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# Immune response following mRNA COVID-19 vaccination in patients with multiple sclerosis treated with the Bruton's tyrosine kinase inhibitor evobrutinib

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## CONCLUSIONS

- **Patients with RMS treated with evobrutinib 75 mg BID* were able to mount an antibody response to two doses of mRNA vaccination**
- **The marked increase in antibody levels in seronegative and seropositive patients demonstrates a preserved response to novel and recall antigens in patients with RMS undergoing BTK inhibition with evobrutinib**

**This demonstration of a humoral response to vaccination during evobrutinib treatment is the first such evidence for any BTK inhibitor under investigation for the treatment of MS**

**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 and NCT04338061). Please refer to supplementary data via the QR code for further information*

## INTRODUCTION

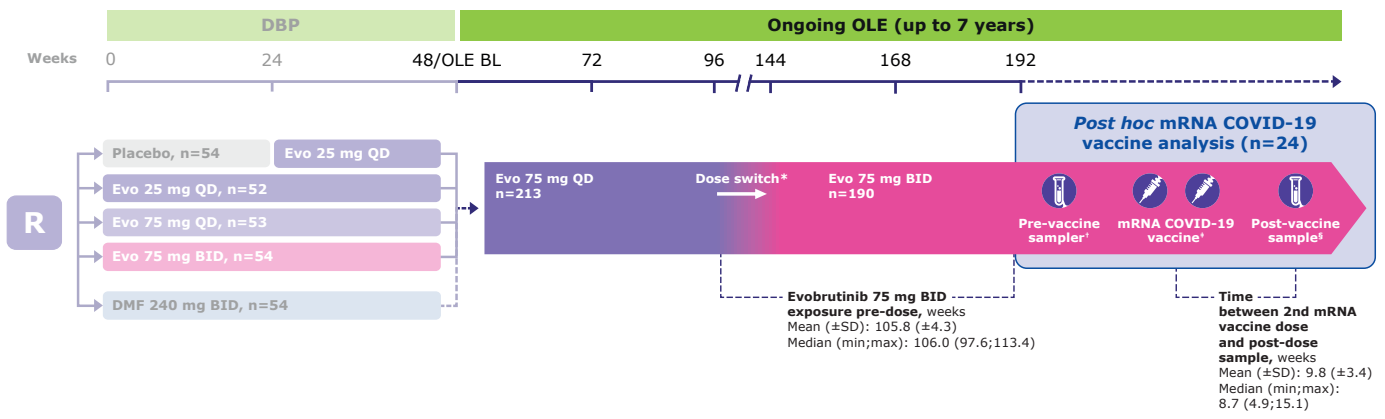
- Evobrutinib is an orally administered, highly selective, CNS-penetrant, covalent BTK inhibitor[1,2]
- In oncology, other BTK inhibitors have been associated with a blunted immune response to recombinant zoster, hepatitis and SARS-CoV-2 vaccines[3,4,5]
  - While BTK inhibitors can blunt the immune response in patients with CLL, dysregulation of the innate and adaptive immune system is a key feature of CLL, and untreated patients can also have a reduced response to vaccines[6]
- In autoimmune diseases the immunogenicity of vaccines may be reduced[7–11]
- A previous analysis showed that patients with SLE receiving evobrutinib could mount a humoral response to seasonal influenza vaccination[12]

## OBJECTIVE

**To examine the humoral response to mRNA COVID-19 vaccination in patients with RMS receiving evobrutinib during the OLE of a Phase II trial (NCT02975349)**

## METHODS

- This *post hoc* analysis included patients with RMS who received evobrutinib 75 mg BID and two doses of mRNA COVID-19 vaccination during the OLE
- Samples were not collected by trial design, but selected:
  - Pre-dose: the latest available sample prior to 1st mRNA vaccine dose
  - Post-dose: sample available ≥28 days after 2nd mRNA vaccine dose



