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P0070

Effect of evobrutinib, a BTK inhibitor, on immune cell and immunoglobulin levels in relapsing MS: an open-label extension to a phase II study

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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 Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, Medday, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

Jamie Shaw, Fernando Dangond, Emily C. Martin, Roland Grenningloh and Ying Li

- Are employees of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA; a business of Merck KGaA, Darmstadt, Germany.

Martin S. Weber

- Has received travel funding and/or speaker honoraria from Biogen-Idec, Merck Serono, Novartis, F. Hoffmann-La Roche, TEVA, Bayer, and Genzyme.

Background

- Evobrutinib, a highly selective BTK inhibitor, has a dual mode of action on B cells and myeloid cells involved in the pathogenesis of MS
- A Phase II randomized study (NCT02975349) investigated the efficacy and safety of evobrutinib, and its effect on immune cells and Ig[1,2]
- After a 48-week randomized DBP, RMS patients treated with evobrutinib showed[1,2]:
  - A significant reduction of T1 Gd-enhancing lesions compared to placebo at Week 24 with continued clinical efficacy through Week 48
  - No clinically relevant changes in the number of total B cells or in memory B cell or mature-naïve B cell subsets over 48 weeks
  - Stable IgG levels, and slight increases in IgA and reductions in IgM levels[2]

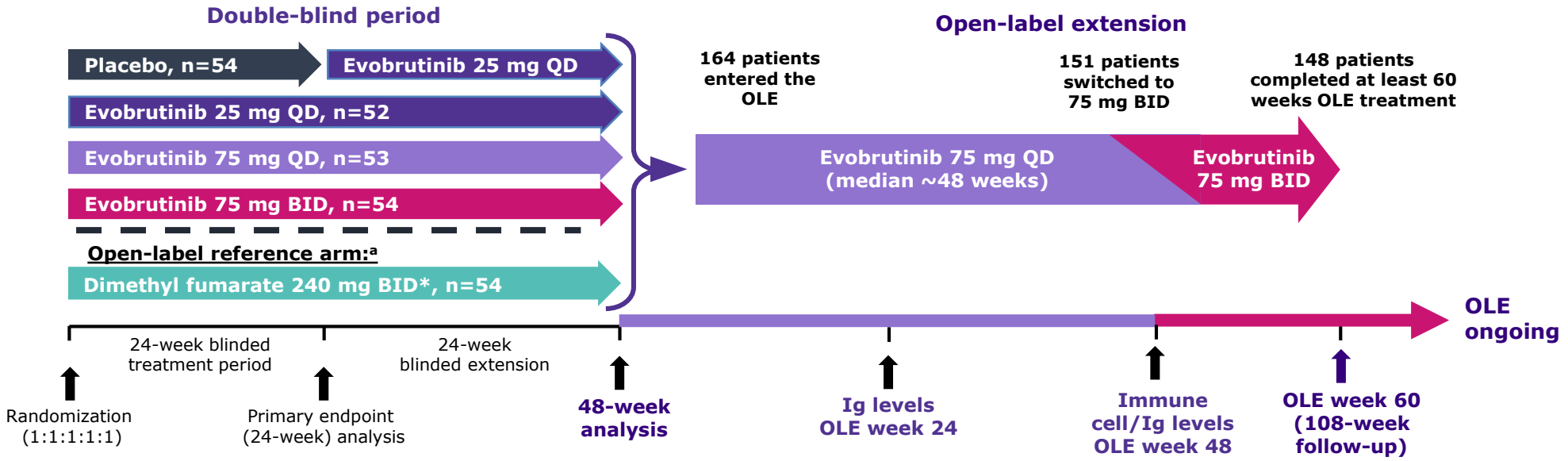
Objectives

- To investigate the long-term effects of evobrutinib on immune cell parameters assessed after 48 additional weeks in the ongoing OLE of the Phase II study:
  - B cells (total, mature-naïve and memory subsets)
  - T cells (total, helper and cytotoxic subsets), NK cells
  - Ig levels

BTK, Bruton's tyrosine kinase; **DBP**, double-blind period; **Ig**, immunoglobulin; **MS**, multiple sclerosis; **NK**, natural killer; **OLE**, open-label extension; **RMS**, relapsing MS

