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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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Disclosures

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Colm Elliott is an employee of NeuroRx Research.

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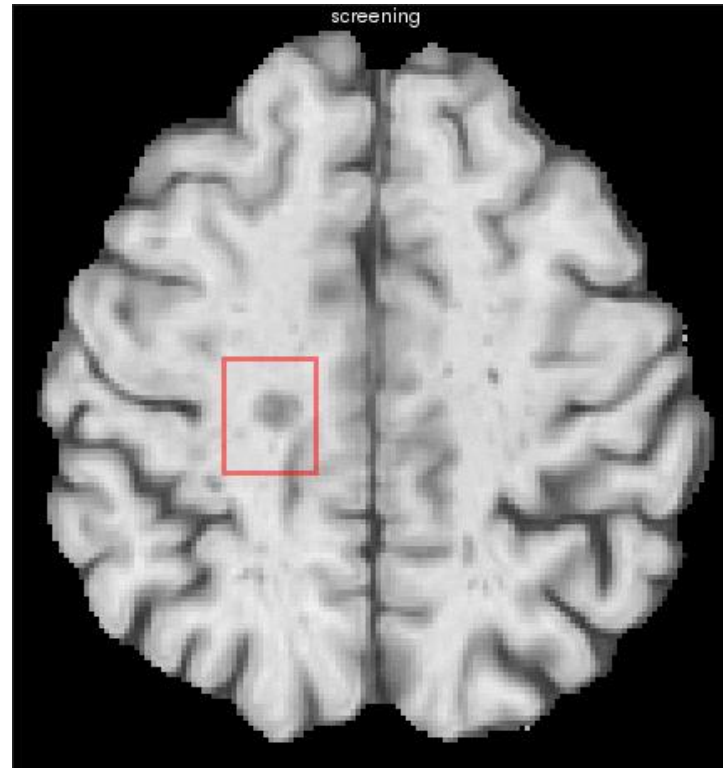
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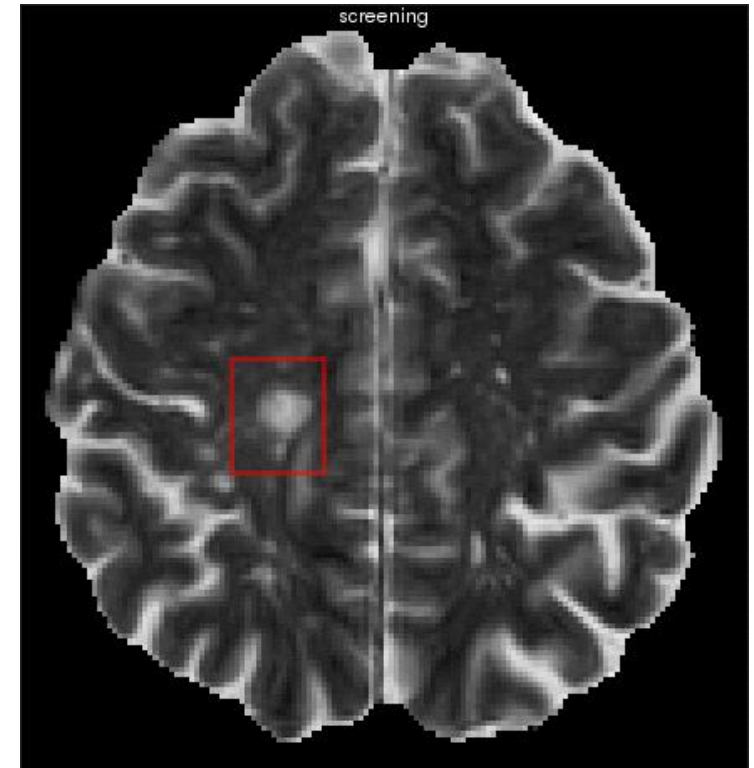
Slowly expanding lesions (SELs) as a marker of clinical progression in MS

- 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 loss¹
- 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 disability²