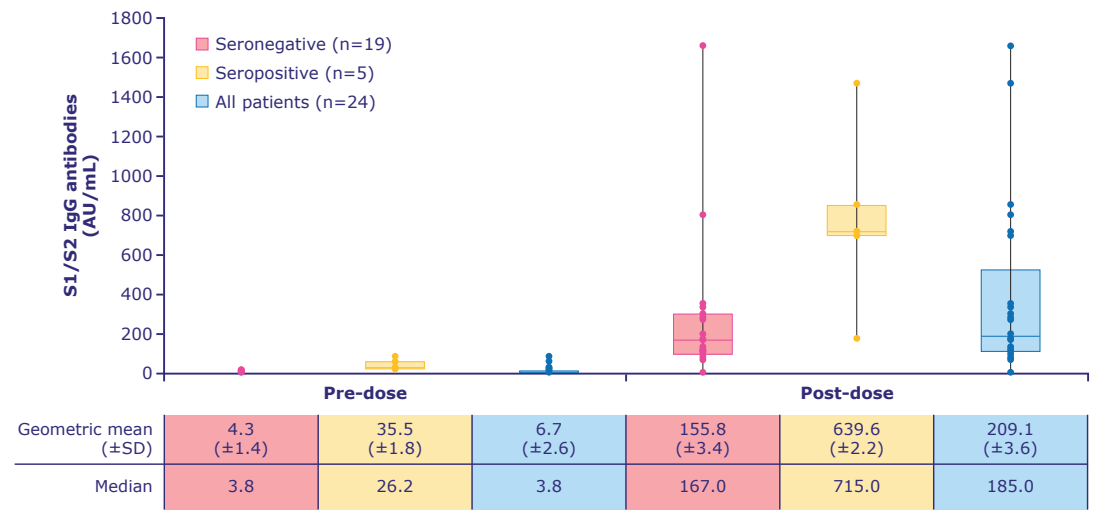

*At Week 48, all patients could enter the OLE, where treatment was initially evobrutinib 75 mg QD before switching to 75 mg BID; †Latest available sample prior to 1st mRNA vaccine dose; ‡As indicated (not by trial design); §Sample available ≥28 days after the 2nd mRNA vaccine dose; ||DiaSorin Molecular LLC, USA

**IgG anti-S1 and anti-S2 specific antibodies to COVID-19 were measured using an indirect chemiluminescence immunoassay|| (LLoQ: 3.8 AU/mL; seronegative <15.0 AU/mL, seropositive ≥15 AU/mL)**

## RESULTS

### S1/S2 IgG antibody response to two doses of mRNA vaccine

- Baseline characteristics of patients in the analysis were:
  - Age, mean (±SD): 44.6 (±10.1) years
  - Female: 79.2%
  - BMI, mean (±SD): 23.4 (±4.1) kg/m$^2$
  - Seronegative prior to vaccination: n=19
  - Seropositive prior to vaccination: n=5
- Of 24 evobrutinib-treated patients, 23 had an increased S1/S2 IgG antibody level after receiving two doses of mRNA vaccine
- An antibody response after receiving the mRNA vaccine was observed independently of whether patients were seronegative or seropositive prior to vaccination. This response was in the range observed for healthy controls and untreated MS patients receiving an mRNA vaccine[13]
  - Seropositive versus seronegative patients achieved higher antibody levels after receiving the mRNA vaccine




| | Pre-dose | | | Post-dose | | |
|---|---|---|---|---|---|---|
| Geometric mean (±SD) | 4.3 (±1.4) | 35.5 (±1.8) | 6.7 (±2.6) | 155.8 (±3.4) | 639.6 (±2.2) | 209.1 (±3.6) |
| Median | 3.8 | 26.2 | 3.8 | 167.0 | 715.0 | 185.0 |

