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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CONCLUSION

- **Evobrutinib reduces SEL volume 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

INTRODUCTION

- Chronic active lesions (defined on histology and also known as smouldering lesions, mixed active/inactive lesions or SELs) 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]
- Evobrutinib is a highly selective BTK inhibitor that targets B cells and myeloid cells including macrophages and microglia[3-5]
- A Phase II, placebo-controlled, randomized trial (NCT02975349) in patients with relapsing MS showed that evobrutinib 75 mg QD and 75 mg BID reduced total cumulative number of T1 Gd+ and new/enlarging T2 lesions over 24 weeks versus placebo[6]

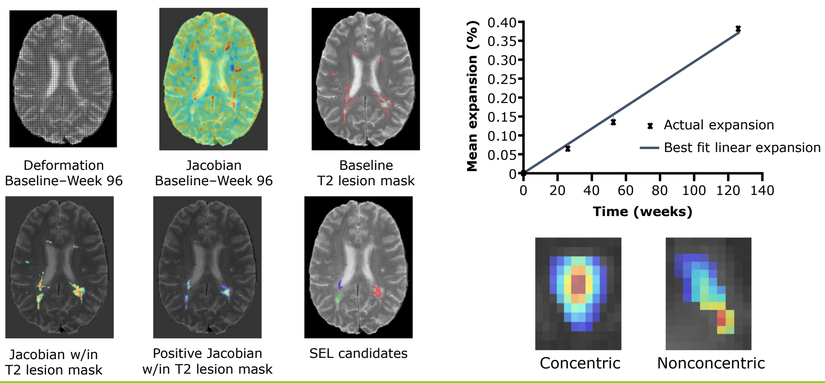
OBJECTIVES

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

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[7]



Statistical analyses

Two stratified analyses* of SEL 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 and stratified Wilcoxon rank sum test
(2) Stratified analysis – completers	Baseline through **Week 48**	Treatment completers		

*Based on the modified intention-to-treat analysis set; †≤8000 mm³, 8000–19,000 mm³, ≥19,000 mm³

Subgroup analyses

Evobrutinib high dose: Evobrutinib 75 mg QD + Evobrutinib 75 mg BID

VERSUS

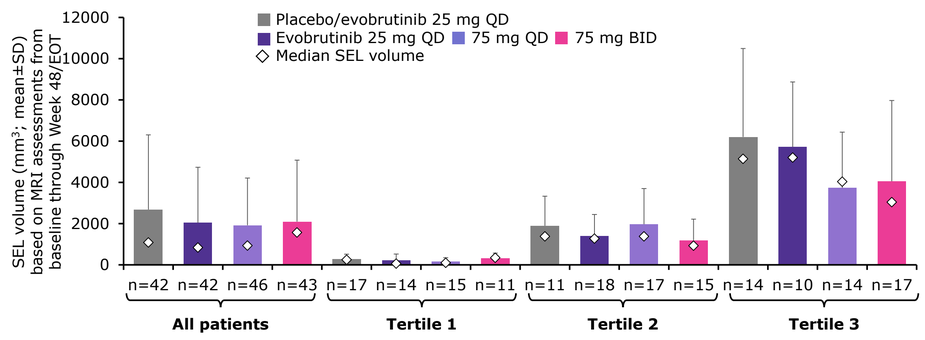
Evobrutinib low dose: Placebo + Evobrutinib 25 mg QD

RESULTS

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

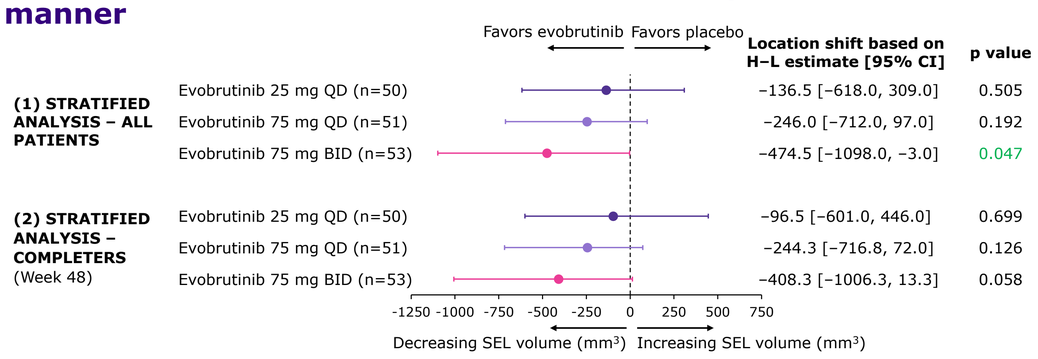
SEL volume by tertiles of baseline T2 lesion volume



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

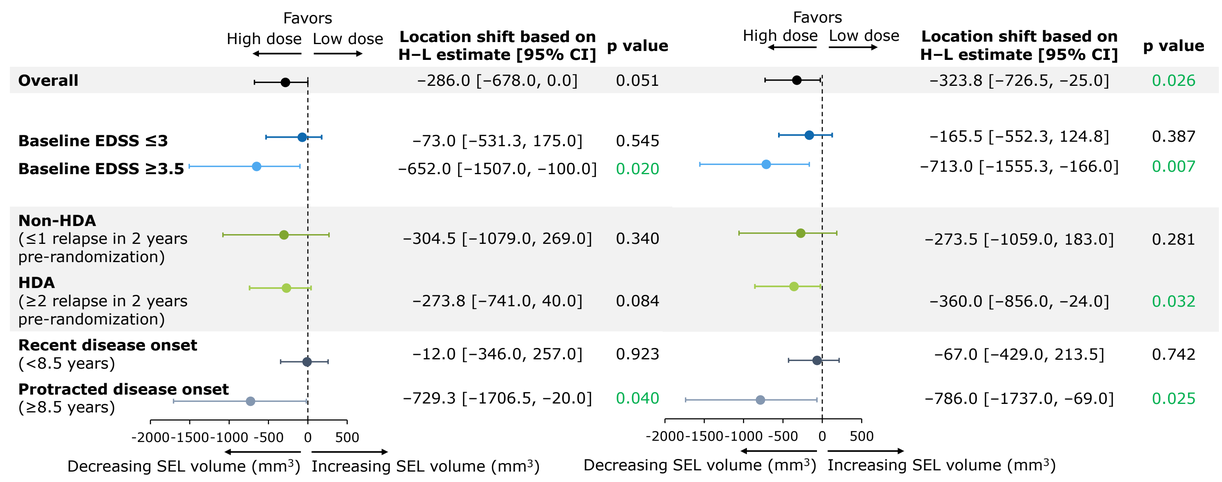
Effect of evobrutinib treatment on SEL volume is evident within Tertiles 2 and 3

Evobrutinib reduced SEL volume in a dose-dependent manner



SEL volume decreased with increasing evobrutinib dose relative to the placebo

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



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

Abbreviations: BID, twice daily; **BTK**, Bruton's tyrosine kinase; **CI**, confidence interval; **CNS**, central nervous system; **EDSS**, Expanded Disability Status Scale; **EOT**, end of treatment; **HDA**, high disease activity; **H-L**, Hodges–Lehmann; **mITT**, modified intention-to-treat; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **QD**, once daily; **RRMS**, relapsing-remitting MS; **SD**, standard deviation; **SEL**, slowly expanding lesions; **SPMS**, secondary-progressive MS; **T2 lesions,** identified via T2-weighted MRI

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