1. Montalban X, et al. N Engl J Med 2019;380:2406-17; 2. Montalban X, ECTRIMS 2019 poster P1358.

Study design: Phase II/OLE



Adults with RMS were randomized double-blind to evobrutinib 25 mg QD, 75 mg QD, 75 mg BID, or PBO

- PBO patients switched to evobrutinib 25 mg QD at Week 24. At Week 48, all patients were eligible for the OLE, and received evobrutinib 75 mg QD (median ≈48 weeks), then 75 mg BID[a]
- Safety of evobrutinib, including assessment of total B cell counts and Ig levels, was a secondary endpoint; effects on B cell subsets, T cells, and NK cells were exploratory
- Immune cell counts were assessed at OLE Week 48 and Ig levels at OLE Weeks 24 and 48, relative to DBP baseline

[a]Only patients treated with evobrutinib are included in the current analysis
*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment
BID, twice daily; **OLE**, open-label extension; **PBO**, placebo; **QD**, once daily

Patient disposition and demographics

Patients, n (%)	Placebo + evobrutinib 25 mg QD	Evobrutinib			Total
		25 mg QD	75 mg QD	75 mg BID	
DBP baseline	54 (100.0)	52 (100.0)	53 (100.0)	54 (100.0)	213 (100.0)
Entered OLE period	39 (72.2)	39 (75.0)	42 (79.2)	44 (81.5)	164 (77.0)
Patients with immune cell levels assessed at OLE 48 weeks	33 (61.1)	35 (67.3)	36 (67.9)	39 (72.2)	143 (67.1)
Switched to 75 mg BID during OLE	35 (64.8)	35 (67.3)	37 (69.8)	44 (81.5)	151 (70.9)
Discontinued treatment during OLE	5 (9.3)	9 (17.3)	5 (9.4)	3 (5.6)	22 (10.3)

Includes data from OLE participants using a data cut-off of 31 Dec 2019
BID, twice daily; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily

Immune cell counts during the OLE period

Change in B cells from DBP baseline to OLE week 48					
Mean ± SD (cells/µL)		Placebo + evobrutinib 25 mg QD (n=54)	Evobrutinib		
			25 mg QD (n=52)	75 mg QD (n=53)	75 mg BID (n=54)
Total B cells	BL	209 ± 134.4	178 ± 82.9	215 ± 157.9	206 ± 123.1
	CFB	-51 ± 80.8	-51 ± 89.8	-106 ± 149.8	-83 ± 141.2
CD19⁺ B cells	BL	250 ± 145.2	209 ± 116.9	246 ± 137.8	219 ± 111.4
	CFB	-72 ± 90.1	-60 ± 72.4	-104 ± 111.3	-81 ± 113.7
Mature-naïve B-cells	BL	138 ± 108.7	111 ± 66.3	141 ± 114.2	127 ± 89.0
	CFB	-41 ± 66.8	-38 ± 64.6	-70 ± 104.4	-54 ± 93.8
Memory B cells	BL	24 ± 19.2	22 ± 17.8	24 ± 22.2	24 ± 23.4
	CFB	0 ± 14.9	0 ± 21.6	-6 ± 16.1	-3 ± 26.9

- CD19+ B cell numbers decrease in all groups originally randomized to evobrutinib compared to DBP baseline; however, mean values were within the normal range*
- The decrease in CD19+ B cells appeared to be accounted for by a decrease in mature naïve B cells
- There was no evidence of a change in memory B cell levels
- There was no evidence of any change in T cell or NK cell parameters

*CD19+ B cell normal range: 107–698 cells/µL

At OLE Week 48, immune cell parameters in patients receiving evobrutinib were consistent with those observed in the 48-week DBP

BID, twice daily; **BL**, baseline; **DBP**, double-blind period; **CFB**, change from baseline; **NK**, natural killer; **OLE**, open-label extension; **QD**, once daily

