P001

Safety and efficacy of evobrutinib, a Bruton's tyrosine kinase inhibitor in relapsing multiple sclerosis over 2.5 years of the open-label extension to a Phase II trial

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Disclosures

Xavier Montalban 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, **Merck KGaA, Darmstadt, Germany,** Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

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Introduction

Evobrutinib

- Highly selective, covalent Bruton's tyrosine kinase inhibitor[1,2]
- Presence in CSF of MS patients demonstrates potential to have effects in the CNS[3]

Phase II RCT in RMS
(NCT02975349)
DBP Results

- Significant reduction in T1 Gd+ lesions vs to placebo at Week 24 (primary endpoint)[4]
- ARR at Weeks 24 and 48 was 0.08 and 0.11, respectively, in patients receiving evobrutinib 75 mg BID[4]
- Transient treatment-related elevated liver aminotransferases reported in the DBP were asymptomatic and reversible[4]

Previous results from ongoing OLE

- ARR at Week 108 (i.e. OLE Week 60) was 0.12 in patients receiving evobrutinib 75 mg BID in DBP[5,6]
- The safety of evobrutinib treatment was similar to that seen in the 48-week DBP[7]
- Elevated liver aminotransferases were not observed in the OLE after the switch to evobrutinib 75 mg BID[7]
- Changes in immune cells and Ig levels over 96 weeks (i.e. OLE Week 48) were consistent with those observed in the DBP and were not associated with an increased risk of infection[7]

ARR, annualized relapse rate; **BID,** twice daily; **CNS,** central nervous system; **CSF,** cerebrospinal fluid; **DBP,** double-blind period; **Gd+**, gadolinium-enhancing; **Ig,** immunoglobulin; **MS**, multiple sclerosis; **OLE,** open-label extension; **RCT**, randomized control trial; **RMS**, relapsing multiple sclerosis

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Objectives

To report safety and efficacy of evobrutinib in the treatment of relapsing MS over 2.5 years (i.e. ≥132 weeks) in an OLE, including:

1. Safety profile of evobrutinib when all OLE participants had been treated with evobrutinib for at least 132 weeks (or discontinued)
2. Effects of evobrutinib on $CD19^{+}$ B cells and incidence of infections
3. Effects of evobrutinib on Ig levels
4. Efficacy of evobrutinib measured as ARR and mean EDSS score

ARR, annualized relapse rate; **EDSS,** Expanded Disability Status Scale; **Ig,** immunoglobulin; **MS,** multiple sclerosis; **OLE,** open-label extension

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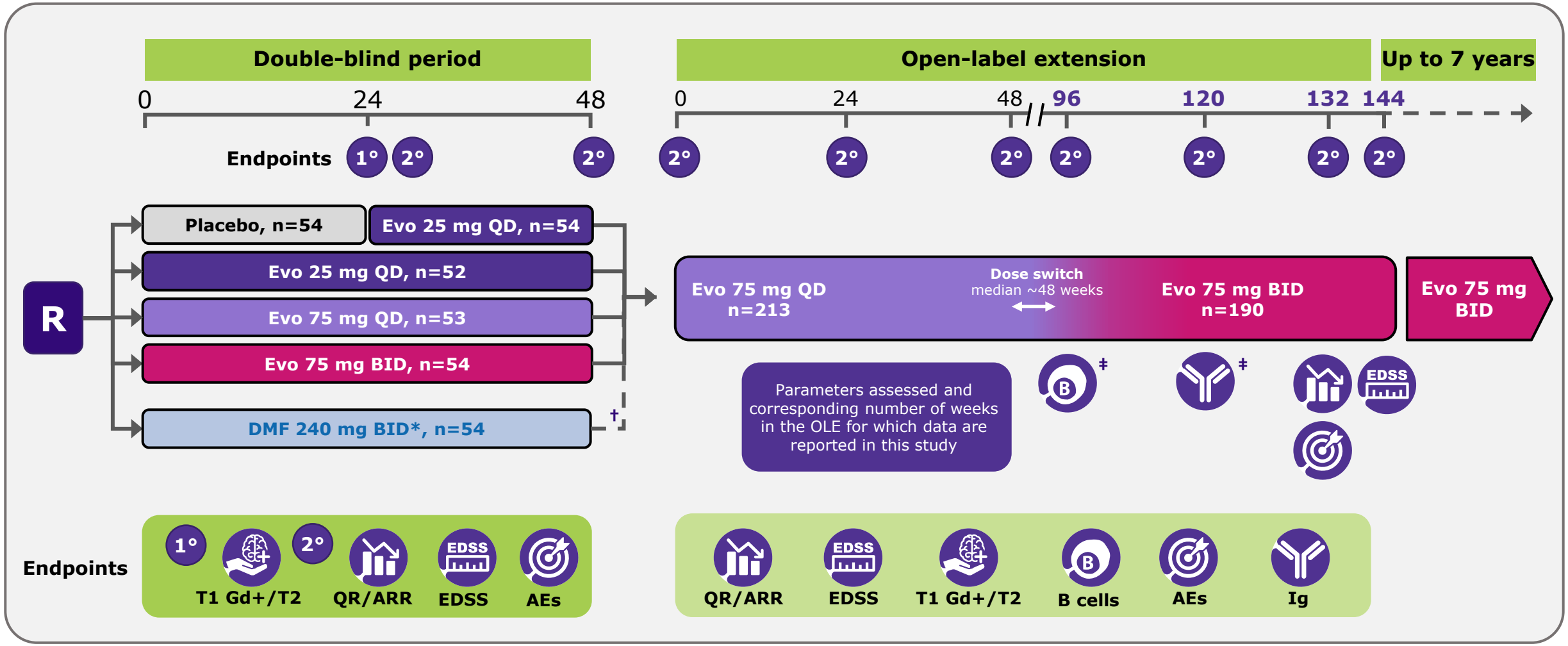
Study design



