Neurofilament Light Chain Levels and Disease Activity During Long-term Treatment of Relapsing Multiple Sclerosis with the Bruton's Tyrosine Kinase Inhibitor Evobrutinib

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Evobrutinib is currently in Phase III trials for relapsing multiple sclerosis and has not yet been approved by any regulatory authority

Evobrutinib

- Highly selective, CNS-penetrant, covalent BTK inhibitor[1–3]
- Currently undergoing Phase III trials (NCT04338022 and NCT04338061) for RMS

Phase II RCT in RMS

(NCT02975349)

DBP Results (Week 0–48)

- Evobrutinib led to significant reductions in T1 Gd+ lesions versus placebo at Week 24 (primary endpoint)[4]
- In patients receiving evobrutinib 75 mg BID, the ARR was as low as 0.08 and 0.11 at Week 24 and Week 48, respectively[4]
- Evobrutinib also reduced new/enlarging T2 lesions[5]

OLE period

- The efficacy of evobrutinib observed during the DBP was maintained in the OLE phase up to Week 192 (beginning at Week 48 from the DBP baseline)[6]
- Sustained reductions in NfL levels, a biomarker of neuroaxonal damage, with evobrutinib treatment were observed as early as Week 12 through to Week 144[7]

1. Haselmayer P, et al. *J Immunol.* 2019;202:2888–2906; 2. Caldwell RD, et al. *J Med Chem.* 2019;62:7643–7655; 3. Boschert U, et al. *Mult Scler.* 2017;23(Suppl. 3):327 (P678); 4. Montalban X, et al. N Engl J Med. 2019;380(25):2406–2417; 5. Kuhle J, et al. Neurology. 2021;96:e2783–e2788; 6. Vermersch P, et al. Presented at ECTRIMS 2022 (P731); 7. Kuhle J, et al. Presented at ECTRIMS 2022 (EP1021).

ARR, annualized relapse rate; **BID**, twice daily; **CNS**, central nervous system; **BTK**, Bruton's tyrosine kinase; **DBP**, double-blind period; **Gd+**, gadolinium-enhancing; **NfL**, neurofilament light chain; **OLE**, open-label extension; **RCT**, randomized clinical trial; **RMS**, relapsing multiple sclerosis

- **To examine the effects of evobrutinib on longitudinal NfL levels**
- **To assess the relationship between NfL levels and relapse/MRI activity**

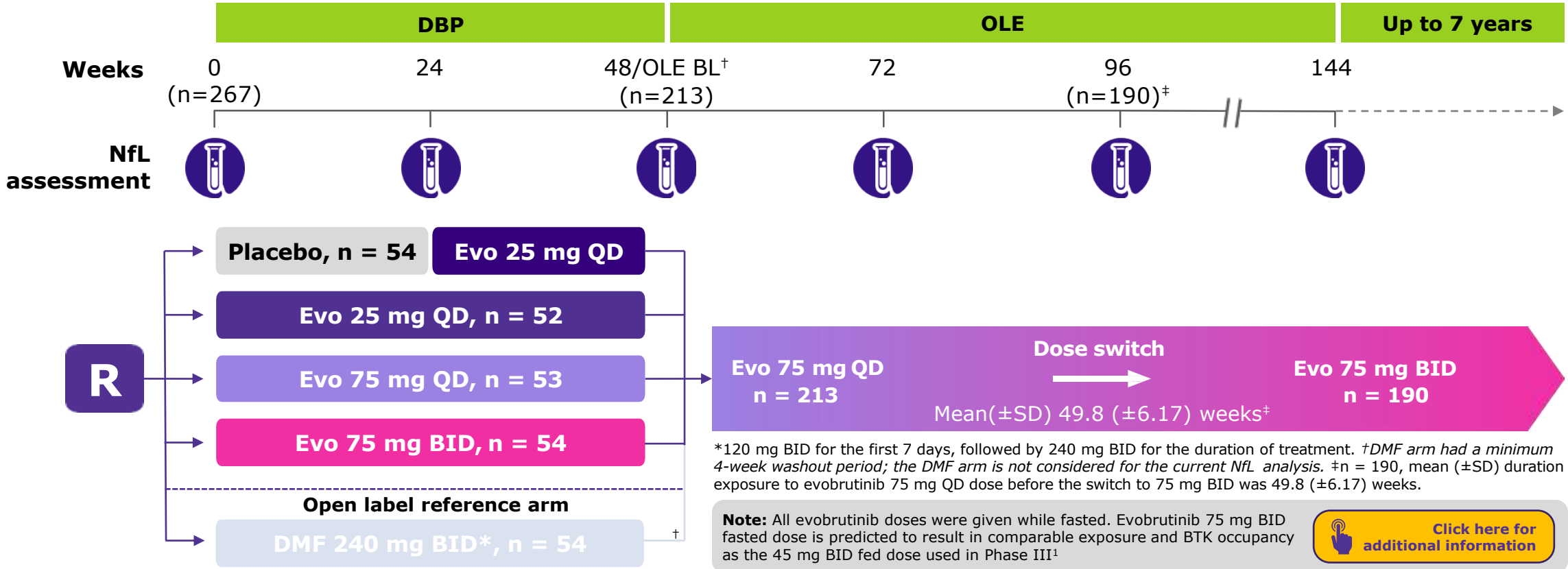
Oral presentation with full safety and efficacy data from the ongoing Phase II open-label extension