CD19+ B cells at OLE Week 48

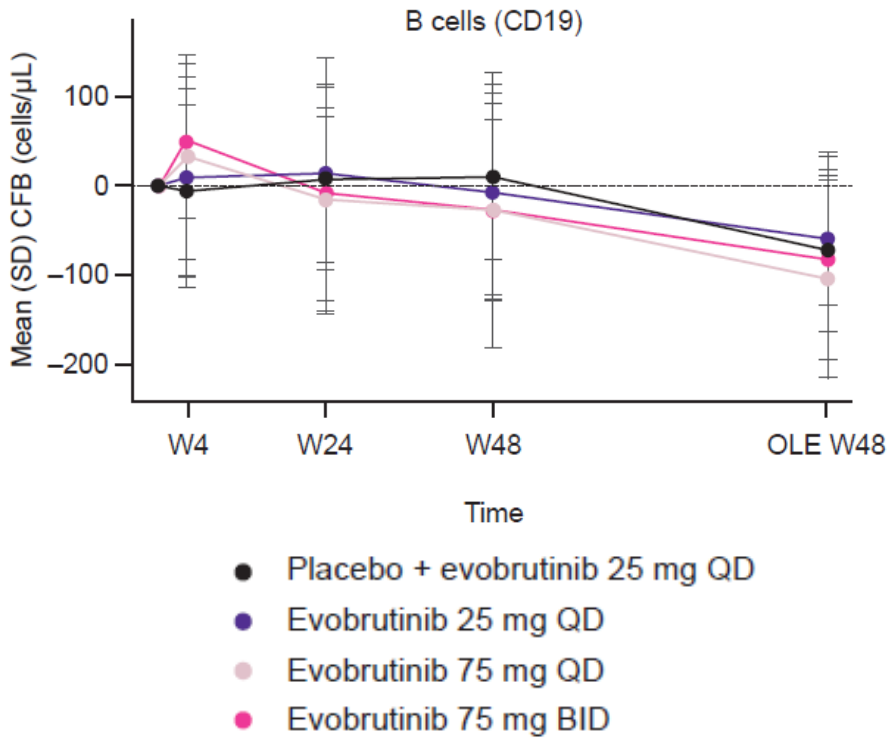
Patients with CD19+ B cell levels within normal range* at BL and subsequently low up to OLE Week 48		
DBP treatment group	**n (%)**	**Mean (SD) CD19+ B-cells (cells/µL) at OLE Week 48**
Placebo + evobrutinib 25 mg QD	4 (7.4)	87.3 (12.8)
Evobrutinib 25 mg QD	6 (11.5)	68.8 (10.7)
Evobrutinib 75 mg QD	13 (24.5)	77.5 (18.5)
Evobrutinib 75 mg BID	9 (16.7)	81.7 (19.3)

Data are for those patients who had complete longitudinal profiles and were categorised as normal at baseline and subsequently low until OLE week 48 with no missing values at baseline, week 4, week 16, week 24, week 48 and OLE week 48.

- In a subgroup of patients (7.4–24.5%), levels of CD19+ B cells were reduced below the normal range* at OLE week 48
- In this subgroup of patients, mean absolute levels of CD19+ B cells were 68.8–81.7 cells/µL

*CD19+ B cell normal range: 107–698 cells/µL

CD19+ B cells: change from DBP baseline



B cell counts remained within the normal range in a substantial proportion of the OLE population

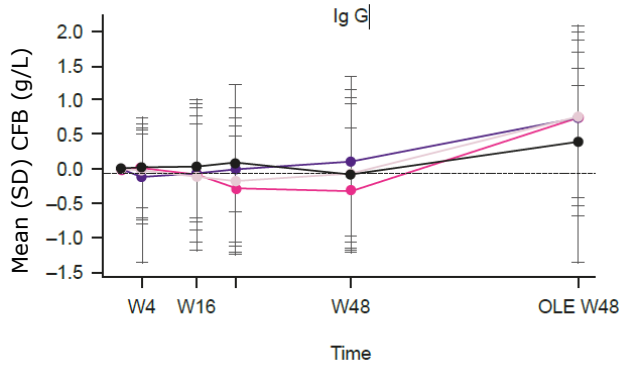
BL, baseline; **BID**, twice daily; **CFB**, change from baseline; **DBP**, double-blind phase; **OLE**, open-label extension; **QD**, once daily; **SD,** standard deviation

