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The effect of evobrutinib, a BTK inhibitor, on blood neurofilament light chain levels in relapsing multiple sclerosis

Jens Kuhle[1], Ludwig Kappos[2], Xavier Montalban[3], Ying Li[4], Karthinathan Thangavelu[4], Yann Hyvert[5], Davorka Tomic[5].

[1]Neurologic Clinic and Policlinic, MS Center and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University Hospital Basel, and University of Basel, Basel, Switzerland.

[2]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Medicine, Clinical Research and Biomedical Engineering, University Hospital Basel, and University of Basel, Switzerland.

[3]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitario Vall d'Hebron, Barcelona, Spain.

[4]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany).

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Background and Objectives

BACKGROUND

- Evobrutinib is a highly selective Bruton's tyrosine kinase inhibitor that targets B cells and myeloid cells including macrophages and microglia[1-3]
- A phase II placebo-controlled, randomized trial (NCT02975349) in patients with relapsing MS showed evobrutinib reduced total T1 Gd+ lesions over 24 weeks versus placebo[4]
- A low annualized relapse rate with evobrutinib 75 mg BID at week 48 (0.11; 95%CI 0.04–0.25) was maintained in a long-term extension through 108 weeks* (0.12; 95%CI 0.06–0.22)[5]
- Blood neurofilament light chain (NfL) levels are a biomarker of neuro-axonal damage in MS, with proposed prognostic value for monitoring disease progression[6,7]

OBJECTIVE

- In a post-hoc analysis of a phase II placebo-controlled, randomized trial in relapsing MS, we evaluated the effect of evobrutinib on blood NfL levels

BID, twice daily; **MS**, multiple sclerosis;
*Evobrutinib dosing in the Open-Label Extension was: 75mg QD for ~48 weeks, then 75mg BID

1. Haselmayer et al. *J Immunol* 2019;202:2888–2906; **2.** Caldwell et al. *J Med Chem* 2019;62:7643–55; **3.** Martin et al. *Brain Plasticity* 2020;5:123–33. **4.** Montalban et al. *N Engl J Med* 2019;380:2406–17; **5.** Montalban et al. *Mult Scler* 2020, 26(Suppl 3):213 (Abstract 0197); **6.** Kuhle et al. *Neurology* 2019;92:e1007–15; **7.** Varhaug et al. *Front. Neurol.* 2019;10:338

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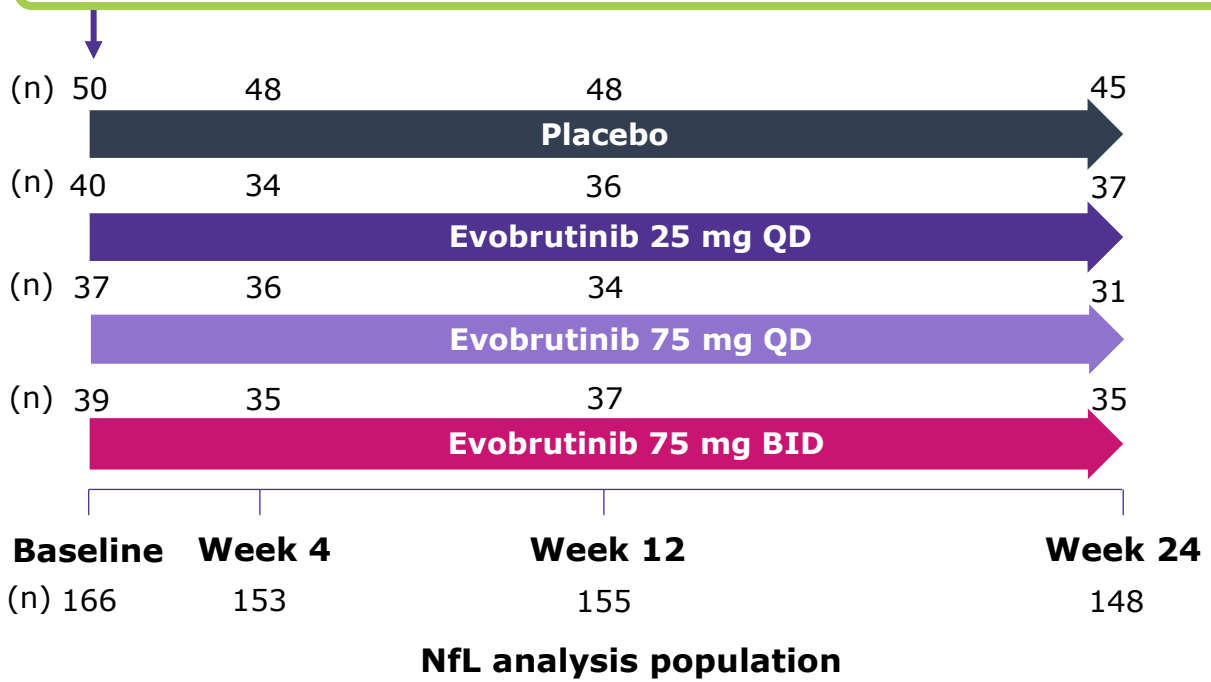
Study design

