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# MRI and clinical outcomes of evobrutinib, a Bruton's tyrosine kinase inhibitor, in relapsing multiple sclerosis over 2.5 years of the open-label extension to a Phase 2 trial

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## CONCLUSIONS

- **Overall, MRI lesion activity remained low and decreased further after switching from evobrutinib 75 mg QD to 75 mg BID***
- **T2 lesion volume remained stable during the OLE up to Week 192**

**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 via the QR code for further information*

- **Clinical endpoints remained stable throughout the OLE up to Week 192:**
  - **ARR remained low (0.13 up to Week 192) for patients who received evobrutinib 75 mg BID in the DBP***
  - **For the pooled patient population, overall EDSS remained stable from Week 0 to Week 192**
- **These data demonstrate the long-term benefit of evobrutinib on both MRI and clinical manifestations of RMS**

## INTRODUCTION

- Evobrutinib is a highly selective, CNS-penetrant, covalent Bruton's tyrosine kinase inhibitor[1–3]
- In a Phase II trial (NCT02975349) in patients with RMS, evobrutinib showed significant reductions in T1 Gd+ lesions versus placebo at Week 24 (primary endpoint), and an ARR of 0.08 at Week 24 and 0.11 at Week 48 in patients receiving evobrutinib 75 mg BID. Evobrutinib also reduced new/enlarging T2 lesions in patients with RMS[4]
- In the OLE of this trial, a low ARR was maintained at Week 108 (0.12) and Week 180 (0.13) in patients who originally initiated on evobrutinib 75 mg BID in the DBP[5-7]

## OBJECTIVES

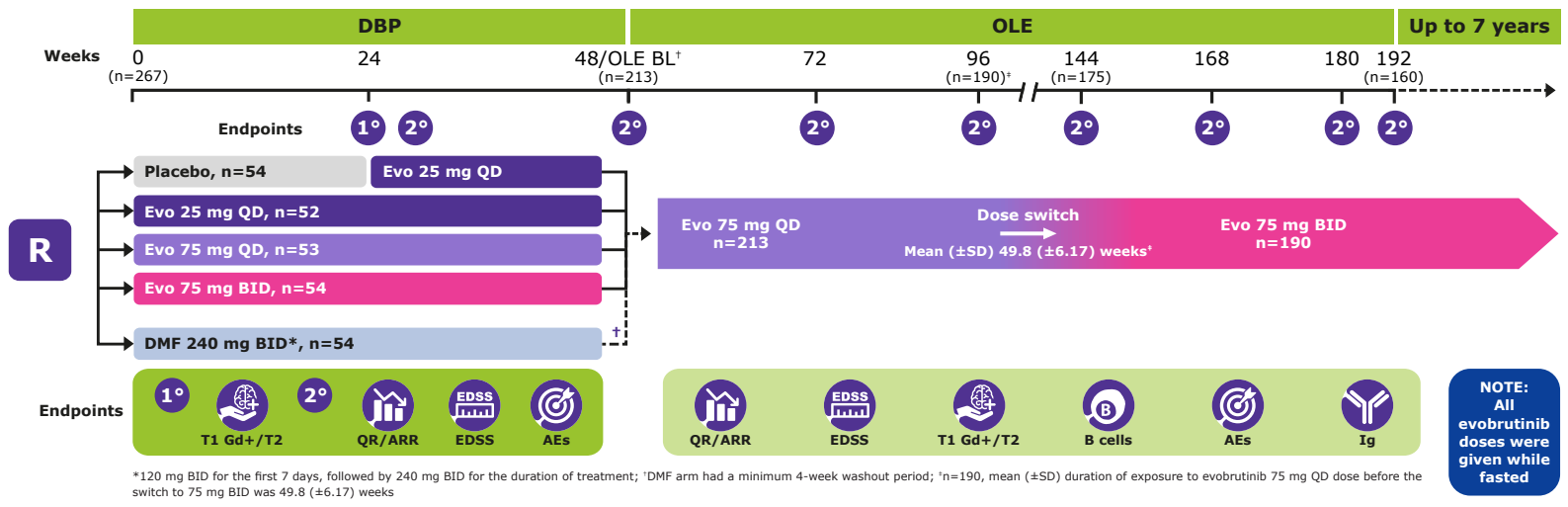
**To report MRI and clinical outcomes of evobrutinib in the treatment of RMS over 2.5 years in an OLE (OLE baseline to Week 192), including:**