*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment; †4 week washout; ‡Ig and B cells also sampled during double-blind period
AE, adverse events; **ARR,** annualized relapse rate; **BID,** twice daily; **DMF,** dimethyl fumarate; **EDSS,** Expanded Disability Status Scale; **Evo,** evobrutinib; **Gd+**, gadolinium-enhancing; **Ig,** immunoglobulin; **OLE,** open-label extension; **QD,** once daily; **QR,** qualifying relapses; **R,** randomization

Safety

TEAEs when all participants have reached at least OLE Week 132 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 (n=49)	
Any TEAE	30 (76.9)	27 (69.2)	38 (90.5)	34 (77.3)	36 (73.5)	165 (77.5)
Any Grade 3 TEAE†	4 (10.3)	6 (15.4)	7 (16.7)	6 (13.6)	13 (26.5)	36 (16.9)
Any Grade 4 TEAE†	0 (0.0)	1 (2.6)	0 (0.0)	2 (4.5)	1 (2.0)	4 (1.8)
Any TEAE leading to death	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.3)	1 (2.0)	3 (1.4)
Any treatment-related TEAE	9 (23.1)	6 (15.4)	11 (26.2)	14 (31.8)	19 (38.8)	59 (27.7)
Any serious TEAE	6 (15.4)	8 (20.5)	5 (11.9)	4 (9.1)	9 (18.4)	32 (15.0)
Any treatment-related serious TEAE	0 (0.0)	1 (2.6)	2 (4.8)	0 (0.0)	3 (6.1)	6 (2.8)‡
TEAEs leading to treatment withdrawal	4 (10.3)	2 (5.1)	0 (0.0)	1 (2.3)	7 (14.3)	14 (6.6)§

- Overall TEAEs were mild/moderate in the OLE period
- No dose dependent increase in TEAEs was observed in those patients who switched to evobrutinib 75 mg BID
- There were nine Grade ≥3 infections; three were fatal but none of these were considered treatment-related (COVID-19 pneumonia [n=2]; *E. coli* sepsis [n=1])

*All patients were switched to evobrutinib 75 mg QD at end of week 48 DBP for an average of ~48 weeks in OLE and then switched to 75 mg BID
†According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. ‡Six treatment-related serious TEAEs were: lipase increased (n=1, evo 25 mg QD); osteonecrosis (n=2, evo 75 mg QD); hepatitis (n=1, DMF); pyelonephritis acute (n=1, DMF); and hepatitis toxic (n=1, DMF). §Seven withdrawals were due to elevated liver enzymes: amylase increased (n=1, placebo/evo 25 mg QD); lipase increased (n=3, placebo/evo 25 mg QD; n=1, evo 25 mg QD; n=1, DMF); liver function test increased (n=1, DMF)
BID, twice daily; **DBP,** double-blind period; **DMF,** dimethyl fumarate; **evo,** evobrutinib; **OLE,** open-label extension; **QD,** once daily; **TEAE,** treatment emergent adverse events

