Evobrutinib significantly reduces relapses and magnetic resonance imaging outcomes in patients with multiple sclerosis: association with baseline neurofilament light chain levels

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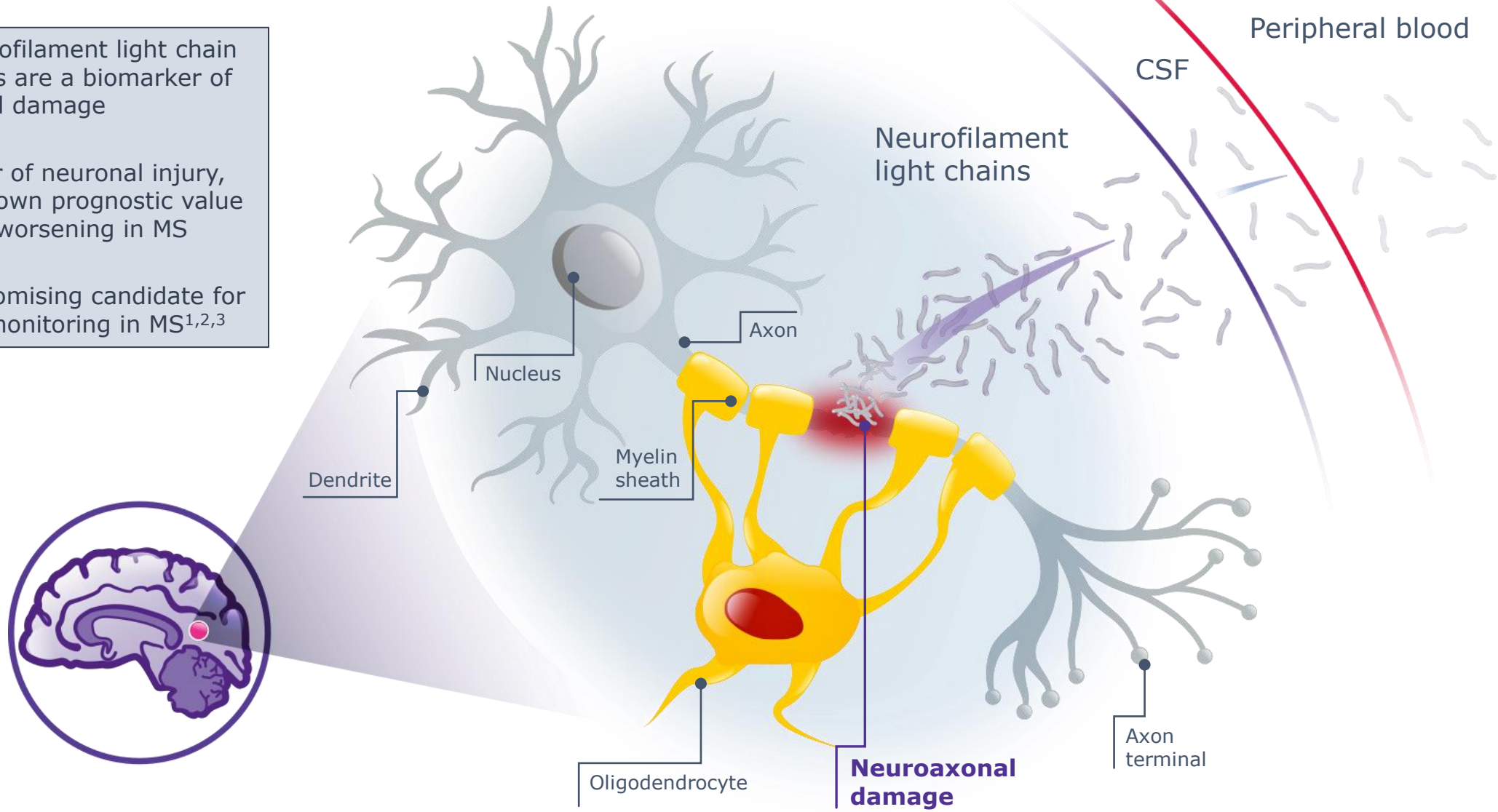
Disease worsening and progression in MS

