Efficacy and safety of the Bruton's tyrosine kinase inhibitor evobrutinib for relapsing multiple sclerosis over 3.5 years of treatment: an ongoing Phase II open-label extension

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CONCLUSIONS

Evobrutinib efficacy and safety data, for >3.5 years of treatment in patients with RMS, continue to show maintained treatment benefits, with no new safety signals

ARR, before and after switch to evobrutinib 75 mg BID in the OLE, support BID dosing* as the optimal dose for maximal efficacy

***Evobrutinib 75 mg BID fasted – predicted to be comparable, with respect to exposure and BTK occupancy, to the 45 mg BID fed dose used in Phase III (NCT04338022, NCT04338061)[1]**

INTRODUCTION

Evobrutinib
- A highly selective, CNS-penetrant, covalent Bruton's tyrosine kinase inhibitor[2–4]

Phase II RCT in RMS (NCT02975349) DBP
- T1 Gd+ lesions versus placebo were reduced with evobrutinib treatment (W24, primary endpoint)[5]
- ARR: 0.08 (W24), 0.11 (W48) for evobrutinib 75 mg BID[5]
- Evobrutinib was generally well tolerated. Transient treatment-related elevated liver aminotransferases reported in the DBP during initiation (<24W) were asymptomatic and reversible on treatment discontinuation[5]

OLE period
- DBP safety profile maintained over 2.5 years in the OLE[6]
- ARR remained low during the OLE (0.12, evobrutinib 75 mg BID DBP arm)[6]

OBJECTIVE

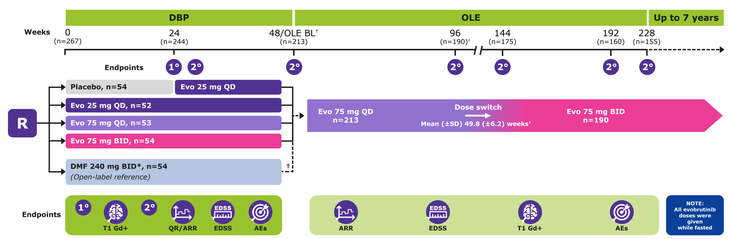
To report the efficacy and safety of evobrutinib for >3.5 years of treatment in the OLE of a Phase II trial in patients with RMS

- ARR
- Number of T1 Gd+ lesions
- Mean EDSS score
- Adverse events

METHODS

DBP (48-weeks), randomized 1:1:1:1:1
- Placebo (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 reference arm

Optional OLE starting at Week 48
- After initial treatment with evobrutinib 75 mg QD at the beginning of the OLE, patients switched to evobrutinib 75 mg BID (mean [±SD] duration: 49.8 [±6.2] weeks)
- Switched to evobrutinib 75 mg BID

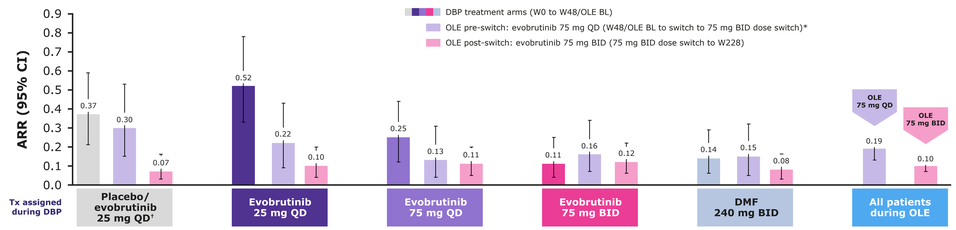


*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment; †DMF arm had a minimum 4-week washout period; ‡n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks

RESULTS

ARR: DBP and OLE (W0–228)
OLE cut-off date: January 28, 2022

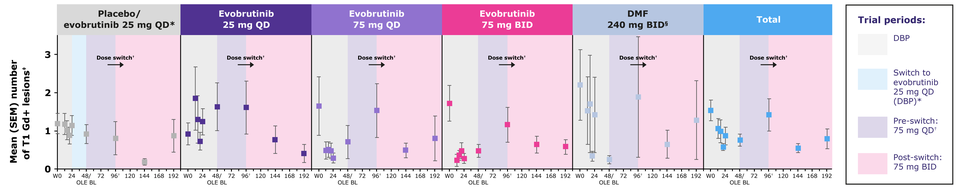
- The total ARR up to W228, pooled across treatment arms, was reduced after patients switched to 75 mg BID dose (0.10), when compared with the pre-switch 75 mg QD dose (0.19)
- Overall, the total ARR, across all treatment arms, remained low during the OLE up to W228 (0.13)



*n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks; †Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP
ARR [95% CI] for the OLE period, from W48/OLE BL to W228, for each DBP treatment arm was: placebo/evobrutinib 25 mg QD, 0.15 [0.08–0.23]; evobrutinib 25 mg QD, 0.14 [0.08–0.23]; evobrutinib 75 mg QD, 0.12 [0.07–0.19]; evobrutinib 75 mg BID, 0.14 [0.08–0.21]; DMF, 0.10 [0.05–0.17]; total, 0.13 [0.10–0.16]

T1 Gd+ lesions: DBP and OLE (W0–192)
OLE cut-off date: January 28, 2022

- Overall, the mean number of T1 Gd+ lesions remained low, except a temporary increase from W48/OLE BL to W96 while on 75 mg QD which was decreased following the switch to 75 mg BID in OLE

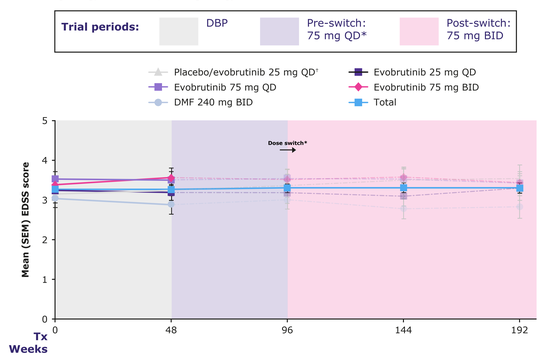


*Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks; ‡T1 Gd+ lesion counts reported here are measured at individual time points (and do not represent annualized or cumulative values); §Wide error bars in the DMF were driven by a small number of patients who exhibited a high number of lesions; ¶Week 48/OLE BL, DMF arm had a minimum 4-week washout period

Number of patients	Week 0	Week 12	Week 16	Week 20	Week 24	Week 48¶	Week 96†	Week 144	Week 192
Placebo + evobrutinib 25 mg QD*	53	51	51	49	43	39	36	32	30
Evobrutinib 25 mg QD	50	46	46	44	46	38	38	30	27
Evobrutinib 75 mg QD	51	49	49	48	48	42	40	35	35
Evobrutinib 75 mg BID	53	47	47	46	47	44	44	39	36
DMF 240 mg BID	54	53	52	50	50	48	46	37	32
Total	261	246	245	237	234	211	204	173	160

Mean EDSS score: DBP and OLE (W0–192)
OLE cut-off date: January 28, 2022

- 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])



*n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks; †Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP

TEAEs during the OLE to W228 or discontinuation
OLE cut-off date: June 27, 2022

- Overall, TEAEs were mild/moderate in the OLE
- No dose dependent increase in TEAEs was observed in the patients who switched to evobrutinib 75 mg BID in the OLE
- There were eleven Grade ≥3 infections.