Safety

Top 5 most common TEAEs during the OLE (occurring in ≥5% of patients across previous DBP treatment groups)

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 (n=49)	
Nasopharyngitis	4 (10.3)	6 (15.4)	6 (14.3)	6 (13.6)	2 (4.1)	24 (11.3)
Lipase increased	3 (7.7)	4 (10.3)	5 (11.9)	7 (15.9)	5 (10.2)	24 (11.3)
Headache	2 (5.1)	2 (5.1)	5 (11.9)	5 (11.4)	3 (6.1)	17 (8.0)
Upper respiratory tract infection	3 (7.7)	2 (5.1)	4 (9.5)	2 (4.5)	1 (2.0)	12 (5.6)
Urinary tract infection	5 (12.8)	4 (10.3)	1 (2.4)	2 (4.5)	1 (2.0)	13 (6.1)

*All patients were switched to evobrutinib 75 mg QD at end of week 48 DBP for an average of ~48 weeks in OLE and then switched to 75 mg BID
BID, twice daily; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily; **TEAEs**, treatment-emergent adverse events

Safety

CD19+ B cell counts for all patients in OLE and relationship to infections and infestations

	Range	OLE W0* N (%) (n=213)	OLE W0 (Mean ± SD cells/µL)	OLE W96 N (%) (n=165)	OLE W96 (Mean ± SD cells/µL)
B cells (CD19+)	**Low** (<107 cells/µL)	27 (13)	84.7 ± 19.1	85 (52)	66.7 ± 22.5
	Normal (107–698 cells/µL)	184 (86)	232.0 ± 113.6	80 (48)	181.2 ± 81.8
	High (>698 cells/µL)	2 (1)	750.0 ± 24.0	0 (0)	N/A

- Observed B cell levels did not appear to be associated with Grade ≥2 infection and infestations incidence:
  - EAIR of infection **before** first low B cell count occurrence: 14.25 [95% CI: 10.35, 19.12]; PY: 309
  - EAIR of infection **after** first low B cell count occurrence: 10.01 [95% CI: 5.72, 16.25]; PY: 160

*OLE W0 visit corresponds to the assessment carried out at the W48 DBP visit
OLE W0 median range (based on original treatment group): CD19+ B cells 175–230 cells/µL; OLE W96 median range: CD19+ B cells 89–128 cells/µL
EAIR indicates events per 100 patient-years for a given B cell condition. EAIR is calculated as number of patients experiencing the TEAE of interest during OLE, divided by the sum of the individual time of patients according to exposure to normal B cells (i.e. prior to first assessment of low B cells or after first assessment of low B cells)
CI, confidence interval; **DBP,** double-blind period; **EAIR,** exposure-adjusted incidence rate; **N/A,** not applicable; **OLE,** open-label extension; **PY**, patient years; **SD,** standard deviation; **TEAEs**, treatment-emergent adverse events; **W,** week

Safety
Change in Ig levels from OLE Week 0 to Week 120

Immunoglobulin	Range	OLE W0* N (%) (n=213)	OLE W0 (Mean ± SD g/L)	OLE W120 N (%) (n=160)	OLE W120 (Mean ± SD g/L)
IgG	**Low** (<7 g/L)	19 (9)	6.3 ± 0.6	14 (9)	6.3 ± 0.6
	Normal (7–16 g/L)	194 (91)	10.0 ± 1.9	146 (91)	10.3 ± 2.0
	High (>8 g/L)	0 (0)	N/A	0 (0)	N/A
IgA	**Low** (<0.7 g/L)	0 (0)	N/A	0 (0)	N/A
	Normal (0.7–4.0 g/L)	208 (98)	2.1 ± 0.7	141 (88)	2.4 ± 0.8
	High (>4.0 g/L)	5 (2)	4.8 ± 0.4	19 (12)	4.7 ± 0.7
IgM	**Low** (<0.4 g/L)	7 (3)	0.3 ± 0.04	25 (16)	0.3 ± 0.06
	Normal (0.4–2.3 g/L)	196 (92)	1.1 ± 0.5	132 (83)	1.0 ± 0.4
	High (>2.3 g/L)	10 (5)	2.8 ± 0.4	3 (2)	3.7 ± 1.5

At OLE W120, most patients had IgG (91.0%), IgA (88.0%) and IgM (83.0%) within normal ranges