Immunoglobulin levels during the OLE period

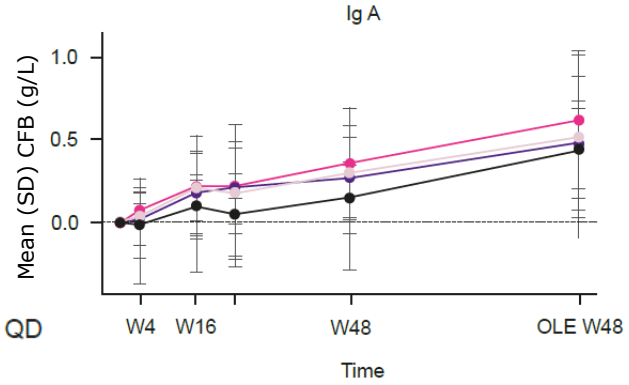
Change in Ig levels from DBP baseline at OLE week 48					
Mean ± SD (g/L)		**Placebo + evobrutinib 25 mg QD (n=54)**	**Evobrutinib**		
			25 mg QD (n=52)	**75 mg QD (n=53)**	**75 mg BID (n=54)**
IgG	BL	9.61 ± 1.90	9.46 ± 2.14	9.81 ± 1.84	9.62 ± 1.96
	CFB	0.38 ± 1.06	0.73 ± 1.26	0.79 ± 1.31	0.75 ± 1.15
IgA	BL	1.99 ± 0.78	1.89 ± 0.77	1.90 ± 0.72	1.87 ± 0.678
	CFB	0.44 ± 0.29	0.48 ± 0.403	0.52 ± 0.50	0.62 ± 0.42
IgM	BL	1.42 ± 0.69	1.27 ±0.55	1.44 ± 0.72	1.33 ± 0.68
	CFB	-0.41 ± 0.30	-0.31 ± 0.25	-0.38 ± 0.40	-0.33 ± 0.17

Normal ranges (g/L)
- **IgG: 7–16**
- **IgA: 0.7–4.0**
- **IgM: 0.4–2.3**

IgG

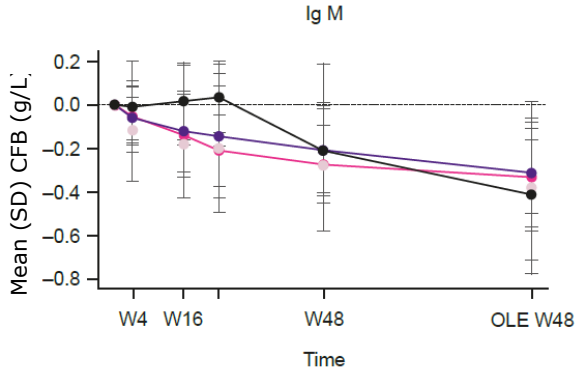


IgA



- Placebo + evobrutinib 25 mg QD
- Evobrutinib 25 mg QD
- Evobrutinib 75 mg QD
- Evobrutinib 75 mg BID

