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Evobrutinib, a Bruton's tyrosine kinase inhibitor, decreases neurofilament light chain levels over 2.5 years of treatment in patients with relapsing multiple sclerosis

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CONCLUSIONS

Evobrutinib significantly reduced NfL levels, versus placebo, by Week 12. Reduction in NfL levels was observed through to Week 144, which may also correspond with reduced MRI activity

This sustained reduction in NfL over time provides evidence that evobrutinib reduces neuroaxonal damage in patients with RMS

After switching to evobrutinib 75 mg BID* in OLE, NfL levels were reduced to similar values, regardless of original DBP treatment group

Fasted dose – predicted to be comparable, with respect to exposure and BTK occupancy, to the 45 mg BID fed dose used in Phase III [NCT04338022, NCT04338061]. Please refer to supplementary data **(Supplementary Figure 1) via the QR code for further information*

INTRODUCTION

- Evobrutinib is a highly selective, CNS-penetrant, covalent BTK inhibitor[1-3], currently in Phase III for RMS (NCT04338022 and NCT04338061)
- Previous analyses from the evobrutinib Phase II trial in patients with RMS (NCT02975349) demonstrated that, versus placebo, evobrutinib 75 mg BID significantly, and in a sustained manner, lowered NfL levels from as early as Week 12[4]
- These findings are of interest as NfL is a biomarker of ongoing neuroaxonal damage, and correlates with relapses, disability worsening and MRI activity[5]

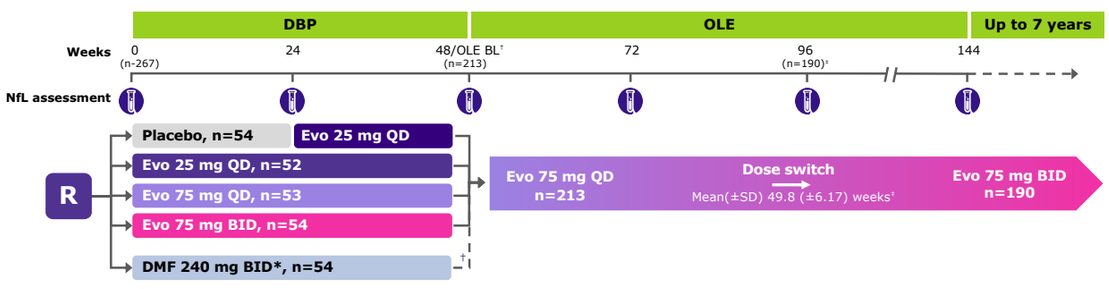
OBJECTIVE

To evaluate the long-term treatment effect of evobrutinib on NfL levels in patients with RMS

METHODS

- Patients who were enrolled in the DBP were able to enter the OLE at Week 48 **(Figure 1)**
- NfL levels were measured over time in the pooled OLE safety population and reported as control-adjusted NfL Z-scores (expression of SD away from mean NfL level in a control population [participants without evidence of CNS disease])[6] and NfL percentiles, based on the Z-scores
- The effect of evobrutinib - 25 mg QD, 75 mg QD or 75 mg BID - on NfL levels over time (up to DBP Week 48) was assessed versus the placebo/ evobrutinib 25 mg QD treatment arm (referred to as placebo for simplicity)
- NfL Z-scores were used to evaluate the treatment effect of evobrutinib using a MMRM model

Figure 1: Phase II NfL clinical analysis



Note: All evobrutinib doses were given while fasted

*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment; †DMF arm had a minimum 4-week washout period; The DMF arm is not considered for the current NfL analysis; †n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.17) weeks

