.416
Protracted disease onset (≥8.5 years)	–4.72 [–8.29, –1.69]	0.003*

Overall: (all patients: high dose/low dose, completers: high dose/low dose) n=89/n=84, n=84/n=77; **EDSS ≤3:** n=40/n=47, n=37/n=42; **EDSS ≥3.5:** n=49/n=37, n=47/n=35; **non-HDA:** n=36/n=46, n=34/n=44; **HDA:** n=53/n=38, n=50/n=33; **Recent onset:** n=33/n=51, n=30/n=46; **Protracted onset:** n=56/n=33, n=54/n=31. **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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