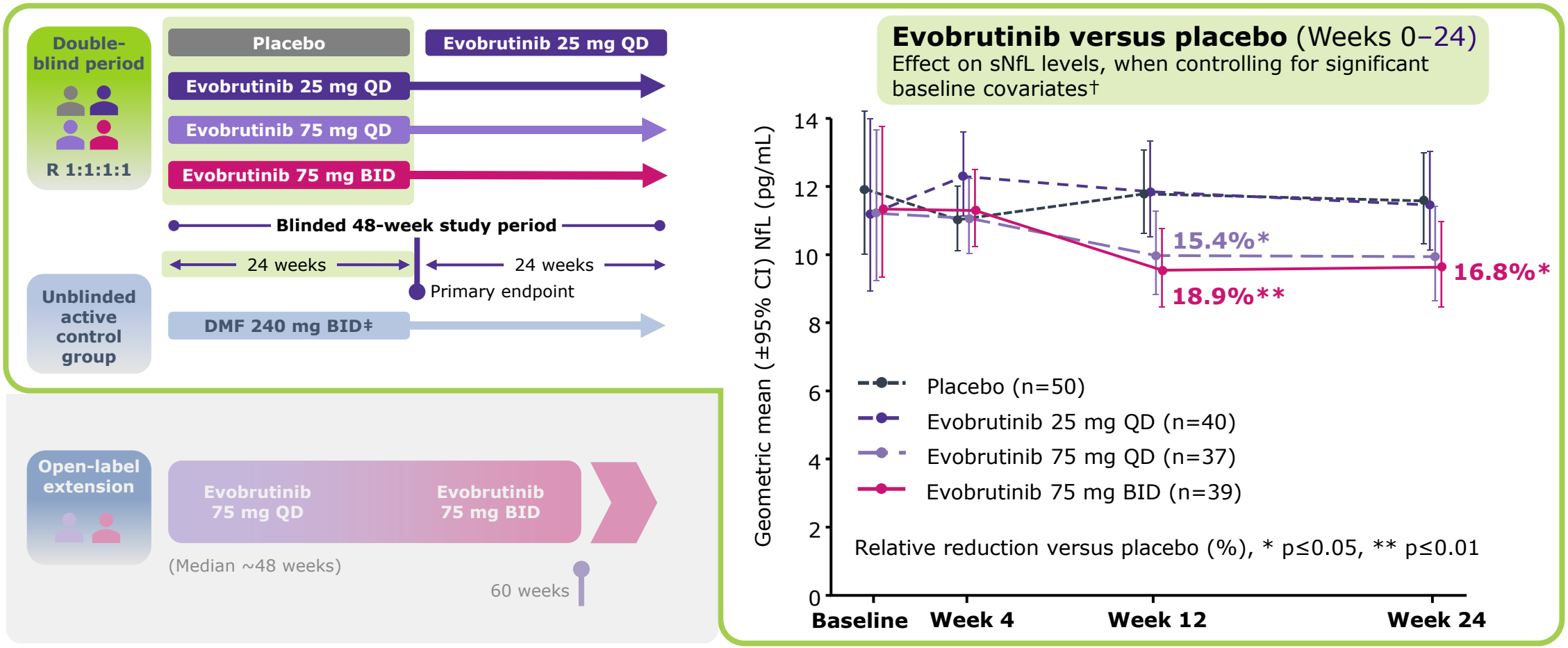
- Serum neurofilament light chain (sNfL) levels are a biomarker of neuroaxonal damage
- As a marker of neuronal injury, sNfL has shown prognostic value for disease worsening in MS
- sNfL is a promising candidate for treatment monitoring in MS[1,2,3]



CSF, cerebrospinal fluid; **MS**, multiple sclerosis; **sNfL,** serum neurofilament light chain

1. Kuhle J, et al. *Neurology.* 2019;92:e1007-15; 2. Varhaug KN, et al. *Front Neurol.* 2019;10:338; 3. Kapoor R, et al. *Neurology.* 2020;95:436–444