RESULTS

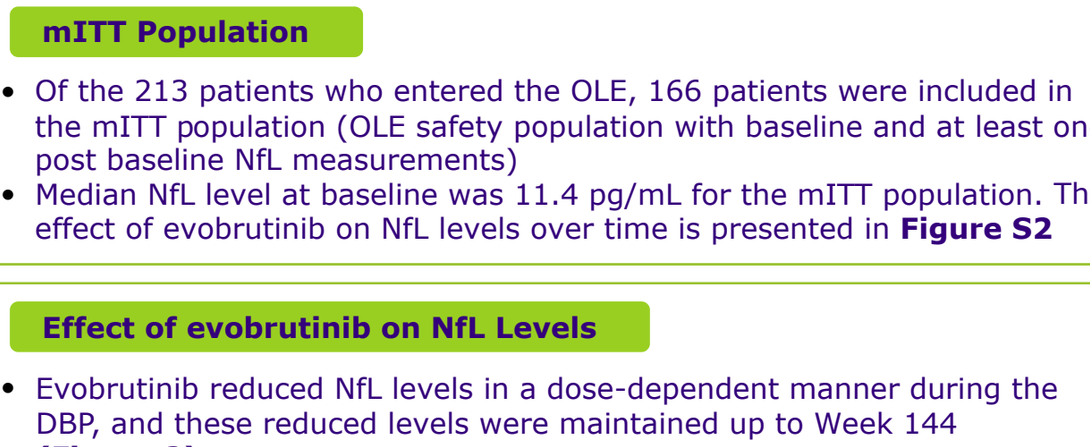
mITT Population

- Of the 213 patients who entered the OLE, 166 patients were included in the mITT population (OLE safety population with baseline and at least one post baseline NfL measurements)
- Median NfL level at baseline was 11.4 pg/mL for the mITT population. The effect of evobrutinib on NfL levels over time is presented in **Figure S2**

Effect of evobrutinib on NfL Levels

- Evobrutinib reduced NfL levels in a dose-dependent manner during the DBP, and these reduced levels were maintained up to Week 144 **(Figure 2)**
- After switching to evobrutinib 75 mg BID in the OLE (mean [± SD] duration of 75 mg QD dosing in OLE: 49.8 [±6.17]) weeks, NfL levels overall and within the original DBP treatment groups were reduced to similar levels

Figure 2: The effect of evobrutinib on NfL levels over time (age- and BMI- adjusted median percentiles based on healthy controls)

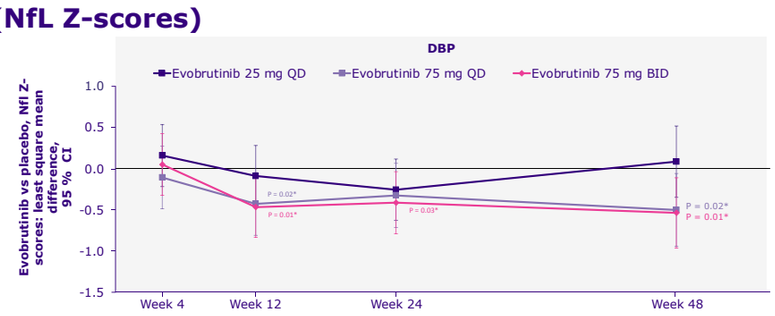


*Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID
The dotted lines post Week 48 represent the original treatment groups during the DBP. All patients from the DBP were switched to receive the same dose of evobrutinib after Week 48 (OLE phase)
Control population was defined as participants without the presence of CNS disease. For derivation of a reference database of NfL values, a control group was created, comprising participants with no evidence of CNS disease taking part in four cohort studies in Europe and North America[6]

Treatment Effect Versus Placebo (NfL Z-scores)

- Evobrutinib reduced NfL Z-scores in a dose-dependent manner from as early as Week 12; evobrutinib 75 mg BID demonstrated a significant and sustained reduction on NfL Z-scores versus placebo up to Week 48 **(Figure 3)**

Figure 3: Evobrutinib versus placebo*: treatment effect on NfL levels until Week 48 (NfL Z-scores)