Montalban *et al.* Presentation: **S16-008:** MS Clinical Trials and Therapeutics. Date: **24 April 14:24 EST**

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

- Patients who were enrolled during the DBP could enter the OLE phase at Week 48
- Of 213 patients who participated in the OLE, 166 were included in the mITT population#

Phase II NfL clinical analysis



*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.

Note: All evobrutinib doses were given while fasted. Evobrutinib 75 mg BID fasted dose is predicted to result in comparable exposure and BTK occupancy as the 45 mg BID fed dose used in Phase III[1]

Click here for additional information

#OLE safety population with baseline and at least one postbaseline NfL measurement *(the DMF arm is not considered for the current NfL analysis)*

1. Papasouliotis O, et al. *Clin Transl Sci.* 2022;15(12):2888–2898.

BID, twice daily; **BL**, baseline; **BTK**, Bruton's tyrosine kinase; **DBP**, double-blind period; **DMF**, dimethyl fumarate; **Evo**, evobrutinib; **mITT**, modified intention-to-treat; **NfL**, neurofilament light chain; **OLE**, open-label extension; **QD**, once daily; **R**, randomization; **SD**, standard deviation

Measurement of NfL levels and Z-score

- NfL levels were measured over time in the pooled OLE safety population and reported as NfL Z-scores (age- and BMI-adjusted based on control population)
  - NfL Z-score is an expression of SDs away from the mean NfL level in a control population; an NfL Z-score of 0 represents reference value of a control population[1]
- High Z-scores ≥1.5 were associated with increased risk of future clinical or MRI disease activity[1]
- Based on the NfL Z-scores at Week 48 and Week 96, patients were stratified into sub-groups of those with NfL Z-scores <1 and ≥1 in order to have sufficient patient numbers for the analyses