T1 weighted MRI



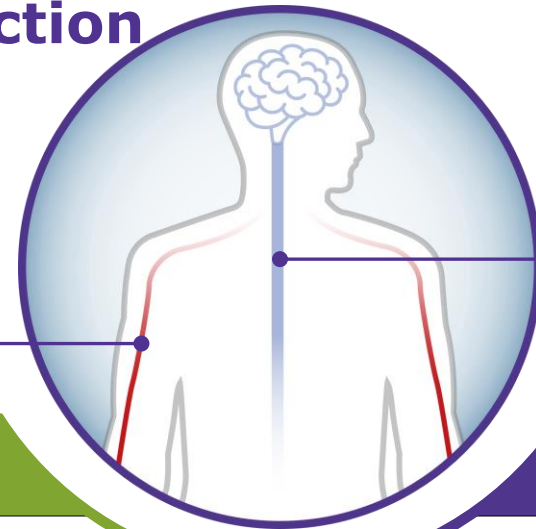
T2 weighted MRI



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

1. Elliott C, et al. *Mult Scler.* 2019;25:1915-1925; 2. Elliott C, et al. *Brain.* 2019;142:2787-2799

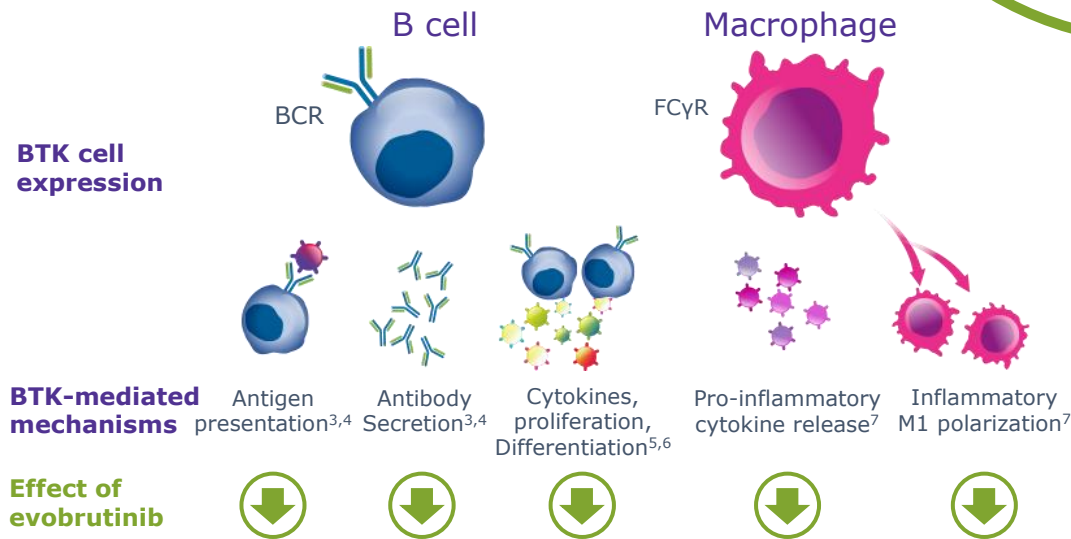
Evobrutinib mechanism of action



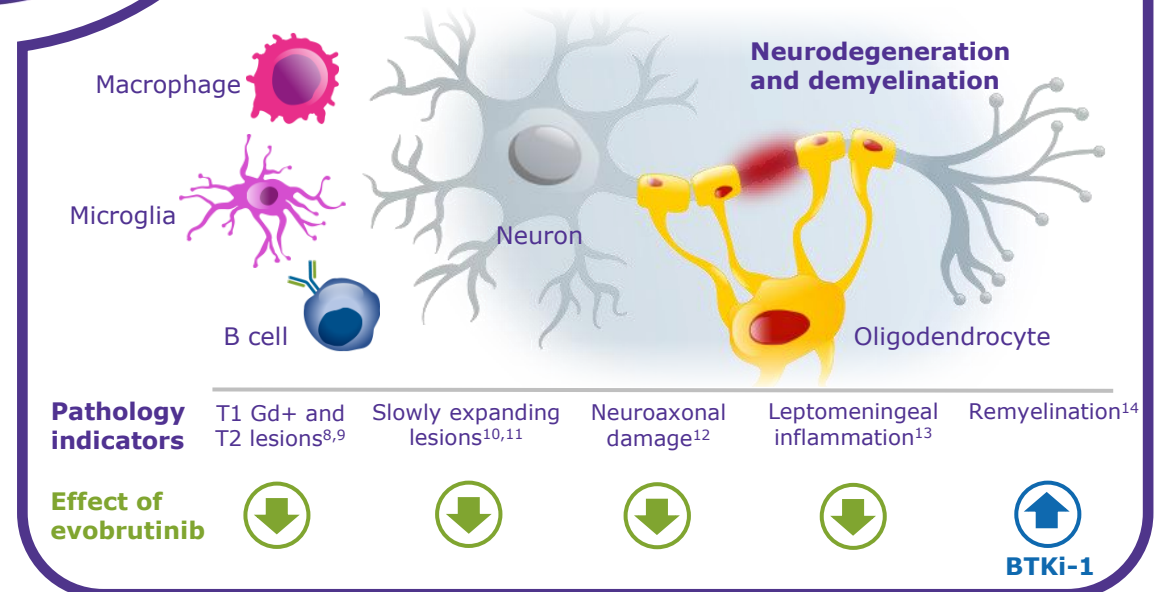
Evobrutinib in the peripheral blood¹

Evobrutinib in CSF²

Peripheral cellular mechanisms



MS disease pathology in the CNS

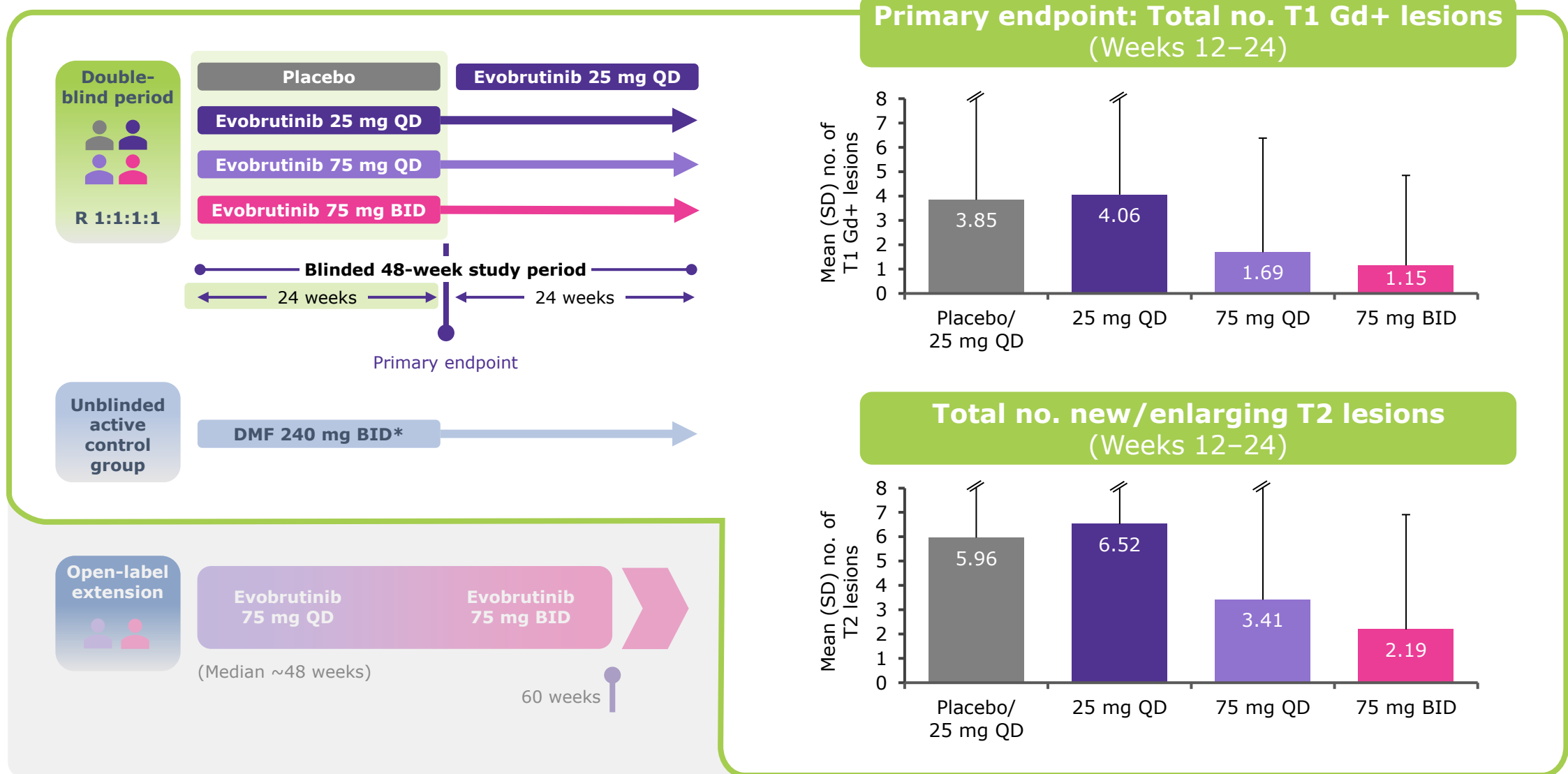