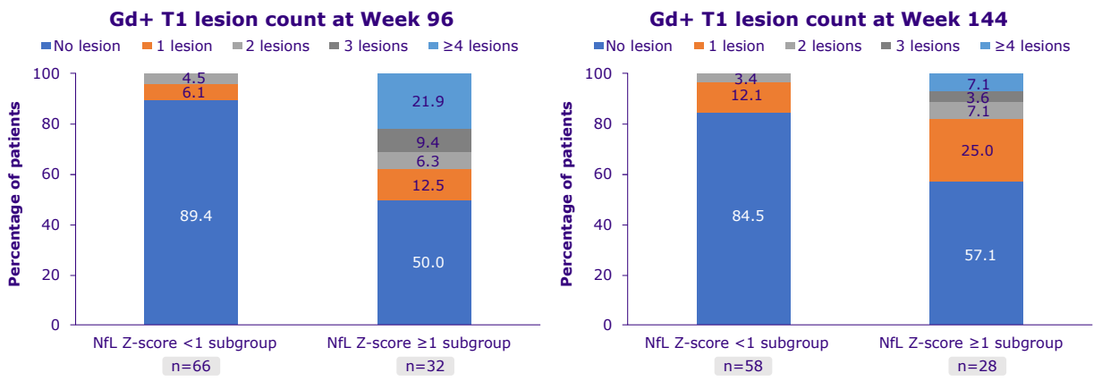


*Placebo/Evobrutinib 25 mg QD; Core MMRM model for NfL Z-score includes fixed effect for treatment, visit (categorical Week 4, 12, 24, 48), baseline NfL Z-score level, treatment-by-visit interaction, baseline NfL Z-score-by-visit interaction and random effect for patient (unstructured covariance matrix). A baseline covariate and covariate-by-visit interaction is added to the core model. Baseline covariates included in this model were: sex and T1 Gd+ lesion counts

NfL Z-scores and MRI Activity

- Stratifying by NfL Z-scores showed an association between lower NfL Z-score and number of T1 Gd+ and new/enlarging T2 lesions **(Figure 4 and Figures S3–S5)**

Figure 4: Association of NfL Z-score and T1 Gd+ lesion count (stratification by NfL Z-score category [<1 and ≥1] at Week 96)



Data are presented for overall group* (placebo, evobrutinib 25 mg QD, evobrutinib 75 mg QD, and evobrutinib 75 mg BID) stratified based on NfL Z-scores at Week 96. T1 Gd+ lesions were assessed at Weeks 96 and 144. *OLE safety patient population

Abbreviations: BID, twice daily; **BMI**, body mass index; **BL**, baseline; **BTK**, Bruton's tyrosine kinase; **CI,** confidence interval; **CNS**, central nervous system; **DBP**, double-blind period; **DMF**, dimethyl fumarate; **Evo**, evobrutinib; **Gd+**, gadolinium-enhancing **mITT**, modified intention-to-treat; **MMRM**, mixed model for repeated measures; **MRI**, magnetic resonace imaging; **NfL**, neurofilament light chain; **OLE**, open-label extension; **QD**, once daily; **R**, randomization; **RMS**, relapsing multiple sclerosis; **SD**, standard deviation; **Tx**, treatment

References: 1. Haselmayer P, et al. *J Immunol.* 2019;202:2888–906; 2. Caldwell RD, et al. *J Med Chem.* 2019;62:7643–55; 3. Boschert U et al. *Mult Scler.* 2017;23(Suppl. 3):327 (P678); 4. Kuhle J, et al. *Neurology.* 2021;96(22):e2783–810; 5. Kuhle J. *Neurology*. 2019;92:e1007–15; 6. Benkert P et al. *Lancet Neurol.* 2022;21:246–57

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Medical writing assistance was provided by Nidhi Hans and Rahul Birari of Merck Specialties Pvt. Ltd., Bangalore, India, an affiliate of Merck KGaA, Darmstadt, Germany

