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

- **Evobrutinib 75 mg BID significantly lowers sNfL levels as early as Week 12, with reduced levels maintained until Week 24 (last analysis time point)**
- **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

OBJECTIVES

- **To evaluate the effect of evobrutinib on sNfL levels**
- **To evaluate the prognostic value of baseline sNfL on clinical relapse and MRI lesion activities**

INTRODUCTION

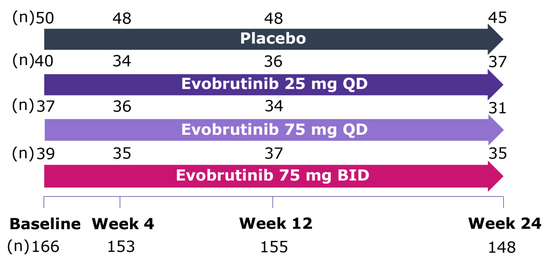
- Evobrutinib is a highly selective BTK inhibitor that targets B cells and myeloid cells, including macrophages and microglia[1-3]
- A Phase II placebo-controlled, randomized trial (NCT02975349) in patients with relapsing MS showed evobrutinib reduced total T1 Gd+ lesions over 24 weeks versus placebo[4]
- A low ARR 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 (75 mg QD for ~48 weeks, then 75 mg BID: 0.12, 95% CI 0.06–0.22)[5]
- sNfL levels are a biomarker of neuro-axonal damage in MS, with proposed prognostic value for monitoring disease progression[6,7]

Analysis 1

Effect of evobrutinib on sNFL levels

METHODS

Figure 1. NfL analysis population



- All patients from the double-blind arms of the Phase II trial (ITT, n=213*) with sNfL values at baseline and ≥1 post-baseline were included (n=166; **Figure 1**)
- sNfL was measured blinded to treatment allocation (Simoa NF-light™)

*Samples were not available from the open-label dimethyl fumarate arm (n=54)

- A MMRM model was used to:
  1) identify key baseline variables that significantly affected sNfL levels over time
  2) evaluate the effect of evobrutinib versus placebo on sNfL over time, controlling for significant baseline covariates

RESULTS

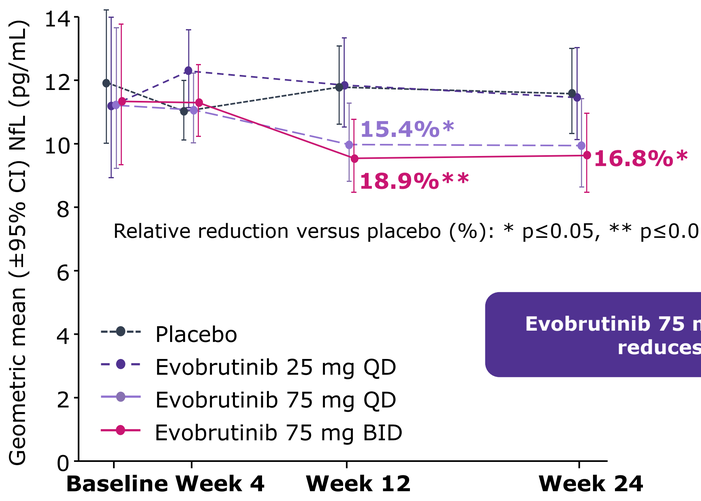
Patient demographics and identification of key baseline covariates

- Baseline demographics were similar between the double-blind arms in the ITT and the NfL population
- Baseline covariates that significantly affected log(NfL) over time, in the MMRM model, included: age, T2 lesion volume and EDSS score (**Table 1**)

Table 1. Tested baseline covariates

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

Figure 2. The effect of evobrutinib versus placebo on sNfL levels over time, controlling for significant baseline covariates: age, T2 lesion volume, and EDSS score