Association of NfL Z-scores with relapse and MRI outcomes

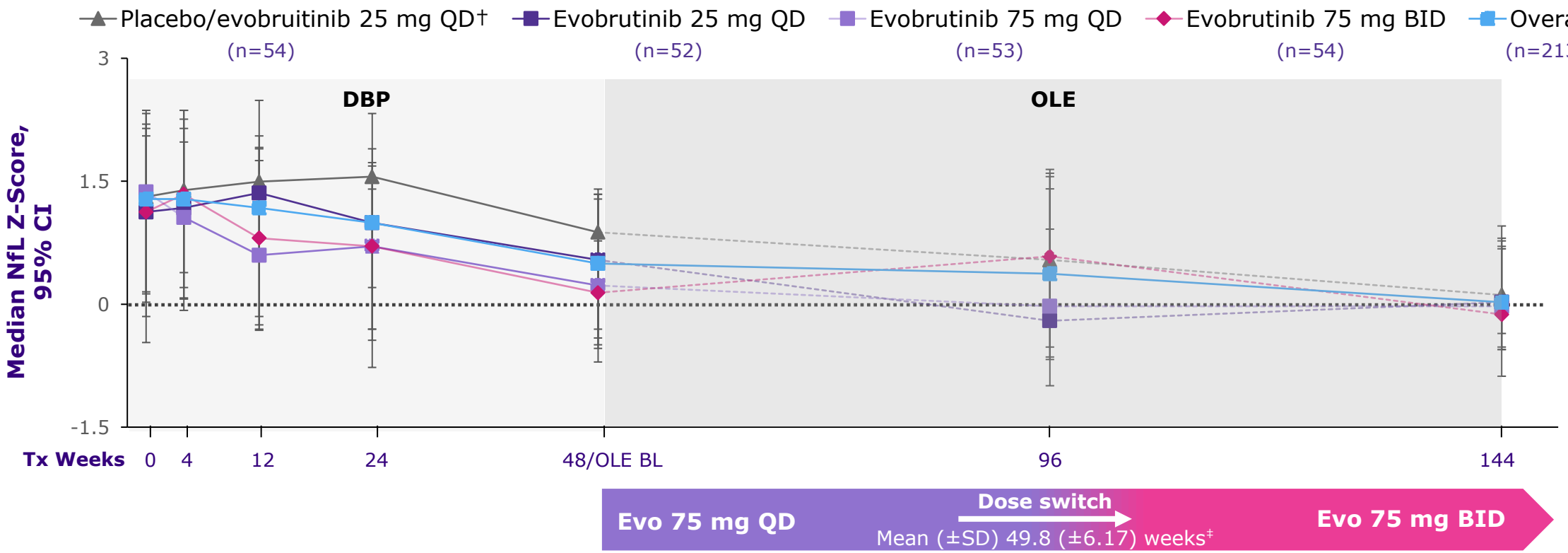
- Qualified relapses over Week 48–96 as well as MRI outcomes (number of T1 Gd+ and new/enlarging T2 lesions) at Week 48 and Week 96 were evaluated using stratified Week 48 NfL Z-scores
- Qualified relapses over Week 96–144 and MRI outcomes at Week 96 and Week 144 were also evaluated using stratified Week 96 NfL Z-scores

1. Benkert P, et al. *Lancet Neurol.* 2022;21:246–257.

BMI, body mass index; **Gd+**, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **NfL**, neurofilament light chain; **OLE**, open-label extension; **SD**, standard deviation

Effect of evobrutinib on NfL levels over time

- Evobrutinib reduced NfL levels* in a dose-dependent manner during the DBP, and these reduced levels were maintained up to Week 144 with the mean NfL Z-score for all evobrutinib treated patients approached values seen in the control group[1]
- After switching to evobrutinib 75 mg BID in the OLE, NfL levels overall and within the original DBP treatment groups were reduced to similar levels



†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). All n values are based on the ITT population.

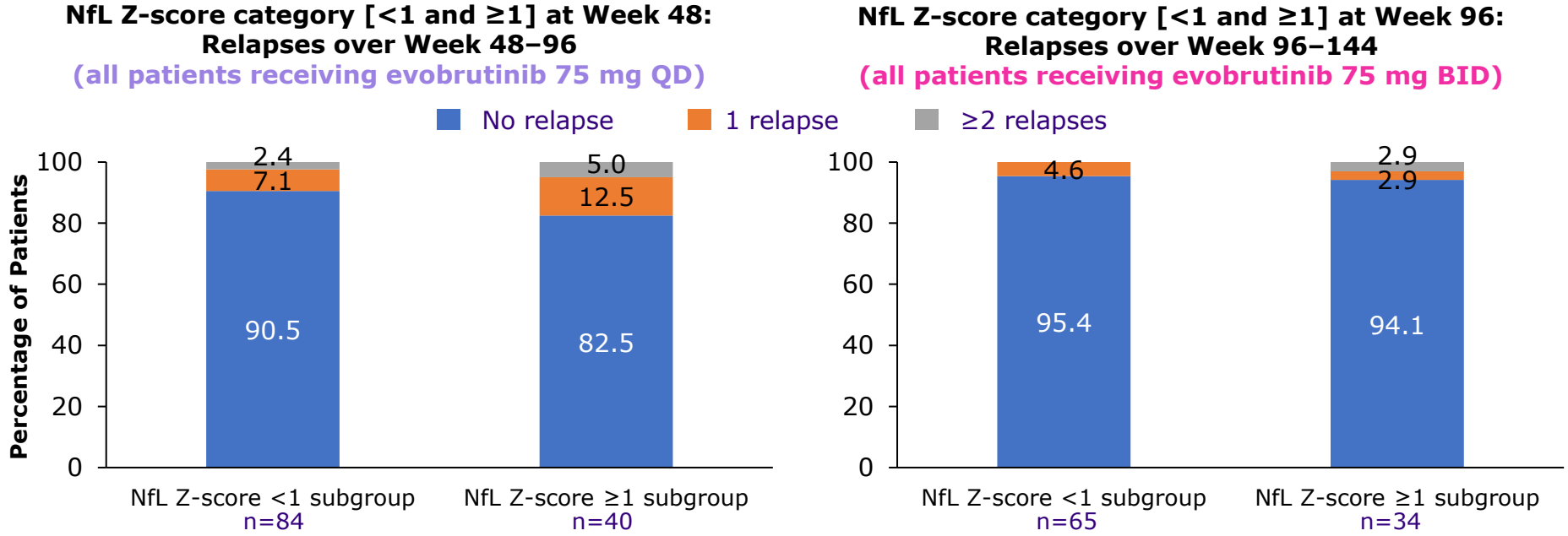
*Reported as NfL Z-scores (age- and BMI-adjusted based on control population). The control population was defined as participants without presence of CNS disease. To derive a reference database of NfL values, a control group was developed, comprising participants with no evidence of CNS disease participating in four cohort studies in Europe and North America[1]