Evobrutinib Phase II sNfL levels



Evobrutinib 75 mg BID significantly lowers sNfL levels as early as Week 12, with reduced levels maintained until 24 weeks (last analysis time point). *Kuhle J, et al. (AAN 2021)*

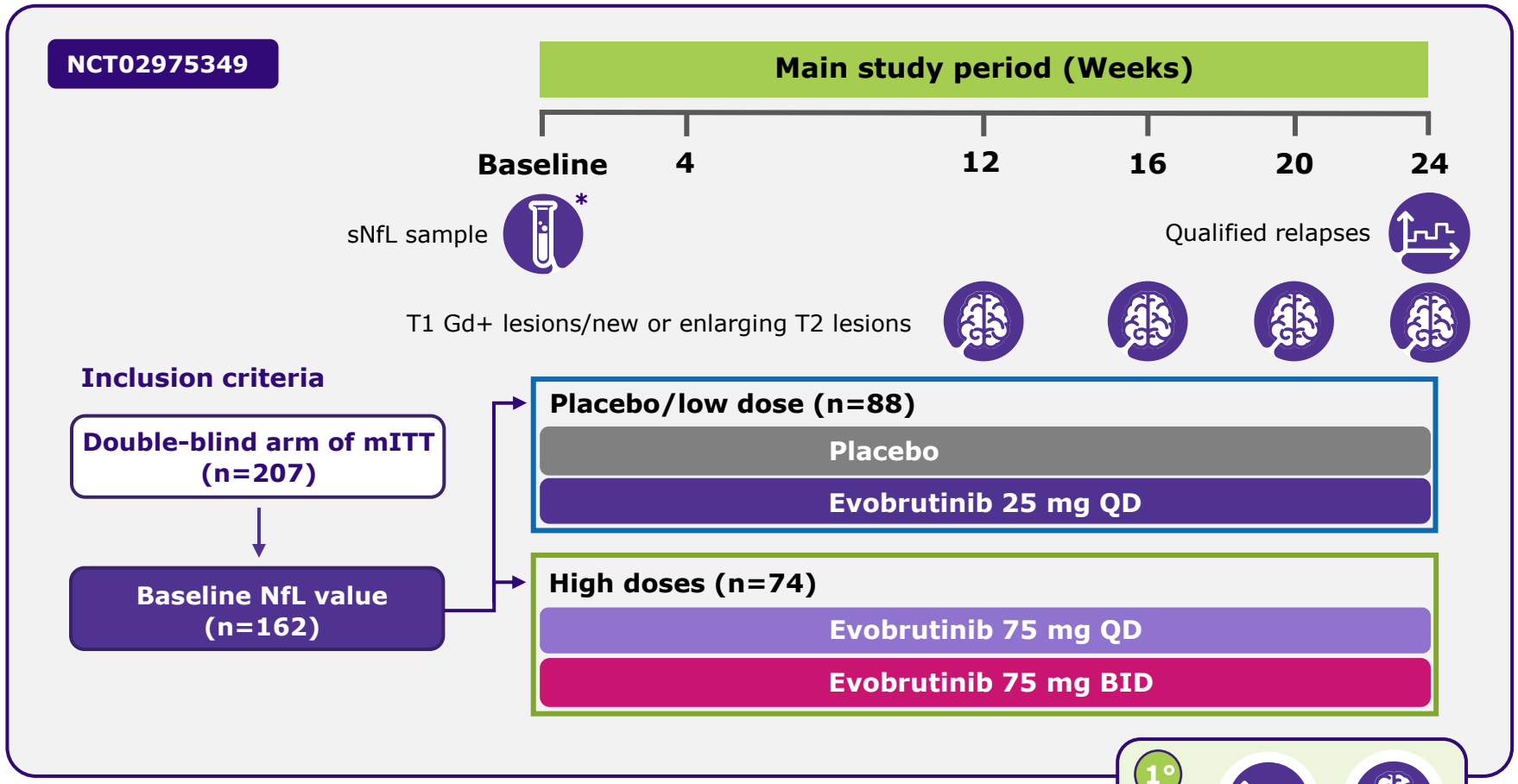
Only patients in the double-blind arms, with baseline and ≥1 post-baseline sNfL value are included in this analysis;
†Significant baseline covariates were age, T2 lesion volume, and EDSS score; ‡120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment.
CI, confidence interval; **BID,** twice daily; **DMF,** dimethyl fumarate; **EDSS,** Expanded Disability Status Scale; **QD,** once daily; **sNfL**, serum neurofilament light chain
Kuhle J, et al. *Neurology*. 2021;96(22):e2783–e2788