Up arrow indicates an increase; Down arrow indicates a decrease; **BCR**, B cell receptor; **BTK**, Bruton's tyrosine kinase; **BTKi-1**, tool BTK inhibitor with similar properties to evobrutinib; **CSF**, cerebrospinal fluid; **CNS**, central nervous system; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis. 1. Becker A, et al. *Clin Trans Sci*. 2020;13:325–336; 2. Piasecka-Stryczynska K, et al. *Mult Scler Relat Disord*. 2021;51:103001; 3. Torke S, et al. *Acta Neuropathol*. 2020;140:535–548; 4. López-Herrera G, et al. *J Leukoc Biol*. 2014;95:243–250; 5. Haselmayer P, et al. *J Immunol*. 2019;202:2888–2906; 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;380:2406–2417; 9. Kuhle, J et al. ECTRIMS 2021; 10. Elliott C, et al. *Mult Scler*. 2019;25:1915–1925; 11. Arnold D, et al. ECTRIMS 2021; 12. Kuhle J, et al. *Neurology*. 2021;96(22):e2783–2788; 13. Kebir H, et al. *Neurology*. 2021;96(15 Suppl.):4162; 14. Martin E, et al. *Brain Plasticity*. 2020;5:123–133.

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

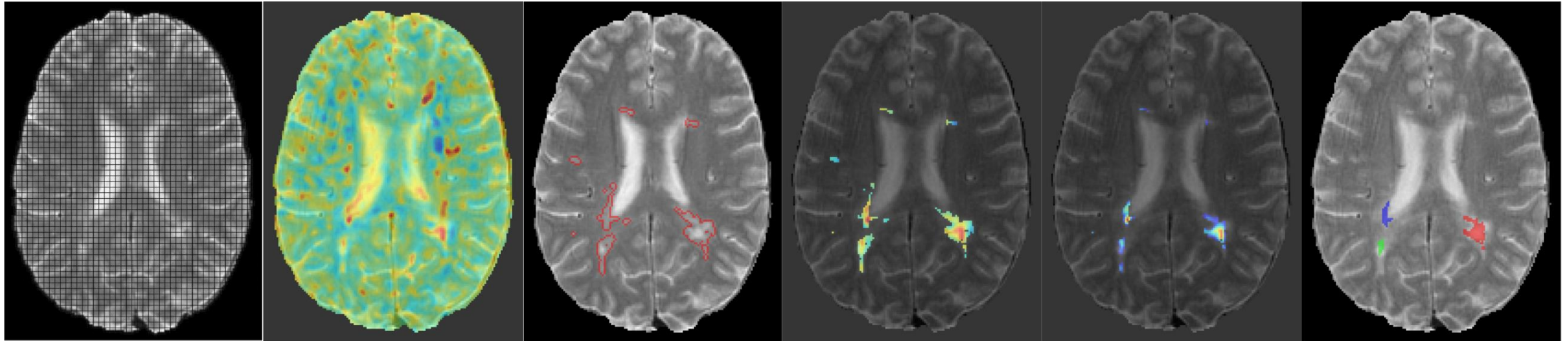
Phase II study: investigation of evobrutinib in patients with relapsing MS