1. Benkert P, et al. *Lancet Neurol.* 2022;21:246–257.

BID, twice daily; **BL**, baseline; **BMI**, body mass index; **CI**, confidence interval; **CNS**, central nervous system; **DBP**, double-blind period; **Evo**, evobrutinib; **ITT**, intention-to-treat; **NfL**, neurofilament light chain; **OLE**, open-label extension; **QD**, once daily; **SD**, standard deviation; **Tx**, treatment

NfL Z-scores and relapse activity

- The proportion of patients who were relapse-free (by NfL Z-score):
  - **Week 48–96** (stratified at Week 48): **NfL Z-score <1** 90.5%; **NfL Z-score ≥1** 82.5%
  - **Week 96–144** (stratified at Week 96): **NfL Z-score <1** 95.4%; **NfL Z-score ≥1** 94.1%



The majority of patients remained relapse free during the OLE period, in particular during treatment with evobrutinib 75 mg BID (>94% relapse-free) so that a difference between high and low NfL levels could no longer be observed

Data are presented for the overall group* (pooled population of placebo, evobrutinib 25 mg QD, evobrutinib 75 mg QD, and evobrutinib 75 mg BID treatment arms) stratified according to NfL Z-scores at (Left) Week 48; number of relapses over Week 48–96 was assessed and (Right) at Week 96; number of relapses over Week 96–144 was assessed. *OLE safety patient population

BID, twice daily; **NfL**, neurofilament light chain; **OLE**, open-label extension; **QD**, once daily

NfL Z-scores and MRI activity

- **Stratified by Week 96 NfL Z-score (<1 [n=66] vs ≥1 [n=34]):**

T1 Gd+ lesions

- **Week 96 T1 Gd+ lesion-free:** 89.4% vs 50.0%
- **Week 144 T1 Gd+ lesion-free:** 84.5% vs 57.1%

T2 new/enlarging lesions

- **Week 96 T2 lesion-free:** 53.0% vs 25.0%
- **Week 144 T2 lesion-free:** 65.5% vs 28.6%

- Similar findings were observed in patients stratified by Week 48 NfL Z-scores (<1 [N=84]; ≥1 [N=40])

The proportion of patients free of MRI lesion activity was consistently higher in patients with lower NfL Z-score

Data are presented for the overall group* (pooled population of placebo, evobrutinib 25 mg QD, evobrutinib 75 mg QD, and evobrutinib 75 mg BID treatment arms) stratified according to NfL Z-scores at Week 48 and Week 96; T1 Gd+ lesions and new/enlarging T2 lesions were evaluated at Week 48–96 and Week 96–144. *OLE safety patient population

Gd+, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **NfL**, neurofilament light chain

Evobrutinib maintained reduced NfL levels up to Week 144 with NfL Z-score values in evobrutinib-treated patients with MS similar to those seen in control reference population

Low NfL levels were associated with improved MRI and relapse outcomes, supporting the role of NfL as a prognostic marker of disease activity

