DMT18

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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CONCLUSIONS

- **High levels of serum neurofilament light chain (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 Bruton's tyrosine kinase (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**

INTRODUCTION

Disease worsening and progression in MS

- 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[1–3]

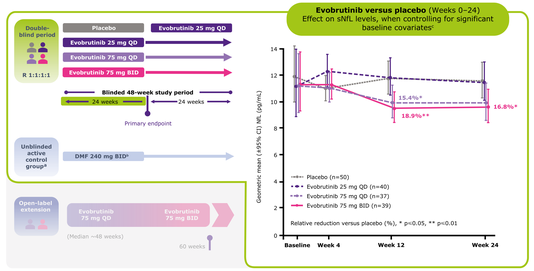
Evobrutinib Phase II sNfL levels

- Evobrutinib 75 mg twice daily (BID) significantly lowers sNfL levels as early as Week 12, with reduced levels maintained until 24 weeks (last analysis time point; **Figure 1**)[4,5]

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

Figure 1. Evobrutinib Phase II sNfL levels

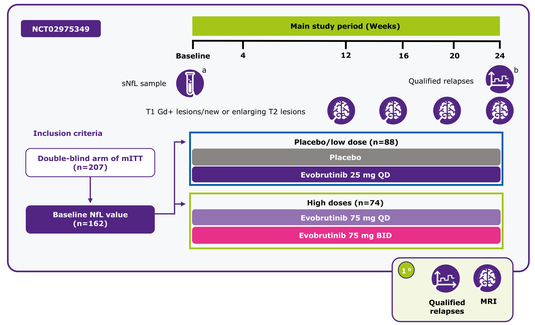


[a]Only patients in the double-blind arms, with baseline and ⩾1 post-baseline sNfL value, are included in this analysis
[b]120 mg BID for the first seven days, followed by 240 mg BID for the duration of treatment
[c]Significant baseline covariates were age, T2 lesion volume, and EDSS score
BID, twice daily; **CI**, confidence interval; **DMF**, dimethyl fumarate; **EDSS**, Expanded Disability Status Scale; **NfL**, neurofilament light chain; **R**, randomization; **sNfL**, serum neurofilament light chain; **QD**, once daily; **T2 lesion**, identified via T2-weighted MRI

METHODS

- Groups were pooled to increase sample size (**Figure 2**). Note, placebo and 25 mg once daily (QD) evobrutinib had no effect on MRI and clinical endpoints, or sNfL levels[5,6]
- The effect of evobrutinib on the cumulative number of Gd+ T1 lesions, as well as new or enlarging T2 lesions, was evaluated over Weeks 12, 16, 20, and 24 and stratified by baseline sNfL levels
- The effects of evobrutinib on patients having a qualified relapse were evaluated during the 24 weeks of the double-blind period, along 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

Figure 2. Phase II sNfL clinical analysis



[a]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 was used for this analysis
[b]Clinical relapses endpoint includes qualified relapses only over the first 24 weeks. 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, as well as 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[6]
BID, twice daily; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium enhancing; **mITT**, modified intention to treat; **NfL**, neurofilament light chain; **sNfL**, serum neurofilament light chain; **QD**, once daily; **T1 lesion**, identified via T1-weighted MRI; **T2 lesion**, identified via T2-weighted MRI

RESULTS

Baseline characteristics

- Patients in the 'High sNfL' group (**Table 1**) had a notably higher disease burden at baseline, with greater:
  - Number of relapses in the last two years
  - Expanded Disability Status Scale (EDSS) score
  - Number of Gd+ T1 lesions
  - T2 lesion volume

Table 1. 2 x 2 analysis matrix (dose stratified by baseline sNfL)

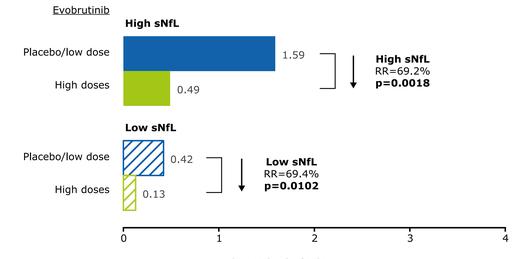
Pooled treatment group	Low sNfL <11.36 pg/mL (n=82)	High sNfL ⩾11.36 pg/mL (n=80)
Placebo/low dose (n=88)	n=44	n=44
High doses (n=74)	n=38	n=36

sNfL, serum neurofilament light chain

Number of Gd+ T1 lesions

- Patients with high sNfL levels at baseline had higher Gd+ T1 activity (**Figure 3**)
- Gd+ T1 activity was significantly reduced in both sNfL groups taking high evobrutinib doses (**Figure 3**)

Figure 3. Effect of evobrutinib on Gd+ T1 lesions, stratified by baseline sNfL levels

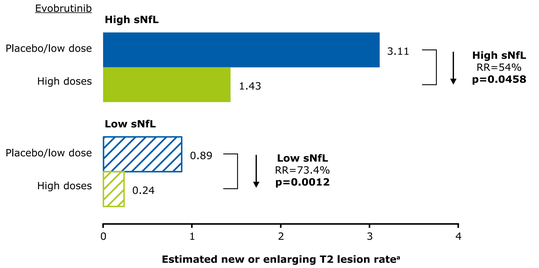


[a]Based on a negative binomial model for cumulative number of Gd+ T1 lesions count (summed over scans)
Gd+, gadolinium enhancing; **RR**, relative reduction; **sNfL**, serum neurofilament light chain; **T1 lesion**, identified via T1-weighted MRI

Number of new or enlarging T2 lesions

- Patients with high sNfL levels at baseline had higher T2 lesion activity (**Figure 4**)
- The number of new or enlarging T2 lesions was significantly reduced in both sNfL groups taking high evobrutinib doses (**Figure 4**)

Figure 4. Effect of evobrutinib on T2 lesions, stratified by baseline sNfL levels



[a]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; **T2 lesion**, identified via T2-weighted MRI

Qualified relapses

- The odds of qualified relapse were:
  - Significantly higher for the high baseline sNfL group (**Table 2**)
  - Significantly reduced for the high evobrutinib doses group (**Table 2**)
- Stratified Cochran–Mantel–Haenszel tests evaluated the effect of evobrutinib stratified by baseline sNfL subgroup, or baseline sNfL effect stratified by evobrutinib dose. Results from these tests showed that:
  - High baseline sNfL versus low baseline sNfL (stratified by evobrutinib dose): p=0.0038, odds ratio: 6.07
  - High doses versus placebo/low dose of evobrutinib (stratified by baseline sNfL): p=0.0028, odds ratio: 0.12

Table 2. Effect of evobrutinib and baseline sNfL on qualified relapses

	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

N (%) was the number of patients with relapses
QR, qualified relapses; **sNfL**, serum neurofilament light chain

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