Update on long-term safety and efficacy of evobrutinib, a Bruton's tyrosine kinase inhibitor, over 5 years from an ongoing Phase 2 open-label extension

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CONCLUSIONS

- **Evobrutinib showed sustained clinical efficacy and safety over 5 years of treatment**
  - **Evobrutinib 75 mg BID showed a rapid effect (Week 12) on new T1 Gd⁺ lesions reduction versus placebo. During the OLE, while on 75 mg BID, the number of T1 Gd⁺ lesions remained low**
  - **A low relapse rate was maintained over 5 years with an ARR of 0.11 following a switch to evobrutinib 75 mg BID in the OLE**
- **9 out of 10 patients on evobrutinib treatment had no evidence of clinical worsening (NEcW) in Year 5, indicating the sustained benefit of long-term BID dosing**
- **No new safety signals were observed in the OLE compared with the DBP**

INTRODUCTION

- Evobrutinib is an oral, CNS-penetrant and highly selective BTK inhibitor[1–3]
- Evobrutinib met its primary endpoint (reduction in total cumulative T1 Gd⁺ lesions at Weeks 12–24) in a Phase 2 trial (NCT02975349) in patients with RMS[4]
- The clinical efficacy and safety profile of evobrutinib has remained consistent over 4.5 years of treatment in the ongoing OLE[5–6]
- Evobrutinib is currently being assessed in two ongoing Phase 3 trials* (evolutionRMS 1 and 2) in patients with RMS

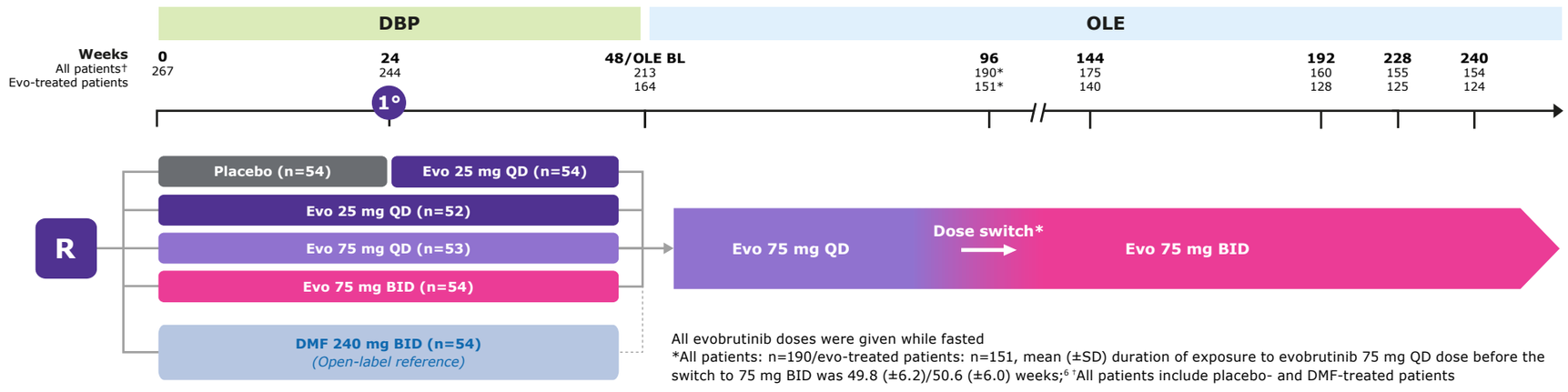
*Evobrutinib 75 mg BID fasted is predicted to be comparable with respect to exposure and BTK occupancy to 45 mg BID with food used in the Phase 3 trials (NCT04338022, NCT04338061)[7]

OBJECTIVES

To report the long-term effect of evobrutinib on efficacy and safety over 5 years (up to Week 240):

- **Mean number of new T1 Gd⁺ lesions**
- **Annualised relapse rate (ARR)**
- **No evidence of clinical worsening (NEcW) in Year 5**
- **Safety profile of evobrutinib**