Higher proportions of relapse-free patients were observed with evobrutinib 75 mg BID compared to evobrutinib 75 QD dosing
(click here to see additional details)

Oral presentation with full safety and efficacy data from the ongoing Phase II open-label extension

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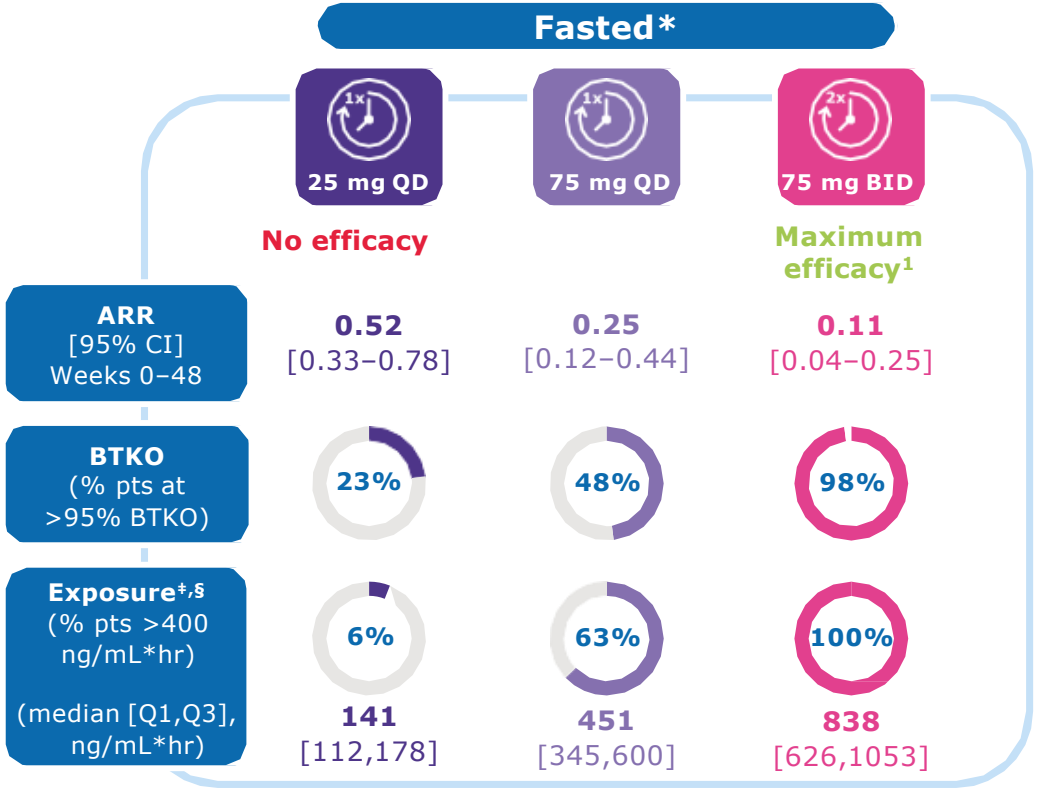
BID, twice daily; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **NfL**, neurofilament light chain; **QD**, once daily