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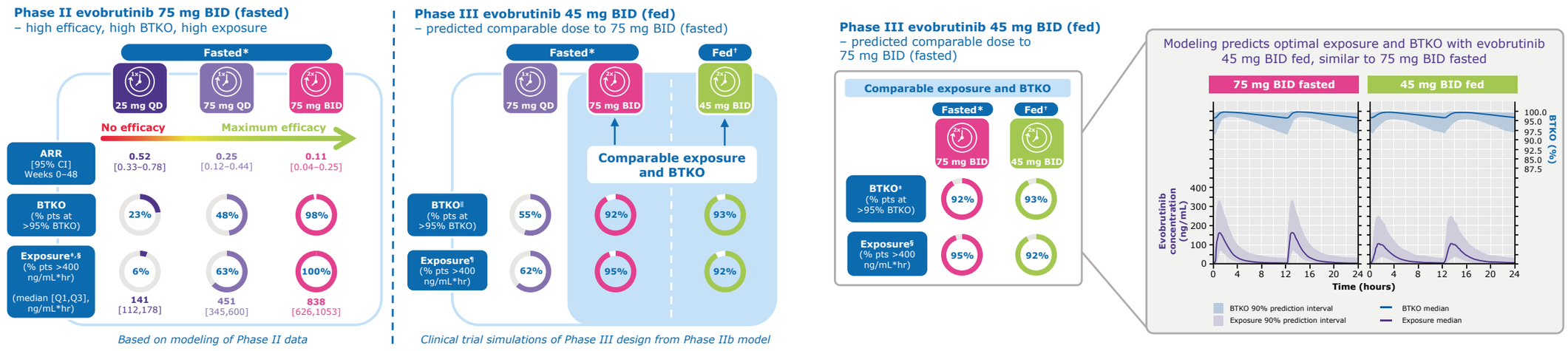
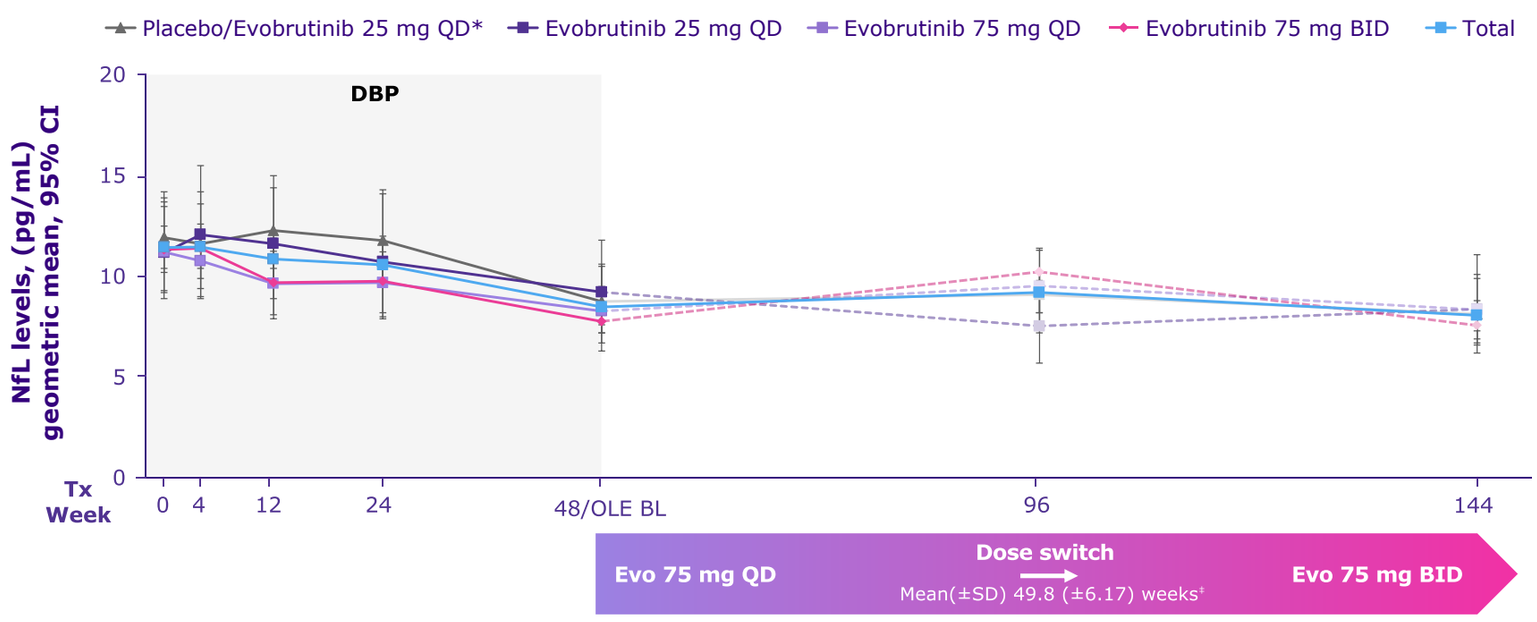
Supplementary appendix