- All patients from the double-blind arms (mITT, n=207[a]) with NfL values at baseline and ≥1 post-baseline were included (n=166)
- Baseline demographics were similar between the double-blind arms in the mITT and the NfL population
- NfL was measured blinded to treatment allocation (Simoa NF-light™)

IDENTIFICATION OF BASELINE COVARIATES

A mixed model repeated measures (MMRM) model identified key baseline variables that significantly affected NfL levels over time



Tested baseline covariates	Significance
Age dichotomised by 42 years	**p=0.023**
Gender	NS
T1 Gd+ lesions	NS
T2 lesion volume	**p=0.008**
EDSS score dichotomised by 3	**p=0.022**
No. relapses in prior 2 years	NS
Time since MS onset	NS
High disease activity	NS
Type of MS	NS

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[a]Samples were not available from the open-label DMF arm (n=54)

BID, twice daily; **DMF**, dimethyl fumarate; **EDSS**, Expanded Disability Status Scale; **mITT**, modified intention-to-treat; **MS**, multiple sclerosis; **NfL**, neurofilament light chain; **NS**, non-significant; **QD**, once daily

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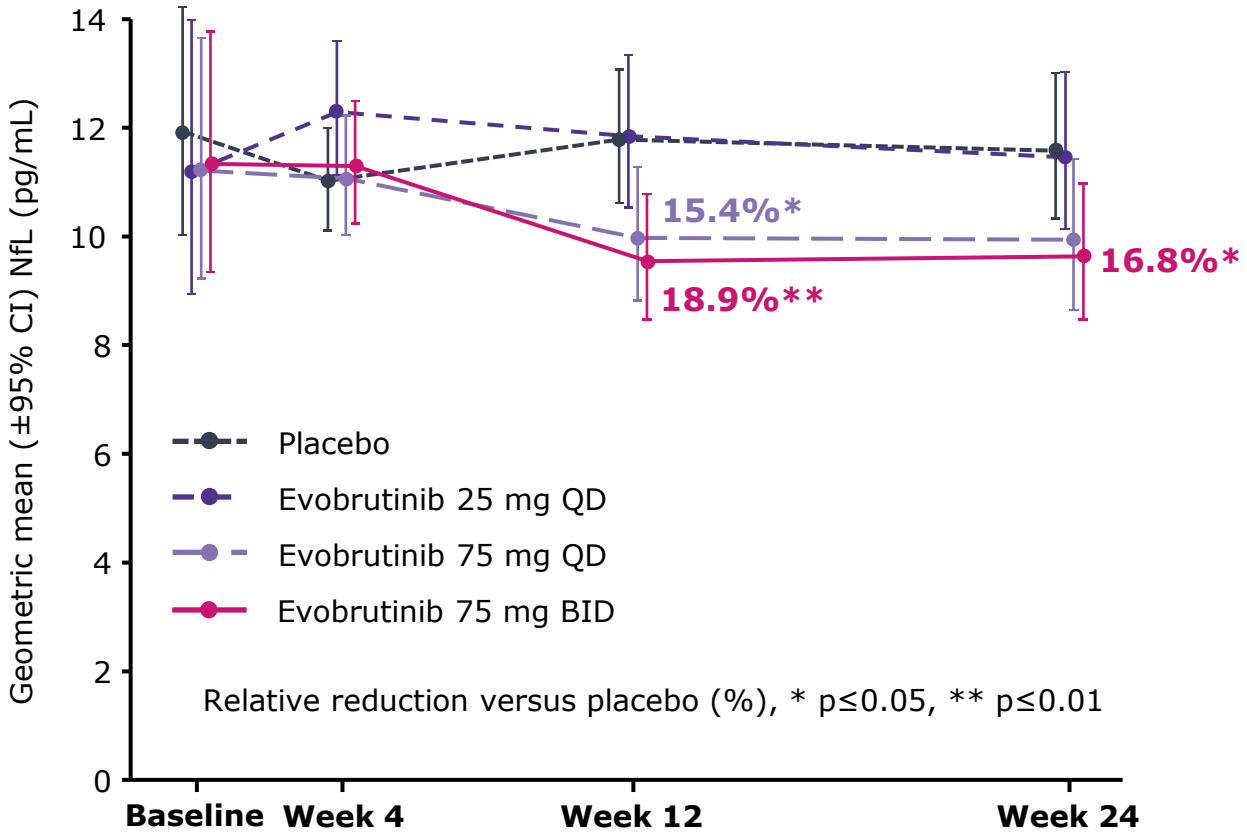
Evobrutinib significantly reduces blood NfL levels

The effect of evobrutinib vs placebo on NfL over time was evaluated using an MMRM model, controlling for significant baseline covariates: age, T2 lesion volume, and EDSS score



CONCLUSIONS

- These data on NfL dynamics are the first to be reported for any BTK inhibitor investigated for MS
- Evobrutinib 75 mg BID significantly lowers blood NfL levels as early as week 12, with reduced levels maintained until 24 weeks (last analysis timepoint)
- These results indicate evobrutinib 75 mg BID has a beneficial effect on reducing neuro-axonal damage in MS

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BID, twice daily; **BTK**, Bruton's tyrosine kinase;
CI, confidence interval; **EDSS**, Expanded Disability Status Scale; **MMRM**, mixed model repeated measures; **MS**, multiple sclerosis; **NfL**, neurofilament light chain; **QD**, once daily

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