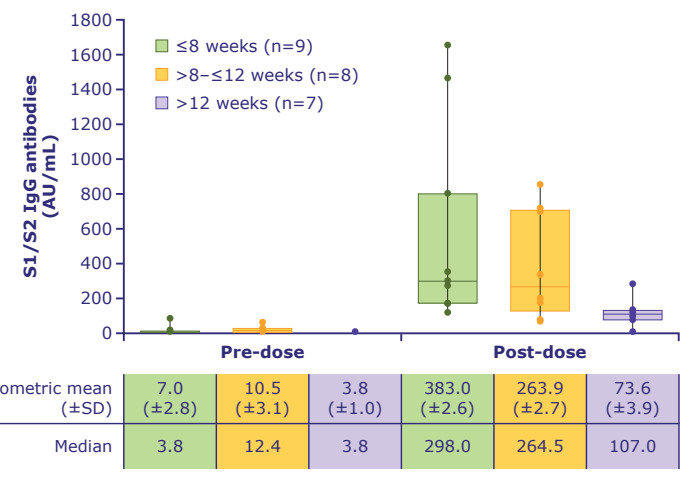
### Antibody levels in patients seropositive or seronegative prior to vaccination

- The majority of patients, whether seronegative or positive, had at least a 10–60 fold induction of S1/S2 IgG antibody levels from pre-dose to post-dose

| Fold changes* | Seronegative patients n=19 | Seropositive patients n=5 | All patients n=24 |
|---|---|---|---|
| ≤1x | 1 (5.3) | 0 (0.0) | 1 (4.2) |
| >1–10x | 0 (0.0) | 1 (20.0) | 1 (4.2) |
| >10–30x | 6 (31.6) | 2 (40.0) | 8 (33.3) |
| >30–60x | 6 (31.6) | 2 (40.0) | 8 (33.3) |
| >60–100x | 5 (26.3) | 0 (0.0) | 5 (20.8) |
| >100x | 1 (5.3) | 0 (0.0) | 1 (4.2) |
| Geometric mean fold change (±SD) | 36.0 (±3.0) | 18.0 (±1.9) | 31.2 (±2.9) |
| Median fold change (min;max) | 34.2 (1.0;275.8) | 18.3 (7.8;34.0) | 32.6 (1.0;275.8) |

*Fold changes are the ratio between the post-dose and pre-dose IgG antibody levels

### Antibody levels over time following mRNA vaccination




| | Pre-dose | | | Post-dose | | |
|---|---|---|---|---|---|---|
| Geometric mean (±SD) | 7.0 (±2.8) | 10.5 (±3.1) | 3.8 (±1.0) | 383.0 (±2.6) | 263.9 (±2.7) | 73.6 (±3.9) |
| Median | 3.8 | 12.4 | 3.8 | 298.0 | 264.5 | 107.0 |

- Time from vaccination to the post-dose sample ranged from 4.9 to 15.1 weeks
- For the majority of patients, the time between 2nd mRNA vaccine dose and antibody assessment was >8 weeks
- With increasing time between the 2nd mRNA vaccine dose and antibody assessment, a lower antibody level was observed

**Abbreviations: AU**, arbitrary units; **BID**, twice daily; **BL**, baseline; **BMI**, body mass index; **BTK**, Bruton's tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **COVID**, coronavirus disease; **CNS**, central nervous system; **DBP**, double-blind period; **DMF**, dimethyl fumarate; **Evo**, evobrutinib; **IgG**, immunoglobulin G; **LLoQ**, lower limit of quantification; **mRNA**, messenger ribonucleic acid; **MS**, multiple sclerosis; **OLE**, open-label extension; **QD**, once daily; **R**, randomization; **RMS**, relapsing multiple sclerosis; **SARS**, Severe acute respiratory syndrome; **SD**, standard deviation; **SLE**, systemic lupus erythematosus; **W**, week