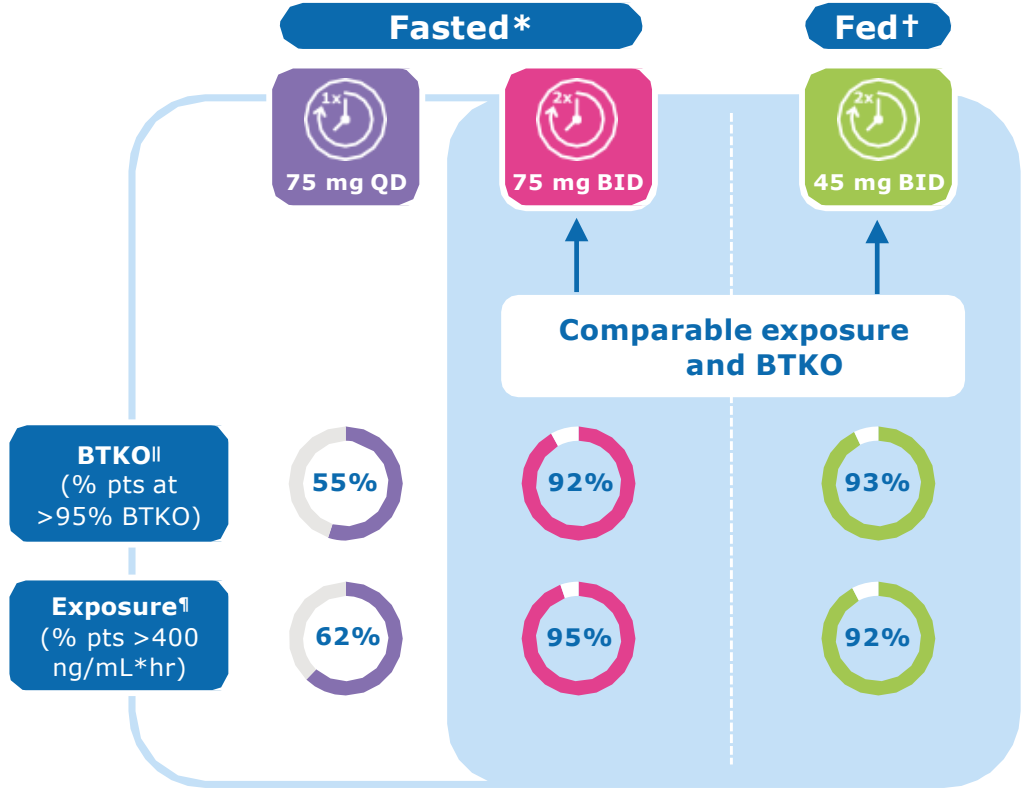
Evobrutinib dosing for the Phase III trials was optimized for exposure and BTKO levels correlating with maximal efficacy

Phase II evobrutinib 75 mg BID (fasted)
– high efficacy, high BTKO, high exposure



Based on modeling of Phase II patient data

Phase III evobrutinib 45 mg BID (fed)[1]
– predicted comparable dose to 75 mg BID (fasted)