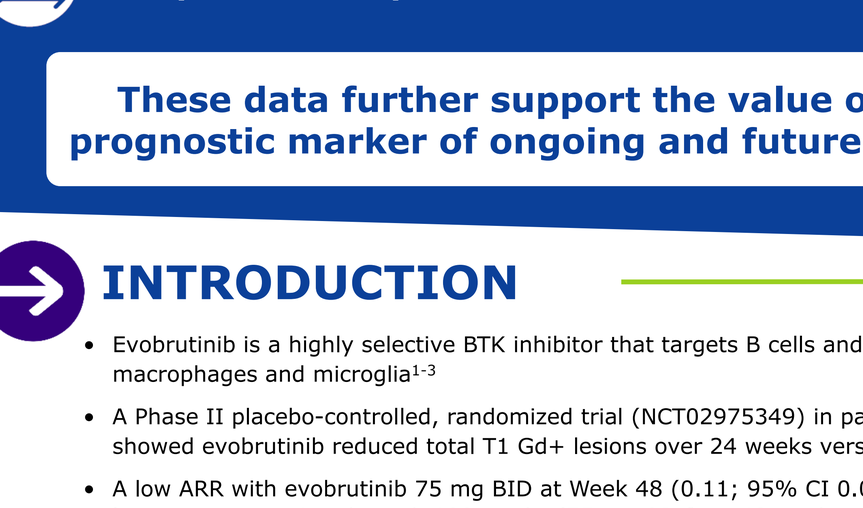
Evobrutinib 75 mg BID significantly reduces sNfL levels

Analysis 2

Prognostic value of sNfL levels on clinical relapse and MRI lesion activities

METHODS

Figure 3. Phase II sNfL clinical analysis



Groups are pooled to increase sample size. Note, placebo and evobrutinib 25 mg QD had no effect on MRI and clinical endpoints or sNfL levels[4,8]

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

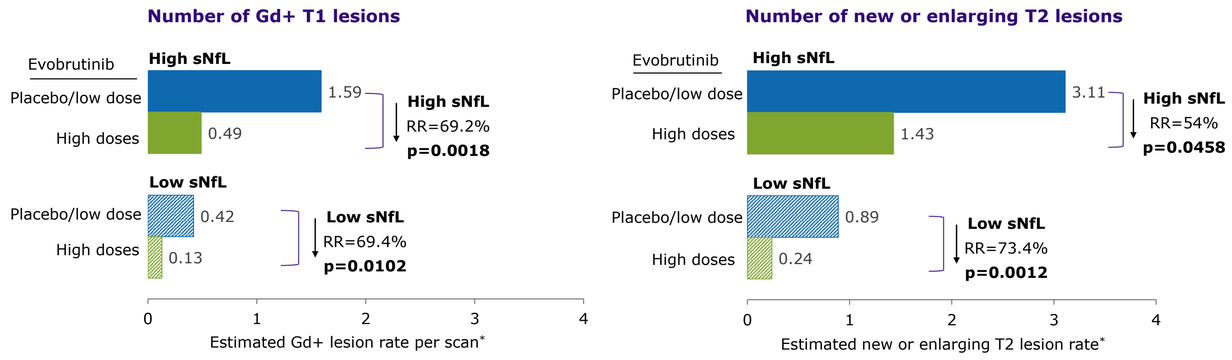
Patients in the High sNfL group had a notably higher disease burden at baseline, with greater:
- number of relapses in last 2 years
- EDSS score
- number of Gd+ T1 lesions
- T2 lesion volume

*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

RESULTS

Figure 4. MRI lesions - effect of evobrutinib stratified by baseline sNfL levels

- Evaluate the effect of evobrutinib on the cumulative number of Gd+ T1 and new or enlarging T2 lesions over Weeks 12, 16, 20 and 24, stratified by baseline sNfL levels



*Based on a negative binomial model for cumulative number of T1 Gd+ lesions count (summed over scans) or total new or enlarging T2 lesions count (summed over scans)

- **Patients with high sNfL levels at baseline had a higher Gd+ T1 and/or T2 lesion activity**
- **The Gd+ T1 activity and the number of new or enlarging T2 lesions was significantly reduced in both sNfL groups with the high evobrutinib doses**

Figure 5. Qualified relapses - Effect of evobrutinib and baseline sNfL

- Evaluate the effects on patients having a qualified relapse during 24 weeks of the double-blind period

	Low sNfL <11.36 pg/mL		High sNfL ≥11.36 pg/mL	
Qualified relapses	**N (%)**	**Total qualified relapses**	**N (%)**	**Total qualified relapses**
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 versus low baseline sNfL (stratified by evobrutinib dose): **p=0.0038, odds ratio: 6.07**
High versus 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 MS 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[4]

Abbreviations: BID, twice daily; **BTK,** Bruton's tyrosine kinase; **CI,** confidence interval; **DMF,** dimethyl fumarate; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **ITT,** intention to treat; **mITT,** modified ITT; **MMRM,** mixed model repeated measures; **MRI,** magnetic resonance imaging; **MS**, multiple sclerosis; **NfL,** neurofilament light chain; **N (%),** number of patients with relapses; **NS,** not significant; **QD,** once daily; **RR,** relative reduction; **sNfL,** serum neurofilament light chain

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