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Safety of evobrutinib in patients with relapsing multiple sclerosis is maintained in a long-term open-label extension of a Phase II study

Xavier Montalban,[1] Douglas L. Arnold,[2] Martin S. Weber,[3] Ivan Staikov,[4] Karolina Piasecka-Stryczynska,[5] Emily C. Martin,[6] Matthew Mandel,[6] Yulia Zima,[6] Jamie Shaw,[6] Fernando Dangond,[6] Roland Grenningloh,[6] Ying Li,[6] Davorka Tomic,[7] Jerry S. Wolinsky[8]

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CONCLUSION

- **Data from the OLE period of a Phase II study, when all patients had completed at least 60 weeks of treatment or discontinued, showed that:**
  - **The safety of evobrutinib was similar to that seen in the 48-week DBP**
  - **The majority of TEAEs were mild or moderate and no new safety concerns were observed. TEAEs (occurring in ⩾5% of patients) were balanced across previous DBP treatment groups**
  - **Transient treatment-related elevated liver aminotransferases reported in the DBP (which were asymptomatic and reversible) were not observed in the OLE after prolonged treatment or after the switch to evobrutinib 75 mg BID**
  - **Evobrutinib 75 mg BID was not associated with an increased incidence of infections**
- **Mean IgG, IgA and IgM levels remained within normal ranges through OLE week 48 in the majority of the OLE population**
- **Changes in immune cells and Ig levels over 96 weeks, which were consistent with those in the DBP, do not appear to be associated with an enhanced risk of infection**
- **Overall, long-term evobrutinib treatment was generally well tolerated in patients with relapsing MS**

BID, twice daily; **DBP,** double-blind period; **Ig**, immunoglobulin; **OLE**, open-label extension; **TEAE**, treatment-emergent adverse event

INTRODUCTION

- In a Phase II randomized controlled study (NCT02975349) in patients with relapsing MS, evobrutinib 75 mg BID reduced total T1 Gd+ lesions and annualized relapse rate over 24 weeks versus placebo, with efficacy maintained through Week 108[1]
- Evobrutinib was generally well tolerated. The most common adverse events were nasopharyngitis and increases in ALT and AST levels and lipase. Elevated aminotransferase levels were asymptomatic and reversible[1]
- After the 48-week randomized DBP, patients with relapsing MS on evobrutinib showed no clinically relevant changes in total B cells or B cell subsets, and stable IgG levels, with slight increases in IgA and reductions in IgM levels[2]

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **Ig**, immunoglobulin

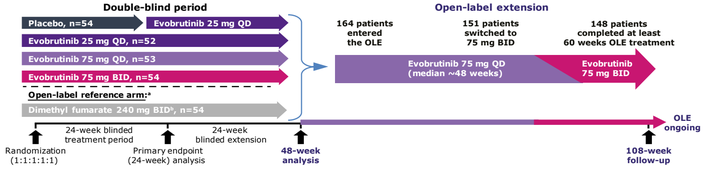
OBJECTIVE

- To describe the safety profile of evobrutinib in the long-term treatment of relapsing MS by reporting detailed safety data from the study's ongoing OLE when all patients had been treated for at least 60 weeks of OLE (or discontinued)
- To investigate the long-term effects of evobrutinib on immune cell parameters and Ig levels after 48 additional weeks in the ongoing OLE

METHODS

- In the 48-week DBP, patients received evobrutinib 25 mg QD, 75 mg QD, 75 mg BID, or placebo for the first 24 weeks. All arms continued with the original treatment assignment until Week 48, except placebo patients who were switched to evobrutinib 25 mg QD
- At Week 48, all patients could enter the OLE, where treatment was initially evobrutinib 75 mg QD (for a median of ≈48 weeks) before switching to 75 mg BID. Safety was assessed throughout the OLE, by assessment of the nature, severity, and occurrence of TEAEs using NCI-CTCAE v4.03 criteria, as well as vital signs, ECGs, and clinical laboratory safety parameters
- Immune cells were assessed at OLE Week 48, and Ig levels were assessed at OLE Weeks 24 and 48