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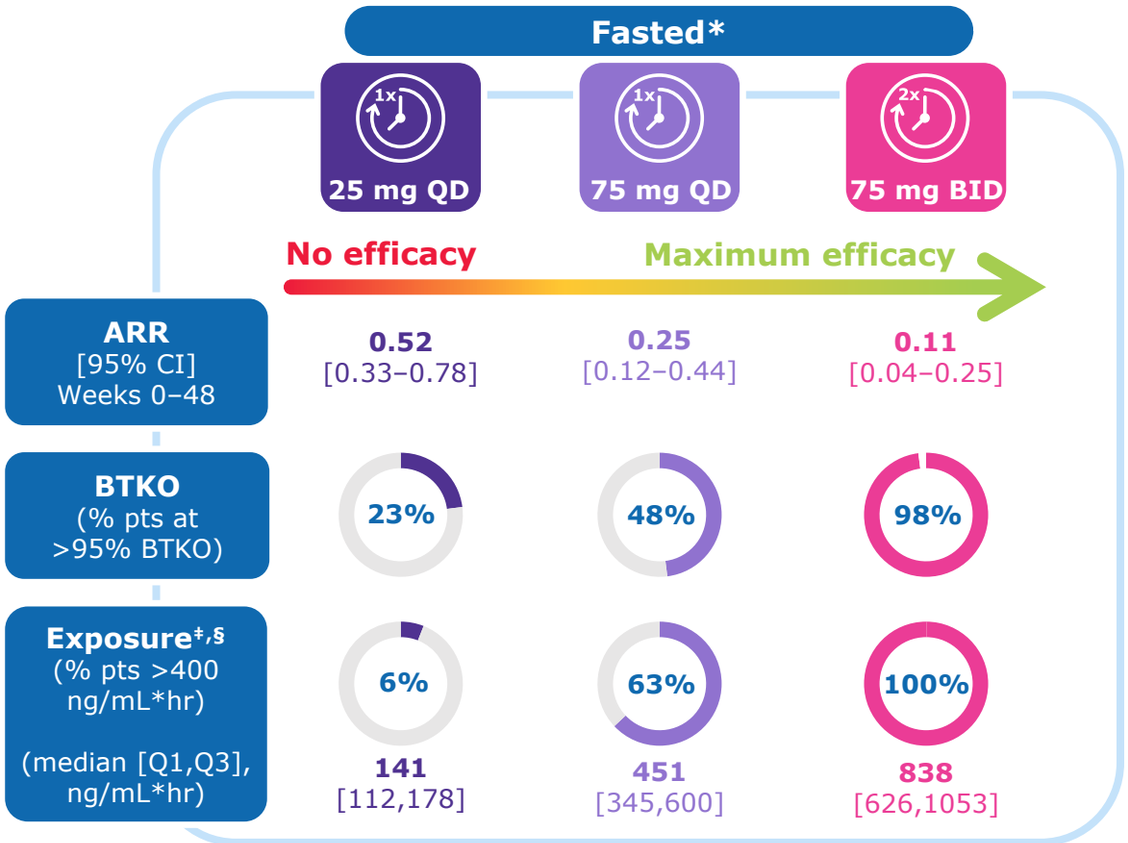
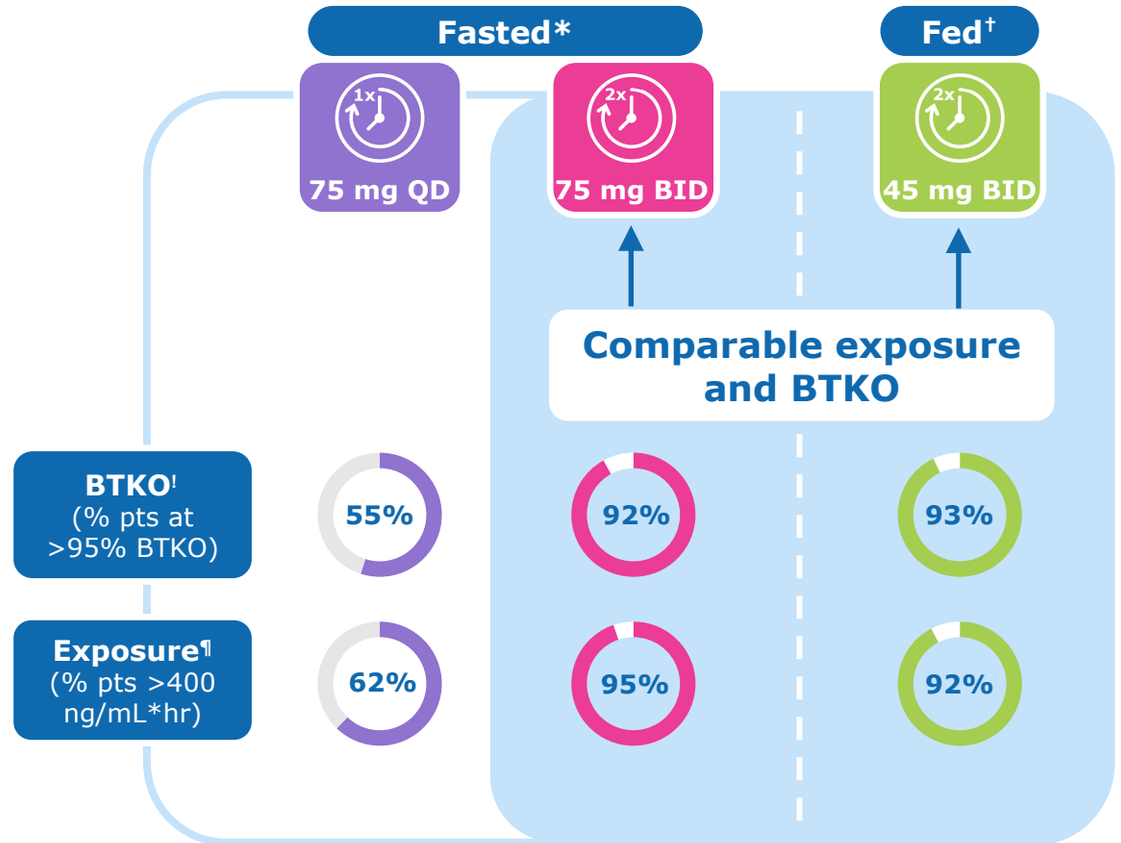
# Evobrutinib dosing for the Phase III trials was optimized for exposure and BTKO levels that correlated with maximal efficacy