*OLE W0 visit corresponds to the assessment carried out at W48 DBP visit
OLE W0 median range (range based on original treatment group): IgG 8.93–9.87 g/L, IgA 1.91–2.28 g/L, IgM 0.88–1.17 g/L
OLE W120 median range: IgG 9.09–10.22 g/L, IgA 2.14–3.04 g/L, IgM 0.73–0.88 g/L
DBP, double-blind period; **Ig,** immunoglobulin; **N/A,** not applicable; **OLE,** open-label extension, **SD,** standard deviation; **W,** week

Efficacy

OLE ARR pre- and post-OLE dose switch from 75 mg QD to 75 mg BID

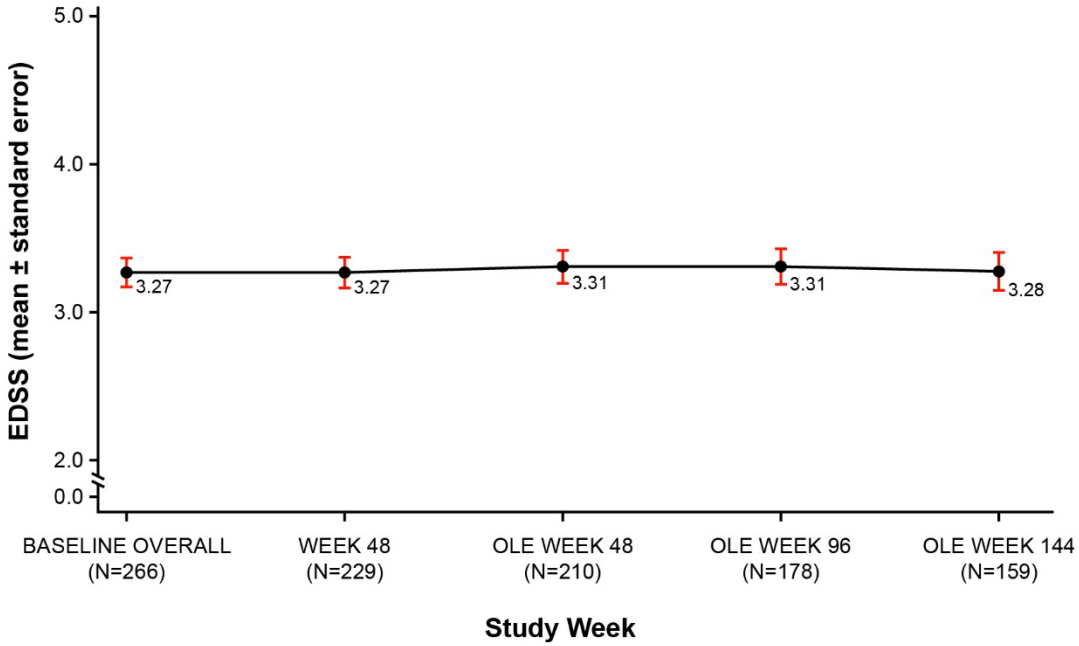
OLE period	Statistics	Dose received in the DBP*					Total (n=213)
		Placebo/ Evobrutinib 25 mg QD (n=39)	Evobrutinib 25 mg QD (n=39)	Evobrutinib 75 mg QD (n=42)	Evobrutinib 75 mg BID (n=44)	DMF (n=49)	
OLE W0 to switch from evobrutinib 75 mg QD to 75 mg BID dose†	**ARR**	**0.30**	**0.22**	**0.13**	**0.16**	**0.15**	**0.19**
	95% CI	[0.15, 0.53]	[0.09, 0.43]	[0.04, 0.31]	[0.07, 0.34]	[0.05, 0.32]	[0.13, 0.26]
From time of switch to evobrutinib 75 mg BID until OLE W132†	**ARR**	**0.10**	**0.13**	**0.07**	**0.11**	**0.10**	**0.10**
	95% CI	[0.03, 0.22]	[0.05, 0.27]	[0.02, 0.18]	[0.04, 0.23]	[0.04, 0.22]	[0.07, 0.14]
OLE W0 to OLE W132	**ARR**	**0.18**	**0.17**	**0.09**	**0.13**	**0.12**	**0.14**
	95% CI	[0.10, 0.29]	[0.09, 0.28]	[0.04, 0.18]	[0.07, 0.22]	[0.06, 0.21]	[0.11, 0.17]

- ARR was numerically lower following switch from evobrutinib 75 mg QD to BID dosing in OLE
- In patients receiving evobrutinib 75 mg BID in the DBP, ARR at OLE Week 132 was 0.13, and for the whole OLE period‡ was 0.12 [95% CI 0.07–0.20]