TEAEs in patients who reached at least W228 or discontinued

Patients, n (%)	Dose received in the DBP*					Total (n=213)
	Placebo/ evobrutinib 25 mg QD (n=39)	Evobrutinib 25 mg QD (n=39)	Evobrutinib 75 mg QD (n=42)	Evobrutinib 75 mg BID (n=44)	DMF 240 mg BID (n=49)	
Any TEAE	33 (84.6)	29 (74.4)	41 (97.6)	39 (88.6)	36 (73.5)	178 (83.6)
Any Grade 3 TEAE†	5 (12.8)	11 (28.2)	7 (16.7)	6 (13.6)	14 (28.6)	43 (20.2)
Any Grade 4 TEAE†	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	1 (2.0)	3 (1.4)
Any treatment-related TEAE	10 (25.6)	5 (12.8)	12 (28.6)	14 (31.8)	19 (38.8)	60 (28.2)
Any serious TEAE	7 (17.9)	11 (28.2)	5 (11.9)	5 (11.4)	10 (20.4)	38 (17.8)
Any treatment-related serious TEAE	1 (2.6)	1 (2.6)	2 (4.8)	0 (0.0)	3 (6.1)	7 (3.3)‡
TEAEs leading to treatment withdrawal	4 (10.3)	3 (7.7)	0 (0.0)	1 (2.3)	8 (16.3)	16 (7.5)
Any TEAE leading to death	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.3)	1 (2.0)	3 (1.4)§

*At Week 48, patients could enter the OLE and received evobrutinib 75 mg QD (mean [±SD] duration: 49.8 [±6.2] weeks) and then switched to 75 mg BID. †According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. ‡Seven treatment-related serious TEAEs were: breast abscess (n=1, placebo/evo 25 mg QD); lipase increased (n=1, evo 25 mg QD); osteonecrosis (n=2, evo 75 mg QD); hepatitis (n=1, DMF 240 mg BID); pyelonephritis acute (n=1, DMF 240 mg BID); hepatitis toxic (n=1, DMF 240 mg BID). §There were three fatal events in the OLE, all were considered not to be treatment related (evobrutinib 25 mg QD [n=1]: COVID-19 pneumonia; DMF 240 mg BID [n=1]: COVID-19 pneumonia; evobrutinib 75 mg BID [n=1]: *E. coli* sepsis with febrile state and acute tubulointerstitial nephritis)

Abbreviations: AE, adverse events; **ARR**, annualized 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; **EDSS**, Expanded Disability Status Scale; **Evo**, evobrutinib; **Gd+**, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **OLE**, open-label extension; **QD**, once daily; **R**, randomization; **RCT**, randomized controlled trial; **RMS**, relapsing multiple sclerosis; **SEM**, standard error of mean; **TEAE**, treatment-emergent adverse event; **Tx**, treatment; **W**, weeks

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XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Bayer, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, F. Hoffmann-La Roche Ltd., Immunic, Janssen Pharmaceuticals, Medday, the healthcare business of Merck KGaA, Darmstadt, Germany, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS. **JW** has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities with Avotres, Brainstorm Cell Therapeutics, Cleveland Clinic Foundation, EMD Serono, Inmagene, MedDay, Novartis/Sandoz, Roche/Genentech, Sanofi Genzyme and University of Alabama; royalties are received for outlicensed monoclonal antibodies through UTHealth from Millipore Corporation. **DA** reports consulting fees from Albert Charitable Trust, Alexion Pharma, Biogen, Celgene, Frequency Therapeutics, Genentech, Med-Ex Learning, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Population Council, Receptos, Roche and Sanofi-Aventis; grants from Biogen, Immunotec and Novartis; and an equity interest in NeuroRx. **MW** has received travel funding and/or speaker honoraria from Biogen-Idec, EMD Serono, Novartis, F. Hoffmann-La Roche, TEVA, Bayer, and Genzyme. **KPS** has received travel funding and/or speaker honoraria from EMD Serono, Sanofi-Aventis, Biogen Idec, TEVA, F. Hoffmann-La Roche, and has served on scientific advisory boards for Sanofi-Aventis and Biogen Idec. **DT** is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany, and received stock or an ownership interest from Novartis. **AS** and **HG** are employees of the healthcare business of Merck KGaA, Darmstadt, Germany. The authors thank the patients and their families, as well as the investigators and study teams, for their participation in this study. Medical writing assistance was provided by Bioscript Group Ltd, Macclesfield, UK and supported by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). Evobrutinib is currently in Phase III trials for relapsing multiple sclerosis and has not yet been approved by any regulatory authority.

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