- **Number of T1 Gd+ lesions**
- **T2 lesion volume**
- **ARR**
- **Mean EDSS score**

## METHODS

### Study design

- In the 48-week DBP, patients were assigned to one of five treatment groups:
  - Placebo (switching to evobrutinib 25 mg QD after 24 weeks)
  - Evobrutinib 25 mg QD
  - Evobrutinib 75 mg QD
  - Evobrutinib 75 mg BID
  - Open-label DMF 240 mg BID as a reference arm
- At Week 48, all patients could enter the OLE, in which treatment was initially evobrutinib 75 mg QD (mean [±SD] duration: 49.8 [±6.17] weeks) before switching to 75 mg BID

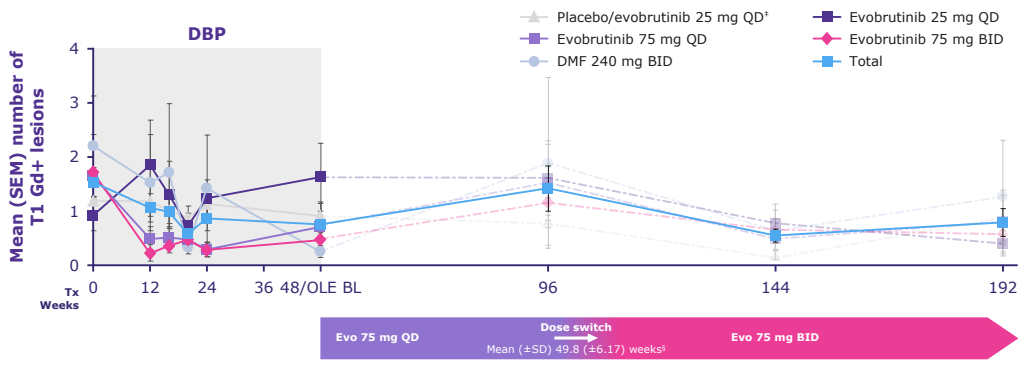



*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment; †DMF arm had a minimum 4-week washout period; ‡n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.17) weeks

## RESULTS

### T1 Gd+ lesions during the DBP and OLE (Week 0 to Week 192)*

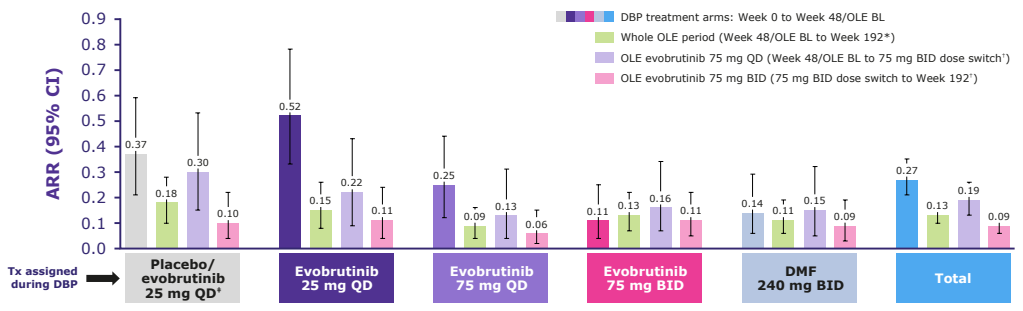
- Overall, the mean number of T1 Gd+ lesions† remained low with some fluctuations (and a small increase from Week 48/OLE BL to Week 96 while on 75 mg QD), and decreased from Week 96 after the switch to 75 mg BID




*Cut-off 30 Sep 2021; †T1 Gd+ lesion counts reported here are measured at individual time points (and do not represent annualized or cumulative values); ‡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