Objectives

- To evaluate the prognostic value of baseline sNfL levels on clinical relapse and MRI lesion activities
- To further evaluate the treatment effect of evobrutinib in MS

MRI, magnetic resonance imaging; **MS**, multiple sclerosis; **sNfL**; serum neurofilament light chain

Phase II sNfL clinical analysis



2x2 Analysis matrix
(Dose stratified by baseline sNfL)

Pooled treatment group	Low sNfL <11.36 pg/mL (n=82)	High sNfL ≥11.36 pg/mL (n=80)
Placebo/low dose (n=88)	n=44	n=44
High doses (n=74)	n=38	n=36

Patients in the High sNfL group had a notably higher disease burden at baseline, with greater:

- number of relapses in last 2 years
- EDSS score
- number of Gd+ T1 lesions
- T2 lesion volume

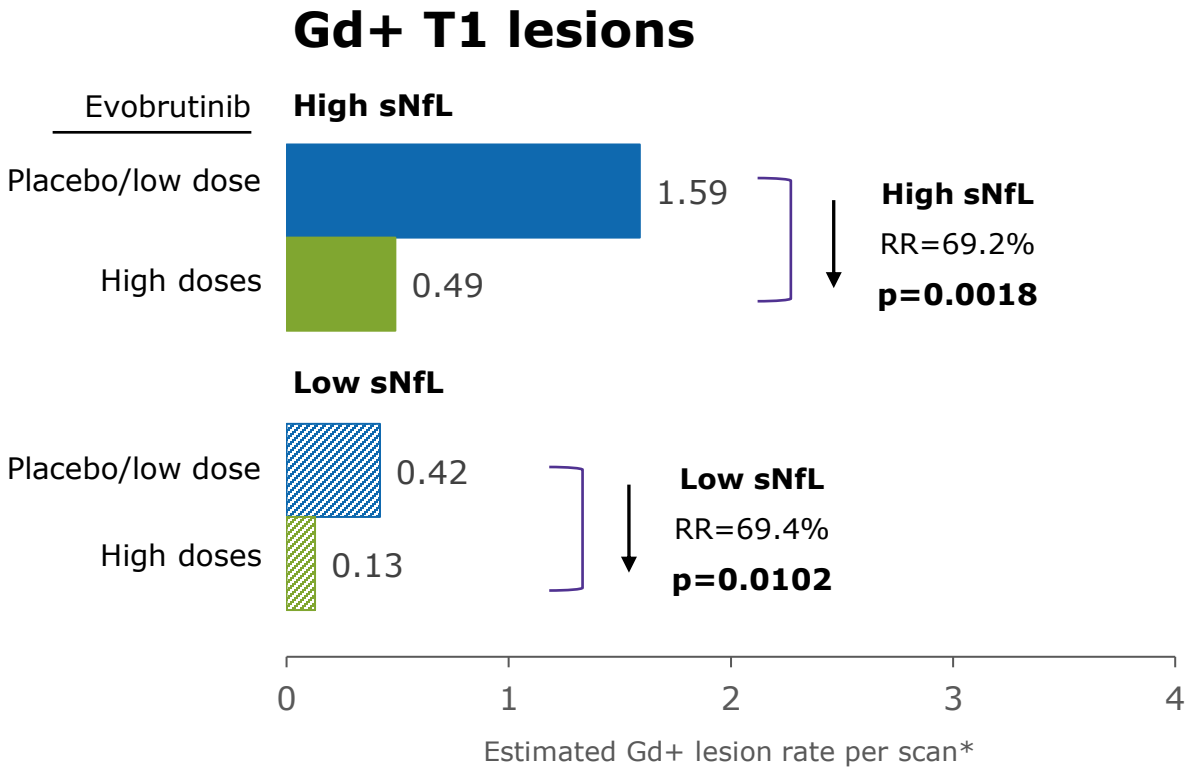
Groups are pooled to increase sample size. Note, placebo and 25 mg QD evobrutinib had no effect on MRI and clinical endpoints or sNfL levels[1,2]