METHODS

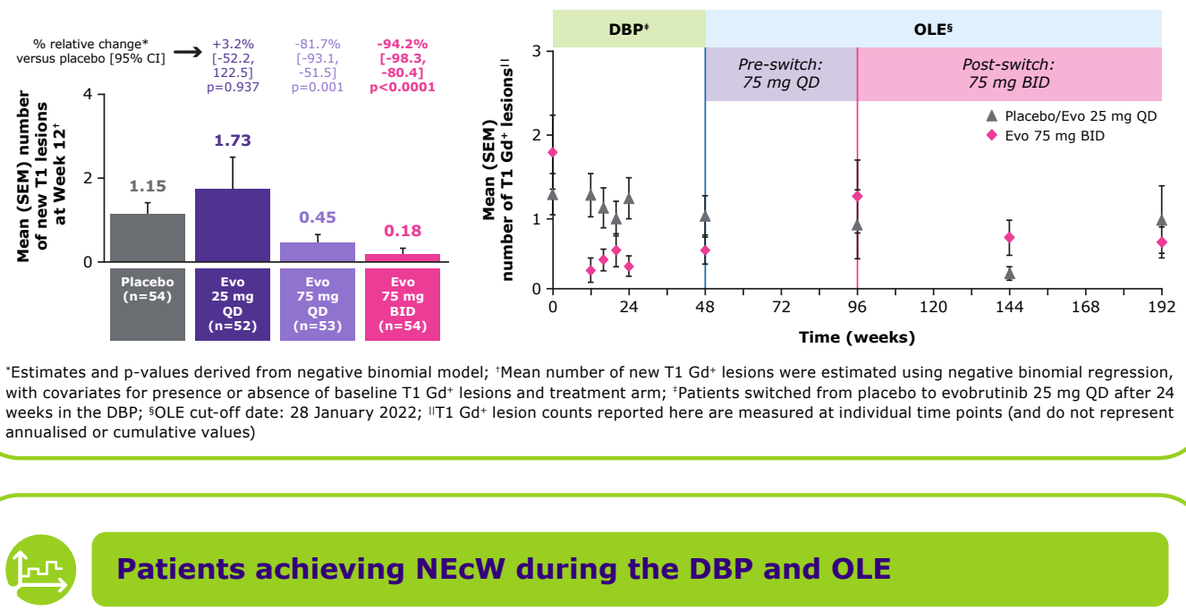


All evobrutinib doses were given while fasted
*All patients: n=190/evo-treated patients: n=151, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2)/50.6 (±6.0) weeks;[6] †All patients include placebo- and DMF-treated patients

RESULTS

Mean number of T1 Gd⁺ lesions

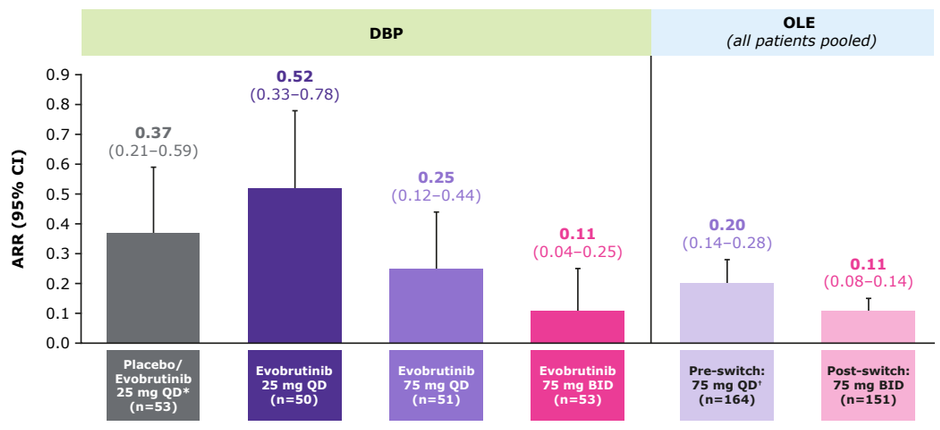
- Evobrutinib 75 mg BID had a rapid effect on new T1 Gd⁺ lesions (94.2% reduction vs placebo at Week 12), sustained up to Week 192 (mean number of T1 Gd⁺ lesions). Notably, the proportion of patients free of new T1 Gd⁺ lesions was higher with BID dosing during the OLE (Week 240: 76.1%) versus QD dosing (Week 96: 70.9%); data not shown



*Estimates and p-values derived from negative binomial model; †Mean number of new T1 Gd⁺ lesions were estimated using negative binomial regression, with covariates for presence or absence of baseline T1 Gd⁺ lesions and treatment arm; ‡Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; §OLE cut-off date: 28 January 2022; ‖T1 Gd⁺ lesion counts reported here are measured at individual time points (and do not represent annualised or cumulative values)

ARR during the DBP and OLE (up to Week 240)