### ARR during the DBP and OLE (Week 0 to Week 192)*

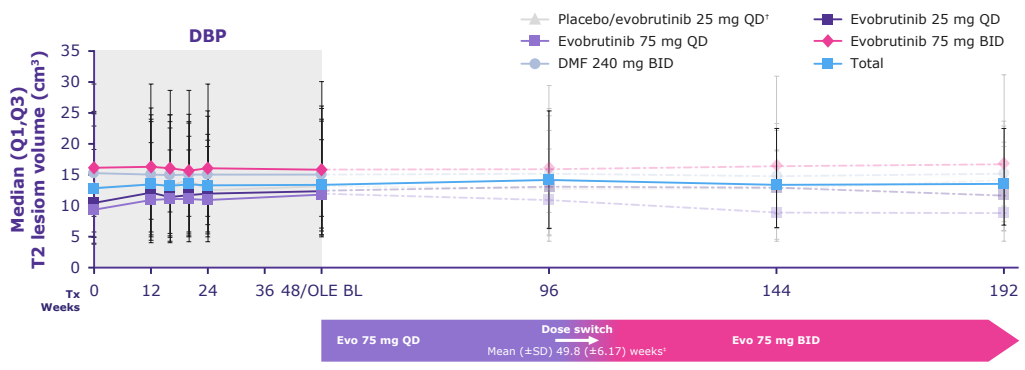
- Switching from evobrutinib 75 mg QD to 75 mg BID in the OLE reduced ARR regardless of treatment during the DBP
- Patients on evobrutinib maintained an ARR of 0.13 throughout the OLE (regardless of DBP treatment), with an ARR of 0.09 reported after all patients were switched to evobrutinib 75 mg BID




*Cut-off 30 Sep 2021; †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; ‡Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP

### T2 lesion volume during the DBP and OLE (Week 0 to Week 192)*

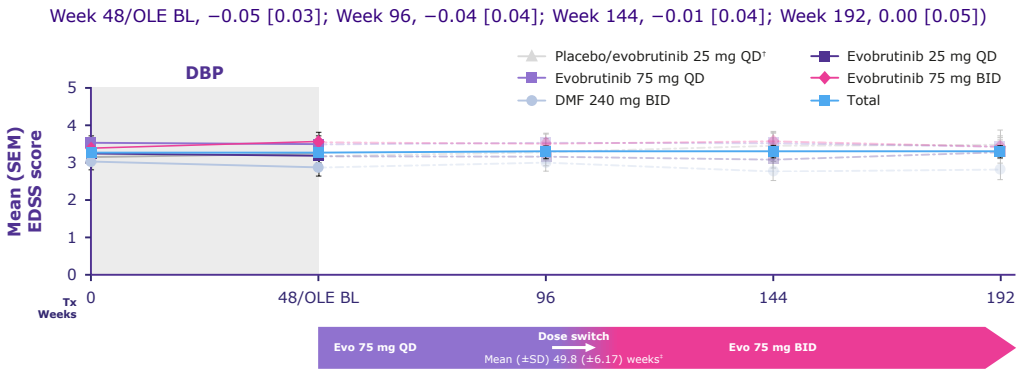
- Overall, T2 lesion volume remained stable during the OLE




*Cut-off 30 Sep 2021; †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

### Mean EDSS score during the DBP and OLE (Week 0 to Week 192)*

- Overall, mean EDSS scores remained low and stable from Week 0 to 192 (mean change from Week 0 [SEM]: Week 48/OLE BL, −0.05 [0.03]; Week 96, −0.04 [0.04]; Week 144, −0.01 [0.04]; Week 192, 0.00 [0.05])




*Cut-off 30 Sep 2021; †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

**Abbreviations: ARR**, annualized relapse rate; **BID**, twice daily; **BL**, baseline; **CI**, confidence interval; **CNS**, central nervous system; **DBP**, double-blind period; **DMF**, dimethyl fumarate; **EDSS**, Expanded Disability Status Scale; **Evo**, evobrutinib; **Gd+**, gadolinium-enhancing; **Ig**, immunoglobulin; **MRI**, magnetic resonance imaging; **OLE**, open-label extension; **QD**, once daily; **QR**, qualifying relapses; **R**, randomization; **RMS**, relapsing multiple sclerosis; **Tx**, treatment; **SD**, standard deviation; **SEM**, standard error of mean

**REFERENCES: 1.** Haselmayer P, et al. *J Immunol.* 2019;202(10):2888–906; **2.** Caldwell RD, et al. *J Med Chem.* 2019;62(17):7643–55; **3.** Boschert U et al. *Mult Scler.* 2017;23(Suppl. 3):327 (P678); **4.** Montalban X, et al. *N Engl J Med.* 2019;380:2406–17; **5.** Montalban X, et al. *Mult Scler.* 2020;26(Suppl. 3):213 (P0197); **6.** Montalban X, et al. *Neurology.* 2021;96(Suppl. 15):4124; **7.** Montalban X et al. *Neurology.* 2022;98(Suppl. 18):2812 (P5–4.001)