*Patients stratified by geometric mean baseline sNfL level: 11.36 pg/mL. Additional sNfL samples were taken at Weeks 4, 12 and 24, but only baseline sNfL is used for this analysis.
Clinical relapses endpoint includes qualified relapses only, over the first 24 weeks.
BID, twice daily; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium enhancing; **mITT,** modified intention to treat; **MRI,** magnetic resonance imaging; **sNfL,** serum neurofilament light chain; **QD,** once daily

1. Montalban X, et al. *NEJM.* 2019;380:2406–2417; 2. Kuhle J, et al. *Neurology.* 2021;96(22):e2783–e2788

Number of Gd+ T1 lesions
Effect of evobrutinib stratified by baseline sNfL levels

- Evaluate the effect of evobrutinib on the cumulative number of Gd+ T1 lesions over Weeks 12, 16, 20 and 24, stratified by baseline sNfL levels



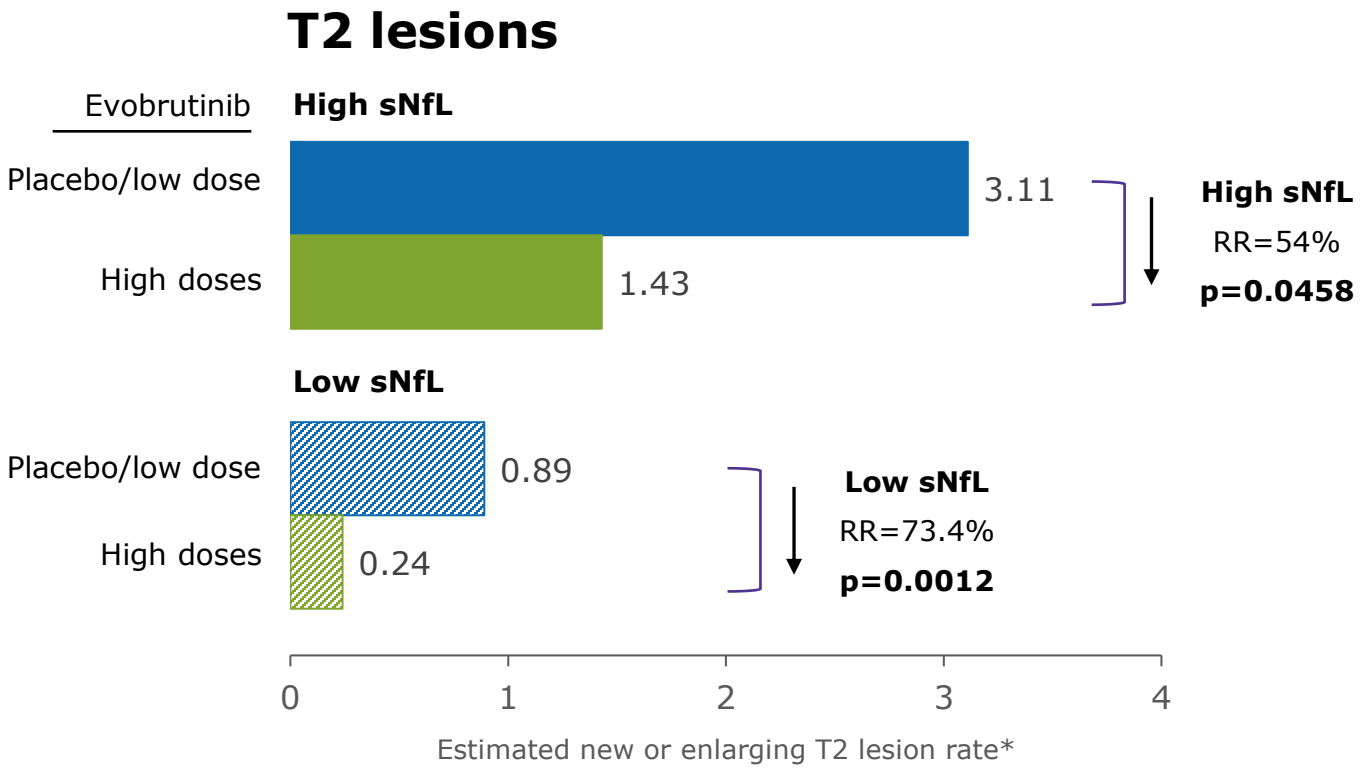
Patients with high sNfL levels at baseline had a higher Gd+ T1 activity