Supplementary Figure 1: Evobrutinib dosing for the Phase III trials was optimized for exposure and BTKO levels that correlated with maximal efficacy



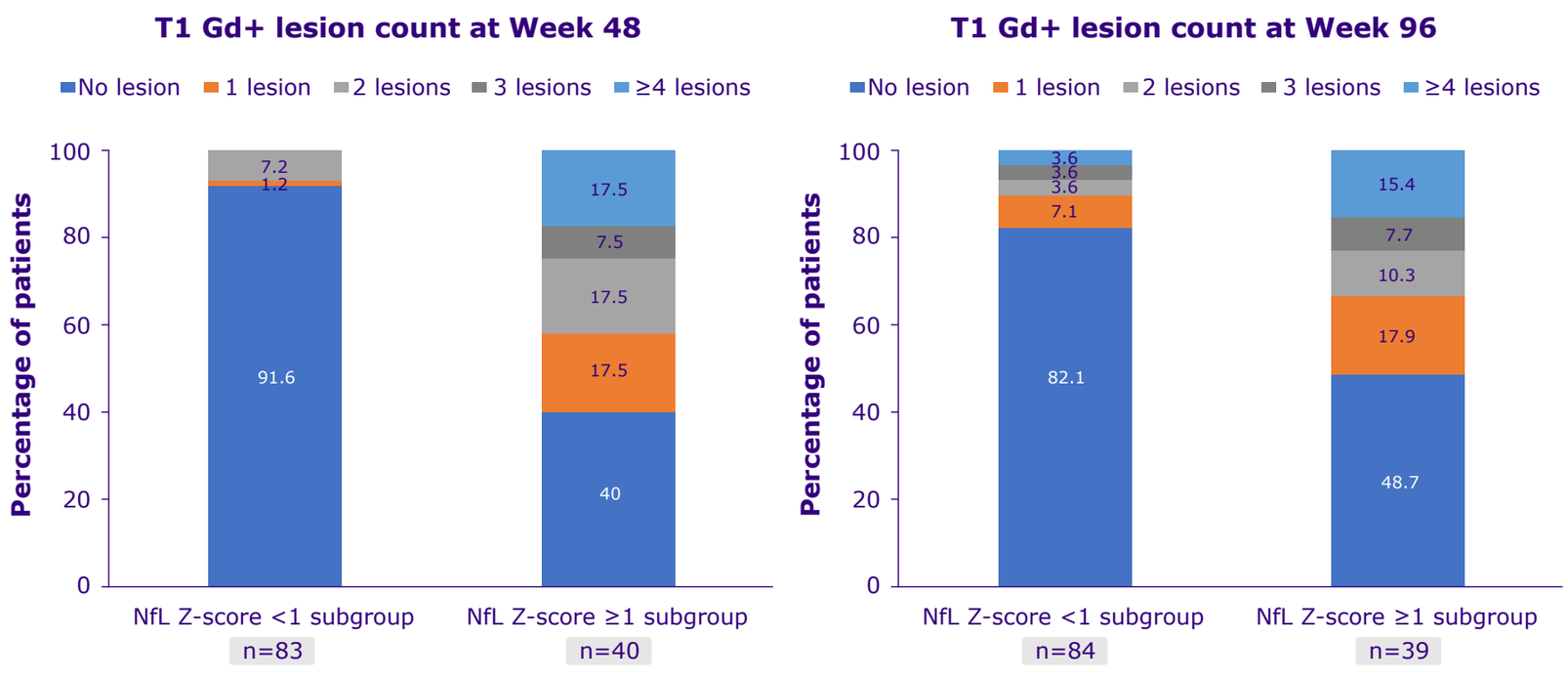
Measurements of evobrutinib concentration and BTKO were made in blood and PBMCs, respectively, from patients with MS in the Phase II trial
*Fasted state: >1 hour pre-meal or >2 hours post-meal; †Fed state: with food (high-fat or moderate-fat meal);
‡percentage of patients with AUC >400 ng/ml*hr over 24 hours; §Modeled maximal efficacy AUC >400 ng/ml*hr and no efficacy AUC <355 ng/ml*hr; ‖Simulated percentage of patients with BTKO >95% over 24 hours at steady state;
¶Simulated percentage of patients with AUC >400 ng/ml*hr over 24 hours
ARR is a measure of clinical efficacy, BTK occupancy indicates the fraction of evobrutinib occupying BTK (in PBMCs), **exposure** is the AUC: the area under concentration time profile of evobrutinib in the blood over 24 hours at steady state