## 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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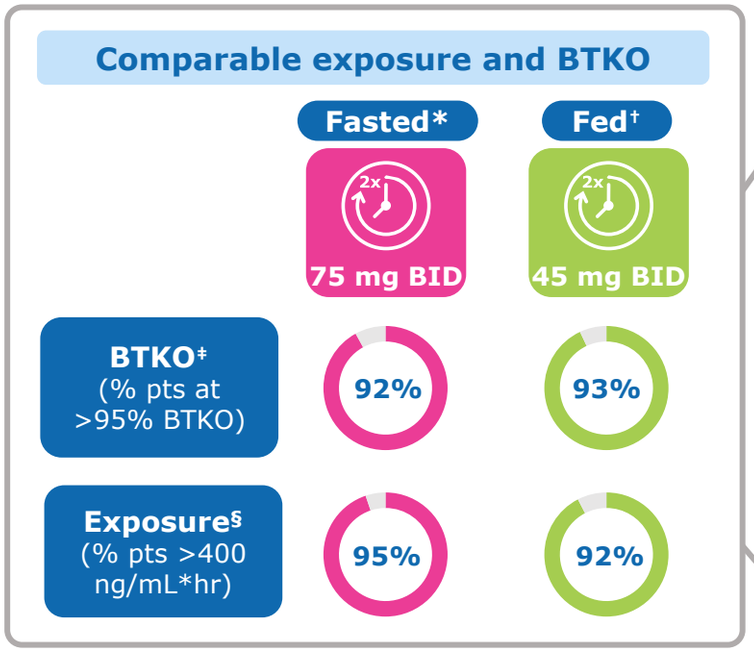