IgM

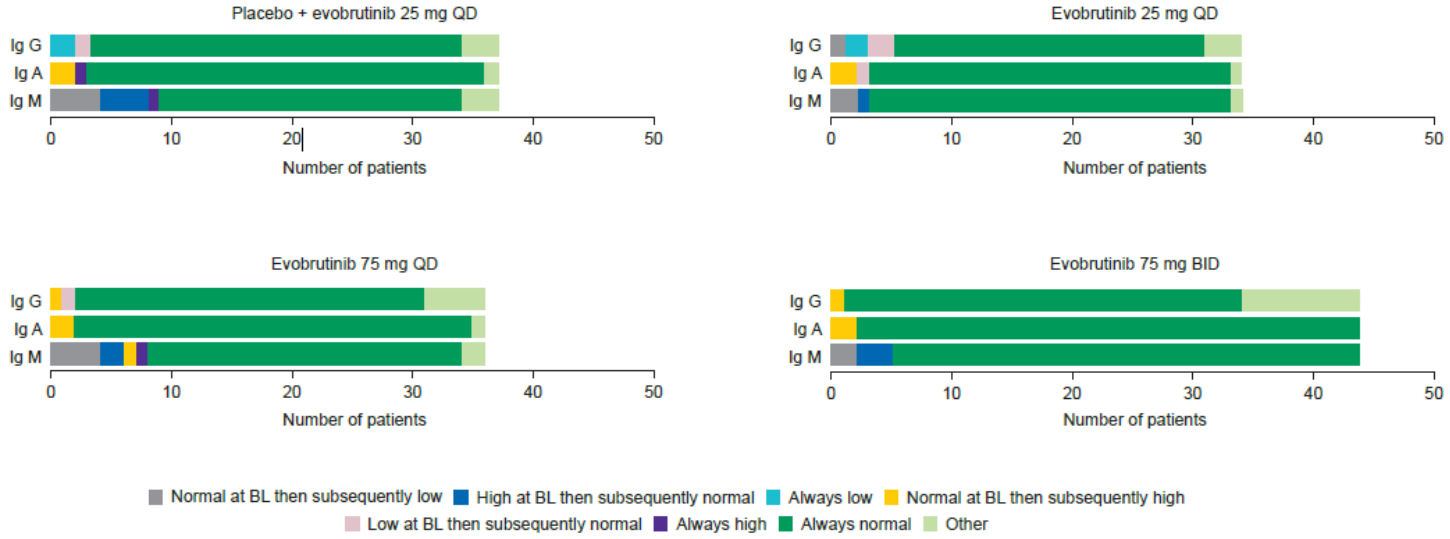


- **IgG levels were stable and no relevant changes were observed at OLE week 48 relative to DBP baseline**
- **Mean IgA and IgM levels increased and decreased, respectively, but were within normal ranges**

BID, twice daily; **BL**, baseline; **DBP**, double-blind period; **CFB**, change from baseline; **OLE**, open-label extension; **QD**, once daily

Immunoglobulin level dynamics categorized at OLE week 48 relative to baseline levels

Immunoglobulin longitudinal profiles from baseline through OLE week 48 categorized based on normal ranges



All patients in the safety population were assigned to one of the longitudinal categories below based on their immune cell assessment (BL, DBP weeks 4, 24, 48, and OLE week 48) and Ig level assessment (BL, DBP weeks 4, 16, 24, 48 and OLE week 48):

- **Always normal**: Normal at BL and the following visits
- **Always Low**: Low at BL and the following visits
- **Always high**: High at BL and the following visits
- **High at BL then subsequently normal**: High at BL and consistently high until transition to normal post-baseline; consistently normal after transition
- **Normal at BL then subsequently high**: Normal at BL and consistently normal until transition to high post-baseline; consistently high after transition
- **Low at BL then subsequently normal**: Low at BL and consistently low until transition to normal post-baseline; consistently normal after transition
- **Normal at BL then subsequently low**: Normal at BL and consistently normal until transition to low post-baseline; consistently low after transition
- **Other**: Change between two levels more than once

Data are for those patients who had complete longitudinal profiles with no missing values at baseline, DBP week 4, week 16, week 24, week 48 and OLE week 48.

IgG and IgG subtypes (subtype data not shown), IgA and IgM levels remained within normal ranges through OLE week 48 in the majority of the OLE population

Normal ranges (g/L)
- **IgG: 7–16**
- **IgA: 0.7–4.0**
- **IgM: 0.4–2.3**

BID, twice daily; **BL**, baseline; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily

Conclusions

- **Immune cell numbers and Ig levels seen in patients receiving evobrutinib for 48 weeks of the OLE were consistent with those observed in the DBP**
- **At OLE week 48, relative to DBP baseline, there was a decrease in CD19+ B cells and mature-naïve B cells but no evidence of a change in memory B cell levels; however, B cell counts remained within the normal range in a substantial proportion of the OLE population**
- **There was no evidence of a change in T cell or NK cell parameters**
- **At OLE week 48, relative to DBP baseline, IgG levels were stable. IgA levels and IgM levels remained increased and decreased, respectively, and mean values of IgA and IgM were within normal ranges**
- **The changes in B cells, IgA and IgM levels over 96 weeks of evobrutinib treatment do not appear to be associated with an enhanced risk of infections (see Poster P0235 at this meeting), however the clinical meaningfulness/functional significance of these changes remains to be determined**

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- The authors thank the patients and their families, as well as the investigators and study teams, for their participation in this study
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For more evobrutinib Phase II study information,
please see other presentations at MS Virtual 2020: 8th Joint ACTRIMS–ECTRIMS Meeting
Efficacy of long-term evobrutinib in patients with MS – Poster P0197
Safety of long-term evobrutinib in patients with MS – Poster P0235