Supplementary Figure 2: The effect of evobrutinib on NfL levels over time (geometric mean)



*Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID. The dotted lines post Week 48 represent the original treatment groups during the DBP. All patients from the DBP were switched to receive the same dose of evobrutinib after Week 48 (OLE phase)

Supplementary Figure 3: Association of NfL Z-score and T1 Gd+ lesion count (stratification by NfL Z-score category [<1 and ≥1] at Week 48)

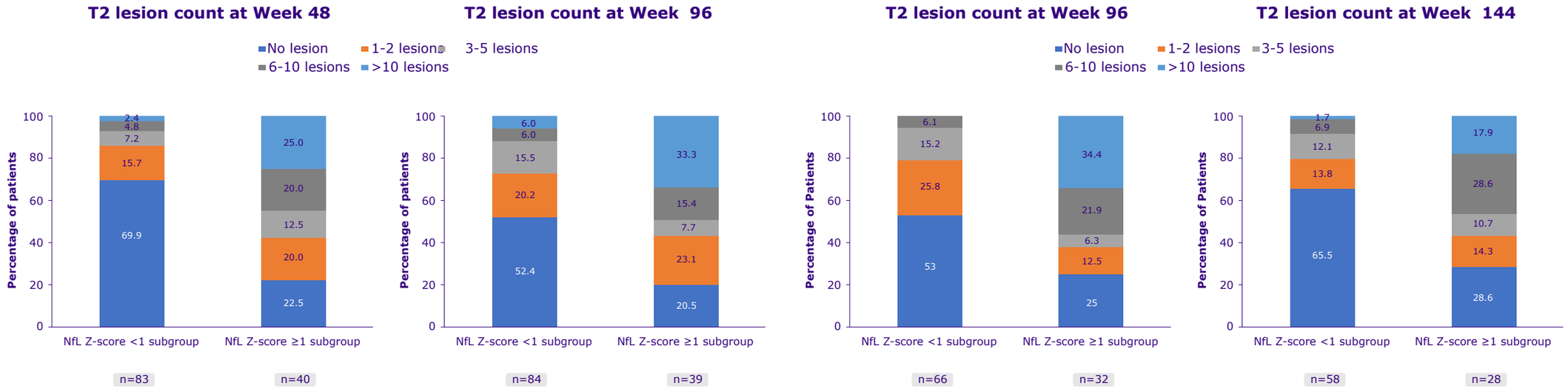


Data are presented for overall group* (placebo, evobrutinib 25 mg QD, evobrutinib 75 mg QD, and evobrutinib 75 mg BID) stratified based on NfL Z-scores at Week 48. T1 Gd+ lesions were assessed at Weeks 48 and 96; *OLE safety patient population

Abbreviations: ARR, annualized relapse rate; **AUC**, area under the concentration-time curve; **BID**, twice daily; **BTKO**, Bruton's tyrosine kinase occupancy; **CI**, confidence interval; **DBP**, double-blind period; **Evo**, evobrutinib; **Gd+**, gadolinium-enhancing; **hr**, hour; **MS**, multiple sclerosis; **NfL**, neurofilament light chain; **OLE**, open-label extension; **PBMCs**, peripheral blood mononuclear cells; **pts**, patients; **SD**, standard deviation; **QD**, once daily