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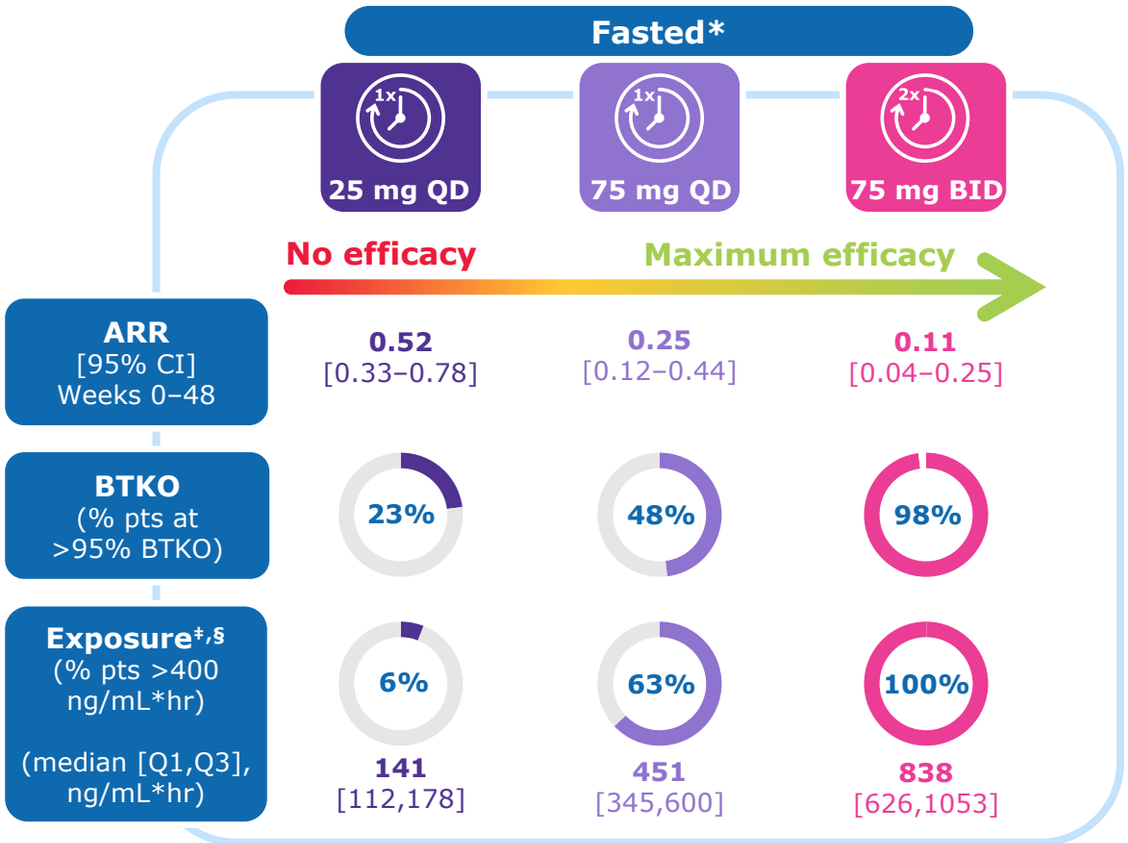
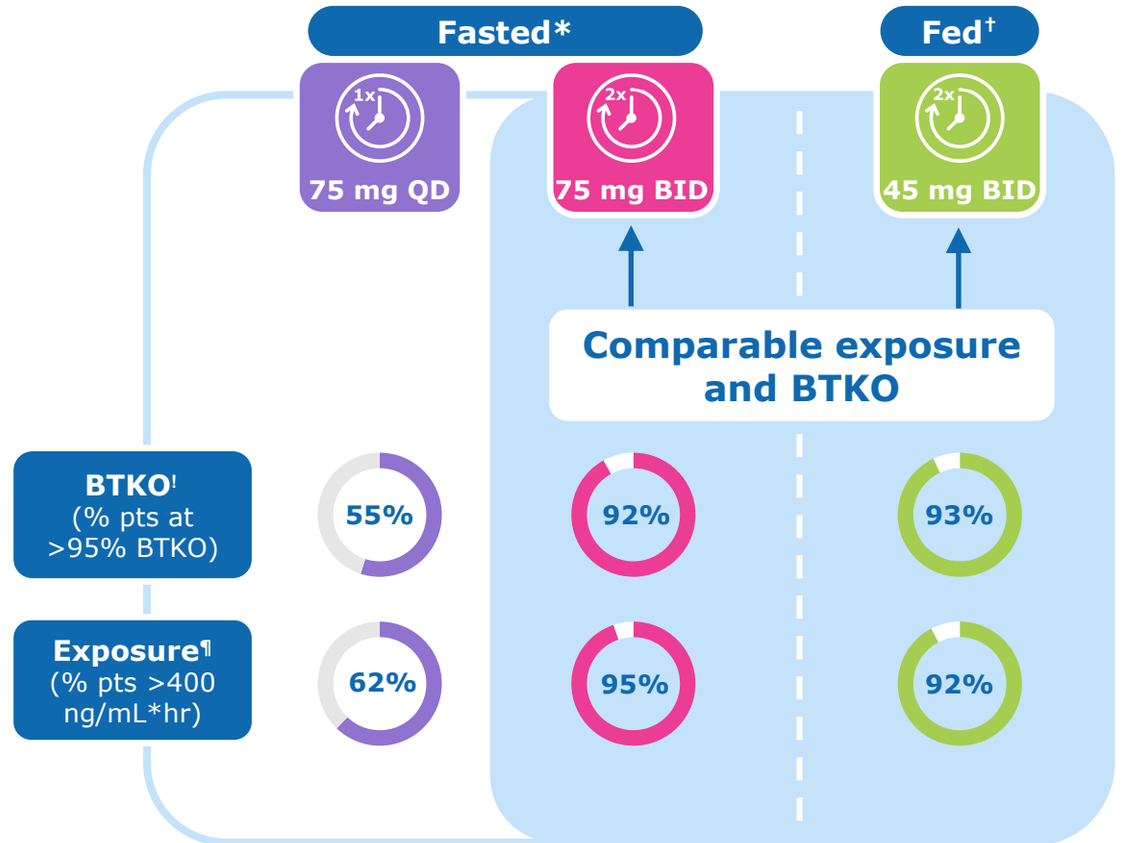
# Evobrutinib dosing for the Phase III trials was optimized for exposure and BTKO levels that correlated with maximal efficacy