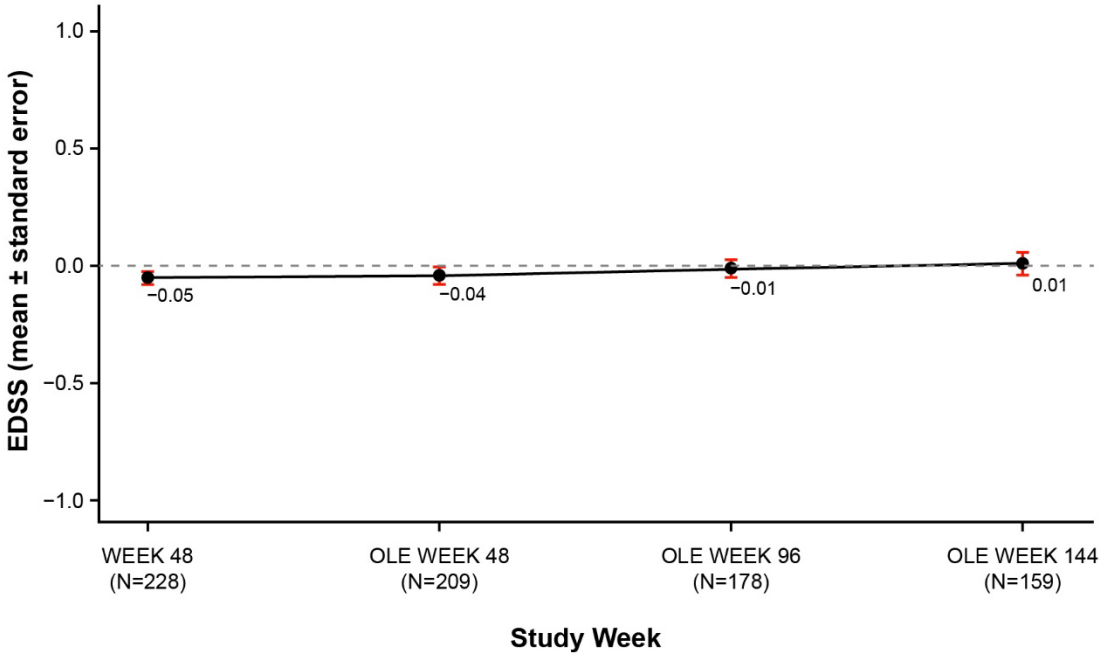
*All patients were switched to evobrutinib 75 mg QD at end of week 48 DBP for an average of ~48 weeks in OLE and then switched to 75 mg BID
†OLE dose switch (from evobrutinib 75 mg QD to evobrutinib 75 mg BID) occurred at a median of 48 weeks; ‡Cut-off 25 May 2021
ARR, annualized relapse rate; **BID,** twice daily; **CI,** confidence interval; **DBP,** double-blind period; **DMF,** dimethyl fumarate; **OLE,** open-label extension; **QD,** once daily; **W,** week

Efficacy
Mean EDSS score up to OLE Week 144

EDSS scores over time
Pooled treatment groups



EDSS scores change from baseline (core study)
Pooled treatment groups



Stable EDSS score and change from baseline were maintained in the OLE period

At the time of a data cut-off (25May2021), all participants had been treated with evobrutinib for at least 132 weeks in an OLE and some participants had not reached OLE Week 144.
EDSS, Expanded Disability Status Scale; **OLE,** open-label extension

Conclusions

SAFETY

- The evobrutinib safety profile observed in the DBP was maintained over 2.5 years in the OLE, with no new safety signals identified
- Liver aminotransferase elevations were not observed in the OLE after prolonged treatment with evobrutinib
- The frequency of severe (Grade ≥3) infections was low up to Week 132 of the OLE

IMMUNE CELLS AND Ig LEVELS

- Most patients had Ig levels within normal ranges through Week 120
- In patients who experience a period of low $CD19^{+}$ B cells, infection incidence did not appear increased

EFFICACY

- In patients who received evobrutinib 75 mg BID in the DBP, ARR remained low (0.13 up to Week 132 and 0.12 over the whole OLE period*)
- EDSS values were stable up to Week 144

*Cut-off 25 May 2021

ARR, annualized relapse rate; **DBP,** double-blind period; **EDSS,** Expanded Disability Status Scale; **Ig,** immunoglobulin; **OLE,** open-label extension; **RMS,** relapsing multiple sclerosis