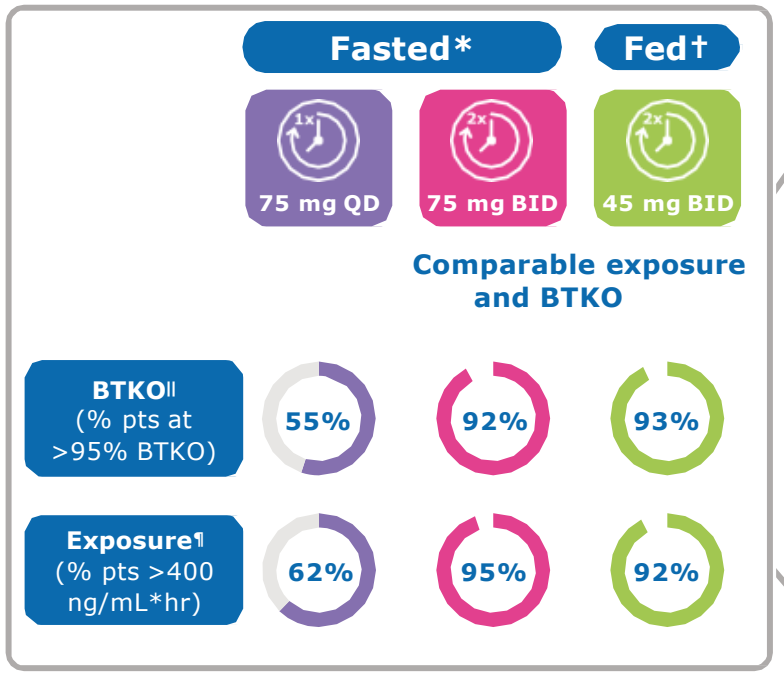


Clinical trial simulations of Phase III design from Phase IIb model

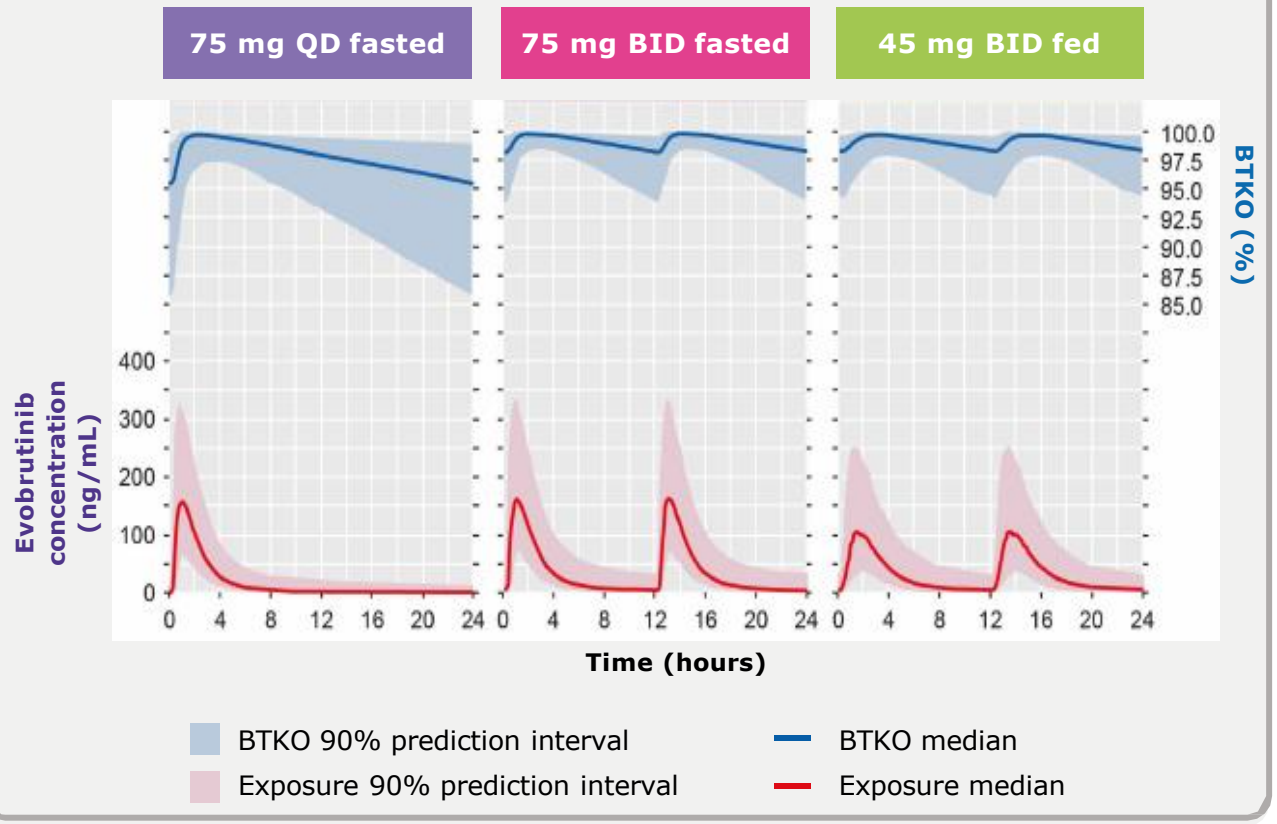
1. Papasouliotis O, et al. *Clin Transl Sci.* 2022;15:2888–2898. Measurements of evobrutinib concentration and BTKO were made in blood and PBMCs, respectively, from patients with MS in the Phase II trial.
*Fasted state: >1 hour pre-meal or >2 hours post-meal; †Fed state: with food (high-fat or moderate-fat meal); ‡Percentage of patients with AUC >400ng/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 >400ng/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
AUC, area under the curve; **ARR**, annualised relapse rate; **BID**, twice daily; **BTK**, Bruton's tyrosine kinase; **BTKO**, BTK occupancy; **MS**, multiple sclerosis; **pts**, patients; **PBMC**, peripheral blood mononuclear cells; **QD**, once daily

Evobrutinib dosing for the Phase III trials was optimized for exposure and BTKO levels correlating with maximal efficacy

Phase III evobrutinib 45 mg BID (fed)[1]
– predicted comparable dose to 75 mg BID (fasted)



Modeling predicts optimal exposure and BTKO with evobrutinib 45 mg BID fed, similar to 75 mg BID fasted



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¶Simulated percentage of patients with AUC >400ng/ml*hr over 24 hours.
BTKO 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
AUC, area under the curve; **BID**, twice daily; **BTK**, Bruton's tyrosine kinase; **BTKO**, BTK occupancy; **MS**, multiple sclerosis; **pts**, patients; **PBMC**, peripheral blood mononuclear cells; **QD**, once daily