*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;380:2406-2417

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

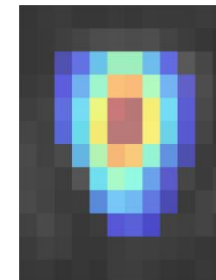
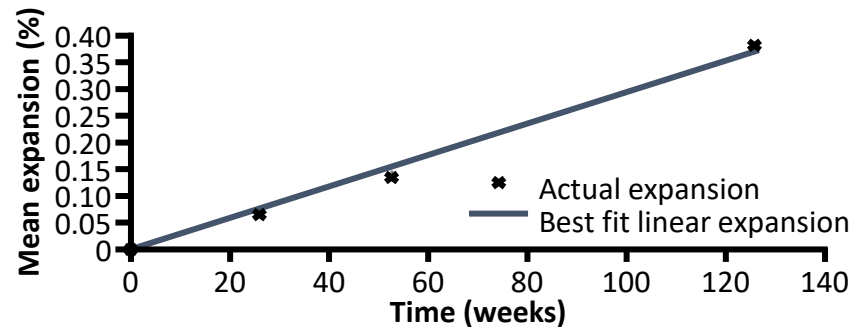
Jacobian
Baseline-Week 96

Baseline
T2 lesion mask

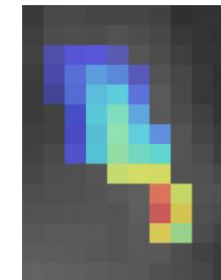
Jacobian w/in
T2 lesion mask

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

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 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†: <ul style="list-style-type: none"> ≤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		

- 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 mm³, 8000–19,000 mm³, ≥19,000 mm³
BID, twice daily; **EOT**, end of treatment; **QD**, once daily; **SEL**, slowly expanding lesions

Baseline characteristics

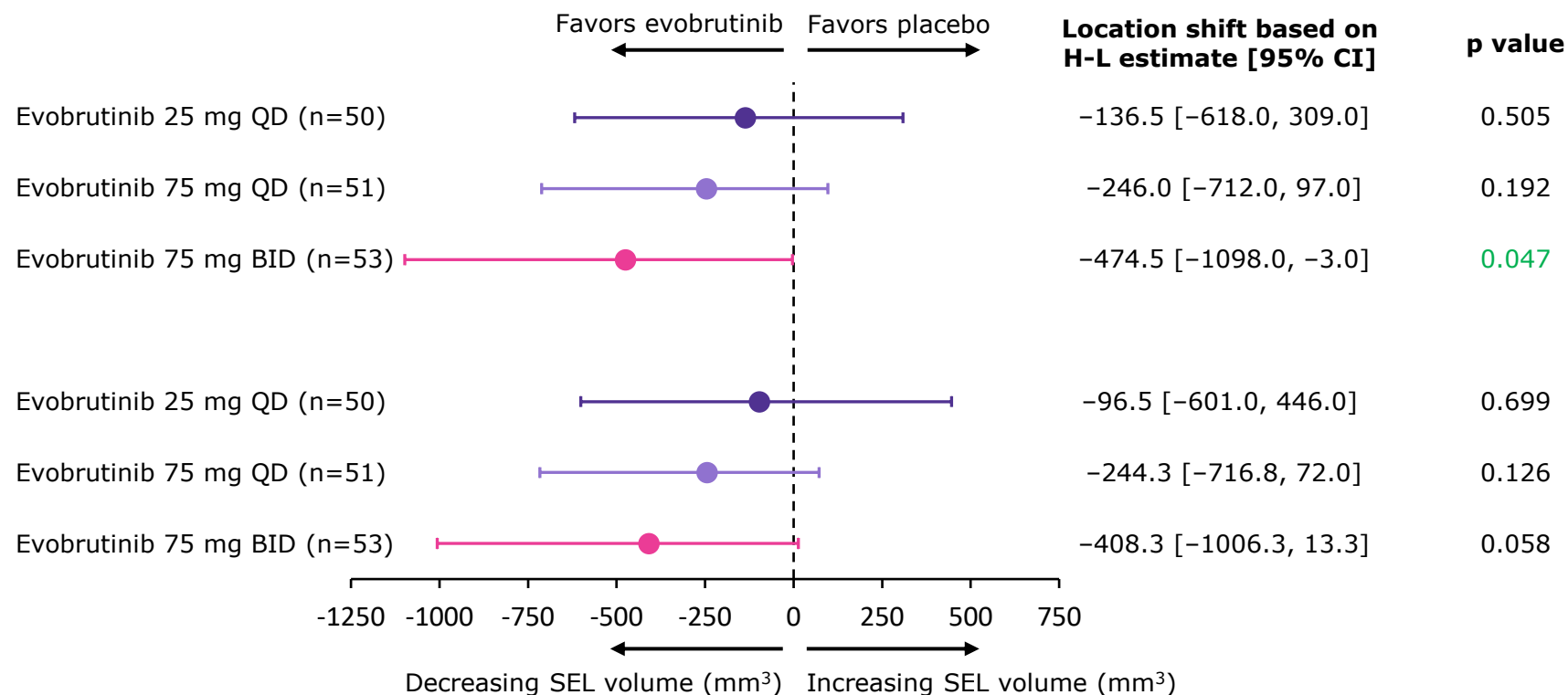
	Placebo/evobrutinib 25 mg QD (n=53)	Evobrutinib 25 mg QD (n=50)	Evobrutinib 75 mg QD (n=51)	Evobrutinib 75 mg BID (n=53)
Sex, n (%)				
Male	14 (26.4)	18 (36.0)	16 (31.4)	17 (32.1)
Female	39 (73.6)	32 (64.0)	35 (68.6)	36 (67.9)
Age, years (mean ±SD)	41.6 ±10.8	42.4 ±9.4	42.9 ±10.1	42.2 ±11.5
Time since 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