Supplementary appendix

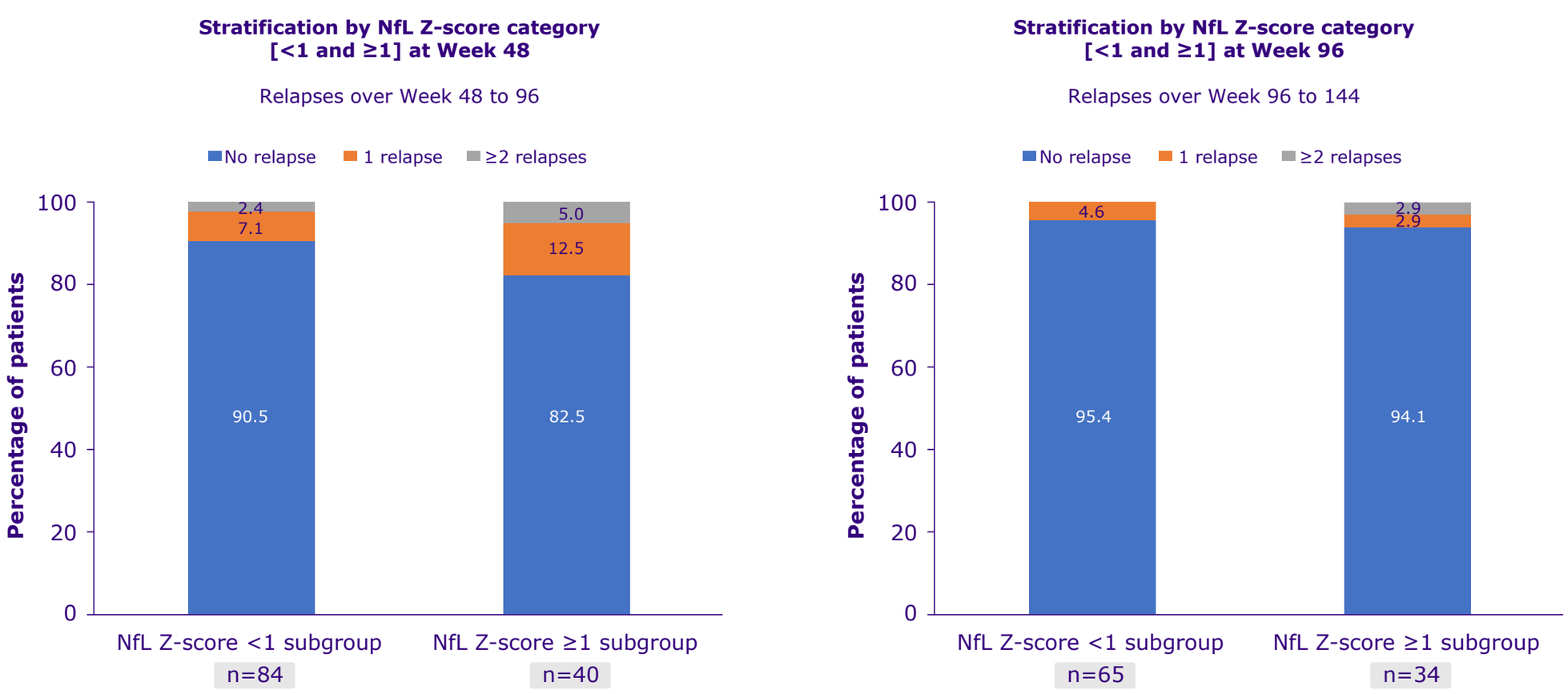
Supplementary Figure 4: Association of NfL Z-score and new/enlarging T2 lesion count



Data are presented for overall group* (placebo, evobrutinib 25 mg QD, evobrutinib 75 mg QD, and evobrutinib 75 mg BID) stratified based on NfL Z -cores at Week 48. T2 lesions were assessed at Weeks 48 and 96
*OLE safety patient population

Data are presented for overall group* (placebo, evobrutinib 25 mg QD, evobrutinib 75 mg QD, and evobrutinib 75 mg BID) stratified based on NfL Z-scores at Week 96. T2 lesions were assessed at Weeks 96 and 144
*OLE safety patient population

Supplementary Figure 5: Association of NfL Z-score and relapses



Data are presented for overall group* (placebo, evobrutinib 25 mg QD, evobrutinib 75 mg QD, and evobrutinib 75 mg BID) stratified based on NfL Z-scores at Week 48 and 96. Number of relapses over Week 48 to Week 96 and Week 96 to Week 144 were assessed
*OLE safety patient population

Abbreviations: BID, twice daily; **DBP**, double blind period, **Evo**, evobrutinib; **NfL**, neurofilament light chain; **OLE**, open-label extension; **QD**, once daily