Figure 1. Study design



[a]Only patients treated with evobrutinib are included in the current analysis
[b]120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment
BID, twice daily; **DBP**, double-blind period; **ECG**, echocardiogram; **Ig**, immunoglobulin; **NCI-CTCAE v4.03**, National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03; **OLE**, open-label extension; **QD**, once daily; **TEAE**, treatment-emergent adverse event

RESULTS

Overall TEAEs were mild/moderate in the OLE period

- Of 213 patients who received evobrutinib during the DBP, 164 (77%) entered the ongoing OLE (safety analysis population)
- In this analysis, 148 (90%) of OLE participants had completed at least 60 weeks of treatment[a]
- 107/164 (65%) patients had a TEAE, the majority of which were mild (48%) or moderate (36%), and none led to death (**Table 1**)
- Thirteen patients (8%) reported a serious TEAE, most frequently related to infections (6 patients, not treatment-related)
- The most common TEAEs during the OLE (occurring in ⩾5% of patients across previous DBP treatment groups) were lipase increase, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection (**Table 2**)

Table 1. TEAEs during the OLE in the safety analysis population

Patients, n (%)	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib			Total safety analysis population (n=164)
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)	
Any TEAE	27 (69)	22 (56)	31 (74)	27 (61)	107 (65)
Any Grade 3 TEAE[b]	3 (8)	2 (5)	2 (5)	3 (7)	10 (6)
Any Grade 4 TEAE[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any serious TEAE	5 (13)	5 (13)	2 (5)	1 (2)	13 (8)
TEAEs leading to treatment withdrawal[c]	4 (10)	1 (3)	–	–	5 (3)

[a]Includes all safety data from the OLE using a data cut-off of December 31, 2019, all patients had received ⩾60 weeks of evobrutinib in the OLE or discontinued
[b]According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03
[c]Of these, three were considered related to treatment (nausea, increased lipase, and concurrent increase in both amylase and lipase)
BID, twice daily; **OLE**, open-label extension; **QD**, once daily; **TEAE**, treatment-emergent adverse event

- **Transient asymptomatic treatment-related elevated liver aminotransferases reported in the DBP were not observed in the OLE after prolonged treatment or after the switch to evobrutinib 75 mg BID**
- **The incidence of infections in the OLE was similar to that observed in the DBP**

Table 2. Most common TEAEs during the OLE

Incidence rate (95% CI) per 1000 subject-years	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib			Total safety analysis population (n=164)
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)	
Lipase increase	55 (18; 170)	57 (18; 176)	51 (17; 159)	62 (23; 165)	56
Nasopharyngitis	36 (9; 143)	55 (18; 172)	72 (27; 191)	62 (23; 165)	56
Upper respiratory tract infection	55 (18; 170)	36 (9; 146)	51 (17; 159)	30 (8; 120)	43
Headache	18 (3; 127)	36 (9; 144)	34 (8; 134)	45 (15; 140)	34
Urinary tract infection	57 (19; 178)	56 (18; 173)	17 (2; 118)	15 (2; 106)	34

BID, twice daily; **CI**, confidence interval; **OLE**, open-label extension; **QD**, once daily; **TEAE**, treatment-emergent adverse event

- **TEAEs analyzed by exposure-adjusted incidence rate were balanced before and after patients switched to 75 mg BID (Table 2)**
- **No new safety signals were identified during the OLE (Table 2)**

Immune cell counts during the OLE period

- CD19[+] B cell numbers decreased in all groups originally randomized to evobrutinib compared with DBP baseline; however, mean values were within the normal range (**Table 3**)
- There was no evidence of any change in T cell or NK cell parameters

Table 3. 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[a]	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

[a]CD19[+] B cell normal range: 107–698 cells/μL
BID, twice daily; **BL**, baseline; **CFB**, change from baseline; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily

Immunoglobulin levels during the OLE period

- IgG levels were stable and IgA and IgM levels slightly increased and decreased, respectively, but were within normal ranges (**Table 4**)

Table 4. Change in Ig levels from DBP baseline to 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[a]	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[a]	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[a]	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

[a]Normal ranges (g/L): IgG: 7–16; IgA: 0.7–4.0; IgM: 0.4–2.3
BID, twice daily; **BL**, baseline; **CFB**, change from baseline; **DBP**, double-blind period; **Ig**, immunoglobulin; **OLE**, open-label extension; **QD**, once daily