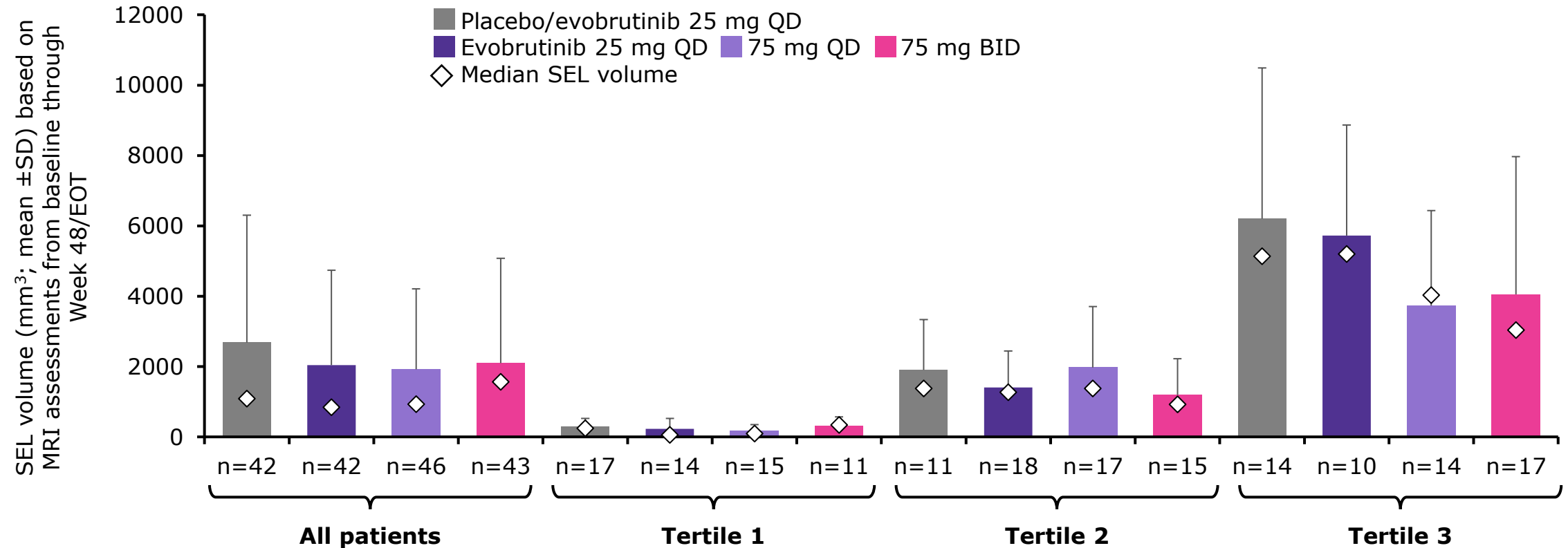
(1) STRATIFIED ANALYSIS – ALL PATIENTS

(2) STRATIFIED ANALYSIS – COMPLETERS (Week 48)