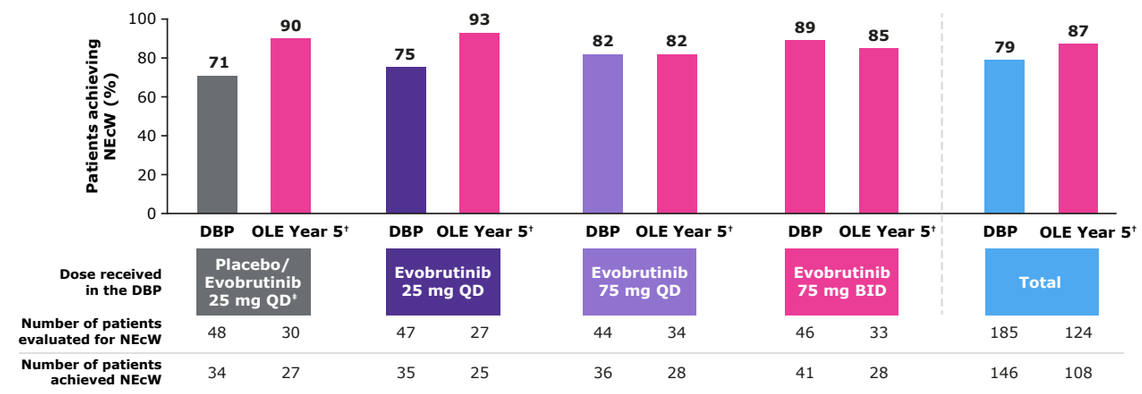
- The reduced ARR observed in the DBP with evobrutinib 75 mg BID was sustained in the OLE



OLE cut-off date: 18 November 2022. Data plotted include evobrutinib DBP treatment arms only and analysis is performed on the mITT population. *Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †Mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 50.6 (±6.0) weeks

Patients achieving NEcW during the DBP and OLE

- Overall, 108/124 (87%) patients achieved NEcW* during OLE Year 5†, indicating the sustained benefit of long-term BID dosing



	Placebo/ Evobrutinib 25 mg QD‡		Evobrutinib 25 mg QD		Evobrutinib 75 mg QD		Evobrutinib 75 mg BID		Total	
Dose received in the DBP										
Number of patients evaluated for NEcW	48	30	47	27	44	34	46	33	185	124
Number of patients achieved NEcW	34	27	35	25	36	28	41	28	146	108

OLE cut-off date: 18 November 2022. *NEcW: no qualified relapses and no 12-week confirmed disability progression (confirmed worsening in Expanded Disability Status Scale). †During OLE Year 5 (Week 192–240), all patients were treated with evobrutinib 75 mg BID; ‡Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP

Safety during OLE period (OLE BL–Week 240)

	Total* N=164 n (%)
Most common TEAEs occurring in ≥5% of patients	
Nasopharyngitis	25 (15.2)
Lipase increased	23 (14.0)
COVID-19	18 (11.0)
Headache	17 (10.4)
Urinary tract infection	16 (9.8)
Upper respiratory tract infection	16 (9.8)
Back pain	10 (6.1)
Pain in extremity	9 (5.5)
Any treatment-related serious TEAE	4† (2.4)
TEAEs leading to treatment withdrawal	9 (5.5)
Any TEAE leading to death *(all considered unrelated to treatment)*	2‡ (1.2)

OLE cut-off date: 18 November 2022. *Total excludes DMF data; †Four treatment-related serious TEAEs were: breast abscess (n=1, placebo/evobrutinib 25 mg QD); lipase increased (n=1, evobrutinib 25 mg QD); osteonecrosis (n=2, evobrutinib 75 mg QD); ‡Two fatal events occurred in patients receiving evobrutinib in the DBP, which were not deemed to be treatment-related by the investigators (evobrutinib 25 mg QD [n=1]: COVID-19 pneumonia [unvaccinated]; evobrutinib 75 mg BID [n=1]: *E. coli* sepsis with febrile state and acute tubulointerstitial nephritis)

Abbreviations: ARR, annualised relapse rate; **BID**, twice daily; **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 intent-to-treat; **NEcW**, no evidence of clinical worsening; **OLE**, open-label extension; **QD**, once daily; **R**, randomisation; **RMS**, relapsing multiple sclerosis; **SD**, standard deviation; **SEM**, standard error of mean; **TEAE**, treatment-emergent adverse events

References: 1. Haselmayer P, et al. *J Immunol.* 2019;202(10):2888–2906; 2. Caldwell RD, et al. *J Med Chem.* 2019;62(17):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. Montalban X, et al. *Eur J Neurol.* 2023;30(Suppl. 1):248 (EPR-191); 6. Montalban X, et al. *Mult Scler.* 2023;29(Suppl. 2):53 (P075); 7. Papasouliotis O, et al. *Clin Transl Sci.* 2022;15(12):2888–2898

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