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1. Montalban X et al. *N Engl J Med* 2019;380:2406–17
2. Montalban X et al. Poster presented at ECTRIMS 2019 (P1358)

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DISCLOSURES

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 Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Inc., Rockland, MA, USA, Genzyme, Immunic, MedDay Pharmaceuticals, Merck KGaA, Darmstadt, Germany, Mylan, NervGen Pharma Corp., Novartis, F. Hoffmann-La Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and MMSS. DLA reports consultant fees and/or has grants from Acorda, Adelphi, Alkermes, Biogen, Celgene, Frequency Therapeutics, Genentech, Genzyme, F. Hoffmann-La Roche, Immune Tolerance Network, Immunotec, MedDay Pharmaceuticals, EMD Serono, Inc., Rockland, MA, USA, Novartis, Pfizer, Receptos, Sanofi-Aventis, and an equity interest in NeuroKi Research. HSW has received travel funding and/or speaker honoraria from Biogen-Idec, EMD Serono, Inc., Rockland, MA, USA, Novartis, F. Hoffmann-La Roche, TEVA, Bayer, and Genzyme. IS has received travel funding, registration fees, and/or speaker honoraria from Sanofi-Genzyme, Ewopharma-Biogen, Shire, Gedeon-Richter, TEVA, Boehringer Ingelheim, Pfizer, Bayer, F. Hoffmann-La Roche, Mylan, Polpharma, Penumbra, Adapt, and EMD Serono, Inc., Rockland, MA, USA. KP-S has received travel funding and/or speaker honoraria from EMD Serono, Inc., Rockland, MA, USA, Sanofi-Aventis, Biogen Idec, TEVA, F. Hoffmann-La Roche, and has served on scientific advisory boards for Sanofi-Aventis and Biogen Idec. JSW has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alkermes, Brainstorm Cell Therapeutics, EMD Serono, Inc., Rockland, MA, USA, GW Pharma, MedDay Pharmaceuticals, NervGen Pharma Corp., Novartis, Roche/Genentech and Sanofi Genzyme. Royalties have been received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation. ECH, MM, YZ, JS, FD, XG and YL are employed by EMD Serono Research and Development Institute, Inc., Billerica, MA, USA. DT is employed by the healthcare business of Merck KGaA, Darmstadt, Germany.

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Supplementary Table 1. Most common TEAEs during the OLE (occurring in ≥5% of patients across previous DBP treatment groups)

Patients, n (%)	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib			Total safety analysis population (n=164)
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)	
Lipase increase	3 (8)	3 (8)	3 (7)	4 (9)	13 (8)
Nasopharyngitis	2 (5)	3 (8)	4 (10)	4 (9)	13 (8)
Upper respiratory tract infection	3 (8)	2 (5)	3 (7)	2 (5)	10 (6)
Headache	1 (3)	2 (5)	2 (5)	3 (7)	8 (5)
Urinary tract infection	3 (8)	3 (8)	1 (2)	1 (2)	8 (5)

BID, twice daily; **DBP,** double-blind period; **OLE,** open-label extension; **QD,** once daily; **TEAEs,** treatment-emergent adverse events

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Supplementary Table 2. Grade 3 TEAEs reported during the OLE

Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib		
	25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)
3 (8)*	2 (5)*	2 (5)*	3 (7)*
For individual TEAEs, values are number of events (evobrutinib-related events)			
ALT increase 1 (0) **AST increase** 1 (0) **Amylase increase†** 1 (1) **Lipase increase†** 2 (1)	**Gastroenteritis** 1 (0) **Pneumonia** 1 (0)	**Dementia Alzheimer's type** 1 (0) **Femur fracture** 1 (1) **Osteonecrosis** 1 (1)	**Lipase increase†** 3 (2)

*Patients with at least 1 Grade 3 event, n (% of group); †Asymptomatic
ALT, alanine aminotransferase; **AST,** aspartate aminotransferase; **BID,** twice daily; **OLE,** open-label extension; **QD,** once daily; **TEAEs,** treatment-emergent adverse events

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