SEL volume decreased with increasing evobrutinib dose relative to the placebo

SEL volume by tertiles of baseline T2 lesion volume



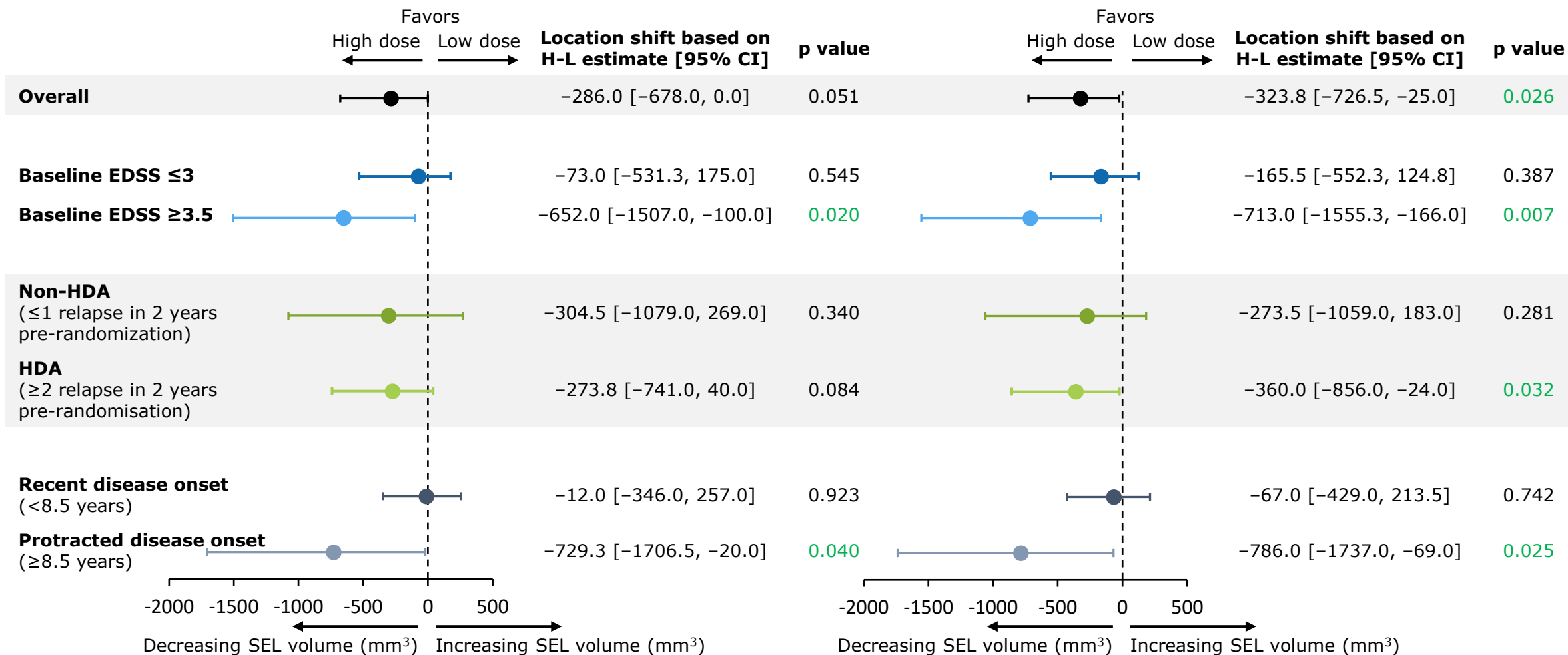
Effect of evobrutinib treatment on SEL volume is evident within tertiles 2 and 3

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 ($\geq 19,000$ 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

(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
BID, twice daily; **CI,** confidence interval; **EDSS,** Expanded Disability Status Scale; **HDA,** high disease activity; **H-L,** Hodges-Lehmann; **QD,** once daily; **SEL,** slowly expanding lesions

Conclusions



- 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

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

1. Elliott C, et al. *Mult Scler*. 2019;25:1915-1925; 2. Elliott C, et al. *Brain*. 2019;142:2787-2799