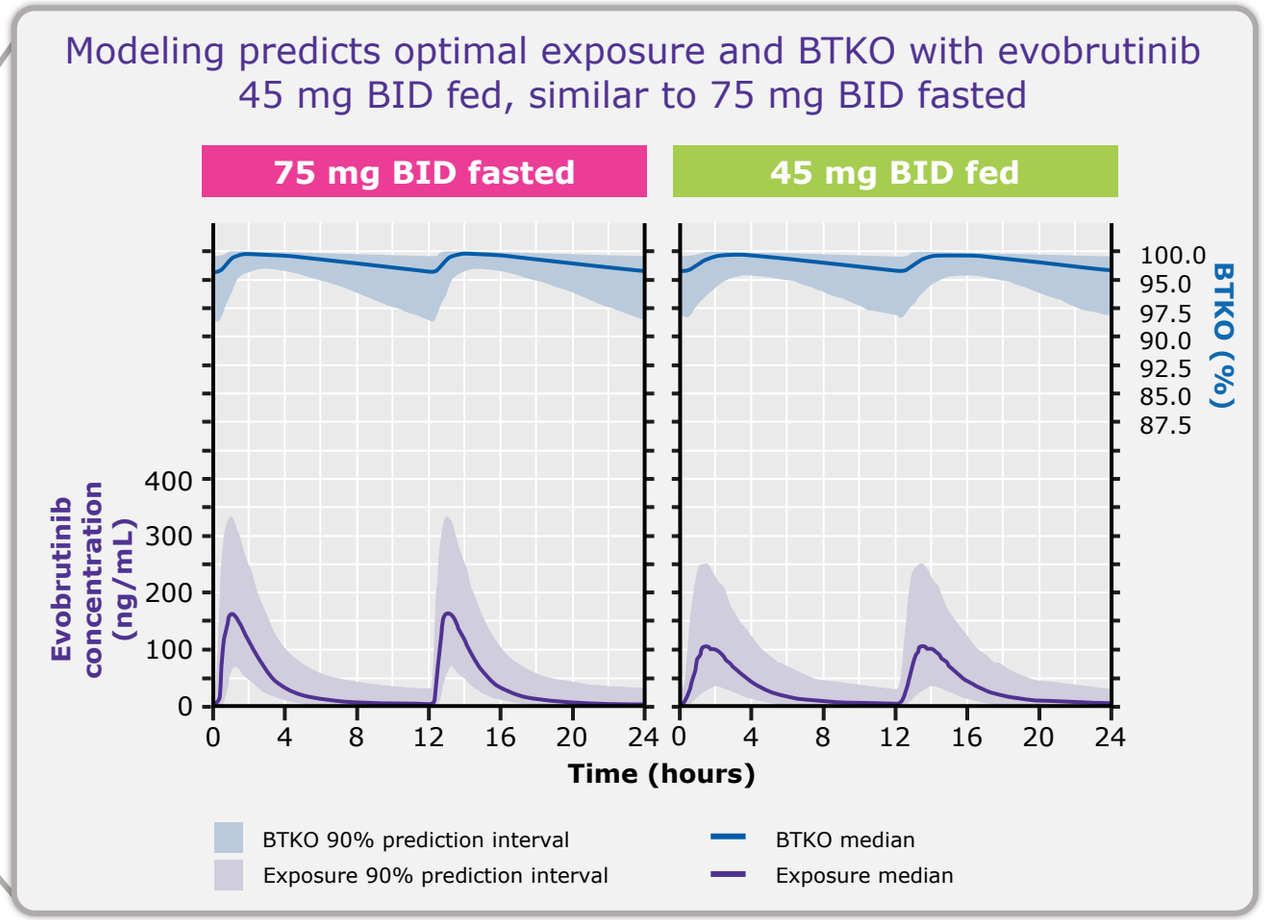


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* Fasted state: >1 hour pre-meal or >2 hours post-meal; † Fed state: with food (high-fat or moderate-fat meal); ‡ Simulated percentage of patients with BTKO >95% over 24 hours at steady state; § Simulated percentage of patients with AUC >400ng/ml*hr over 24 hours

**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