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




*Based on modeling of Phase II data*

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




*Clinical trial simulations of Phase III design from Phase IIb model*

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. **ARR,** annualized relapse rate; **AUC,** area under the concentration-time curve; **BID,** twice daily; **BTKO,** Bruton's tyrosine kinase occupancy; **CI,** confidence interval; **hr,** hour; **MS**, multiple sclerosis; **PBMCs,** peripheral blood mononuclear cells; **pts,** patients; **QD,** once daily

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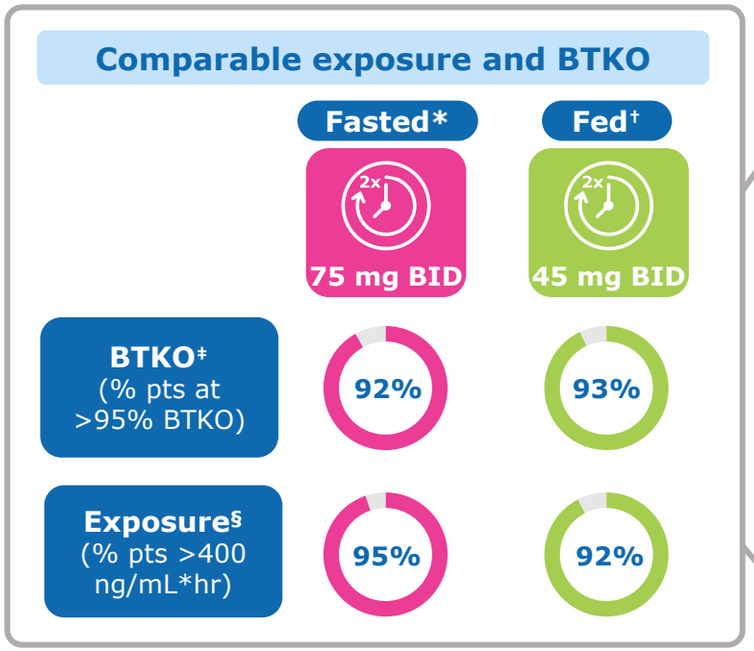