The Gd+ T1 activity was significantly reduced in both sNfL groups with the high evobrutinib doses

*Based on a negative binomial model for cumulative number of T1 Gd+ lesions count (summed over scans).
Gd+, gadolinium enhancing; **RR,** relative reduction; **sNfL**, serum neurofilament light chain

Number of new or enlarging T2 lesions
Effect of evobrutinib stratified by baseline sNfL levels

- Evaluate the effect of evobrutinib on the cumulative number of new or enlarging T2 lesions over Weeks 12, 16, 20 and 24, stratified by baseline sNfL levels



Patients with high sNfL levels at baseline had a higher T2 lesion activity

The number of new or enlarging T2 lesions was significantly reduced in both sNfL groups with high evobrutinib doses

*Based on a negative binomial model for total new or enlarging T2 lesions count (summed over scans).
RR, relative reduction; **sNfL**, serum neurofilament light chain

Qualified relapses
Effect of evobrutinib and baseline sNfL

- Evaluate the effects on patients having a qualified relapse during the 24 weeks of the double-blind period with:
  - high doses versus placebo/low dose of evobrutinib, in relation to stratified baseline sNfL
  - high baseline sNfL versus low baseline sNfL, in relation to stratified evobrutinib dose

	Low sNfL <11.36 pg/mL		High sNfL ≥11.36 pg/mL	
Qualified relapses	**N (%)**	**Total QRs**	**N (%)**	**Total QRs**
Placebo/Low dose	3 (6.8%)	3	12 (27.3%)	16
High doses	0 (0)	0	2 (5.6%)	2

Stratified Cochran–Mantel–Haenszel tests*

High baseline sNfL vs low baseline sNfL (stratified by evobrutinib dose): **p=0.0038, odds ratio: 6.07**

High vs placebo/low dose of evobrutinib (stratified by baseline sNfL): **p=0.0028, odds ratio: 0.12**

The odds of qualified relapse were:

- significantly higher for the high baseline sNfL group
- significantly reduced for the high evobrutinib doses group

*Stratified Cochran–Mantel–Haenszel tests evaluated the effect of evobrutinib stratified by baseline sNfL subgroup, or baseline sNfL effect stratified by evobrutinib dose.
A qualified relapse was defined as new, worsening, or recurrent neurologic symptoms attributed to multiple sclerosis that lasted for at least 24 hours without fever, infection, or adverse reaction to a prescribed medication and that was preceded by a stable or improving neurologic status of at least 30 days. A qualified relapse was accompanied by new clinical signs, such as changes in the neurologic examination or an increase in the EDSS score. Montalban X, et al. *NEJM.* 2019;380:2406–2417

EDSS, Expanded Disability Status Scale; **N (%),** number of patients with relapses; **QR,** qualified relapses; **sNfL**, serum neurofilament light chain

Conclusions

High levels of sNfL at baseline were highly prognostic of increased relapse and MRI lesion activity during this study

This is the first study exploring the relationship of baseline sNfL levels and the effects of a BTK inhibitor on clinical and MRI measures in patients with MS

In patients with both high and low baseline sNfL levels:

- evobrutinib significantly reduced MRI activity
- evobrutinib significantly reduced the number of patients with qualified relapses

These data further support the value of sNfL levels as a prognostic marker of ongoing and future MS disease activity

BTK, Bruton's tyrosine kinase; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **sNfL**, serum neurofilament light chain