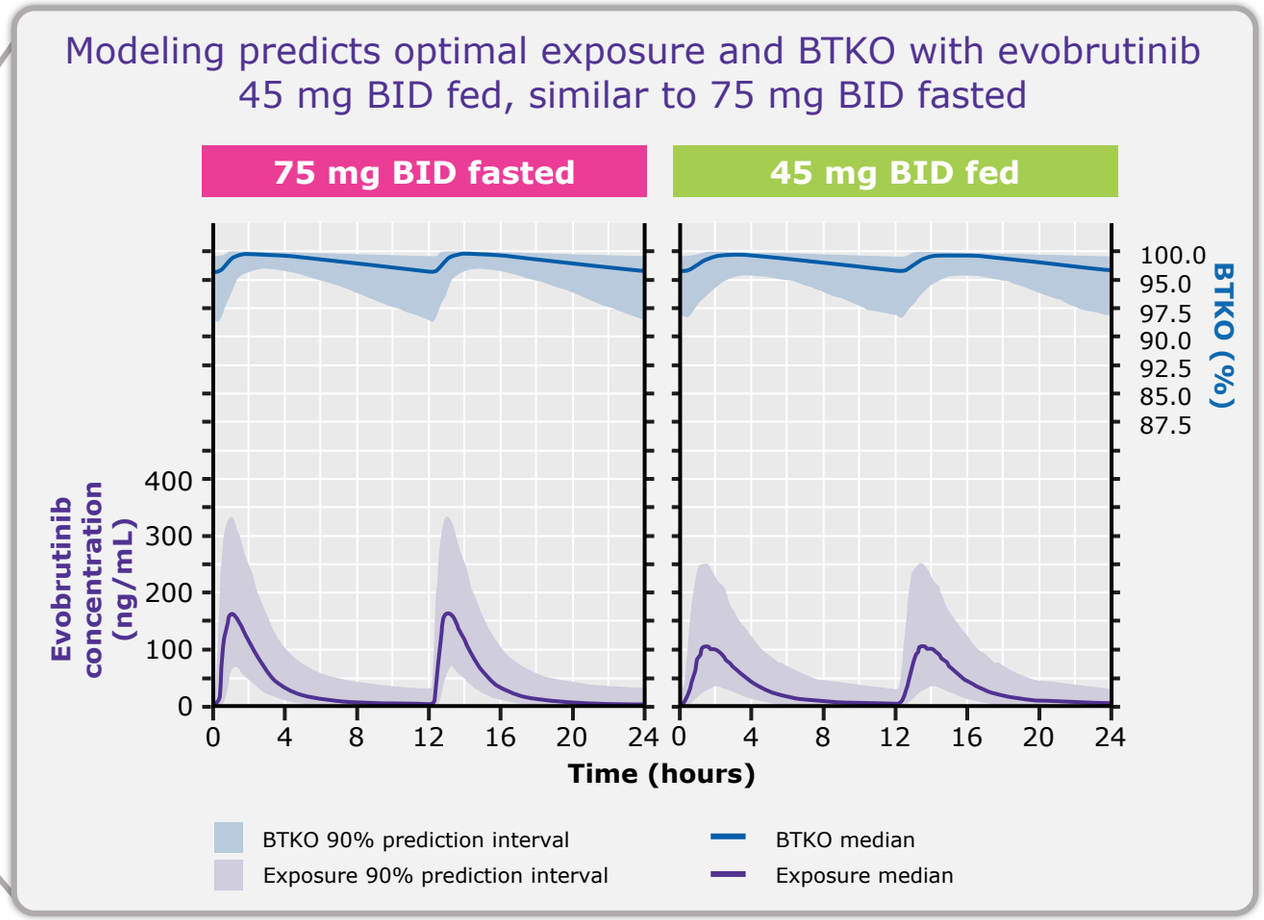


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**BTK occupancy** indicates the fraction of evobrutinib occupying BTK (in PBMCs), **exposure** is the AUC: the area under concentration time profile of evobrutinib in the blood over 24 hours at steady state

**AUC,** area under the concentration-time curve; **BID,** twice daily; **BTKO,** Bruton's tyrosine kinase occupancy; **hr,** hour; **MS**, multiple sclerosis; **PBMCs**, peripheral blood mononuclear cells; **pts,** patients; **QD,** once daily