Safety profile characterization of evobrutinib in over 1000 patients from Phase II clinical trials in multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus

Xavier Montalban[1], Daniel Wallace[2], Mark C. Genovese[3], Davorka Tomic[4], Dana Parsons-Rich[5*], Claire Le Bolay[6], Amy Kao[5], Hans Guehring[6]

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*Affiliation at the time the research was conducted

CONCLUSION

- This is the first integrated analysis of a BTK inhibitor with safety data derived from Phase II trials across MS, RA and SLE indications
- The rate of TEAEs was similar for evobrutinib and placebo by indication and across trials
- There was no enhanced risk of serious infections with evobrutinib (despite background immunosuppressant therapy in the RA and SLE trials)
- Elevations in ALT and AST observed with evobrutinib treatment were asymptomatic and reversible
  - Other drug class-associated TEAEs were not observed with evobrutinib compared with placebo

Overall, the evobrutinib safety profile supports the continued development for MS and the ongoing Phase III program

INTRODUCTION

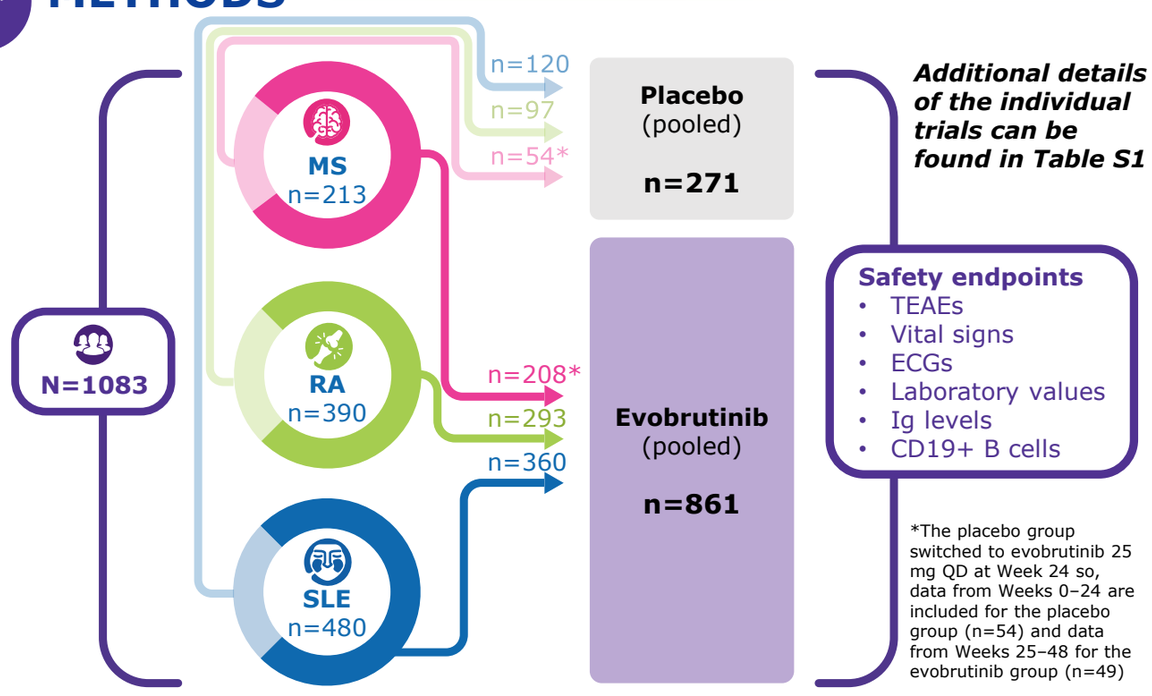
- Evobrutinib is a highly selective, orally administered, covalent BTK inhibitor, with a low potential for off-target related adverse effects[1,2]
- Evobrutinib has been investigated in patients with MS, RA and SLE in Phase II trials:
  - **Evobrutinib was well tolerated** in all three Phase II trials[3–5]
    - In the MS trial, data from the double-blind period and the open-label extension have demonstrated that the safety of evobrutinib was maintained over 2 years[6]
  - **Evobrutinib met the efficacy endpoints** in the MS trial: reduced clinical and subclinical MRI disease activity in relapsing MS patients over 24 weeks[3]
- Given the ongoing clinical development of evobrutinib in MS there is a rationale to characterize the overall safety profile of evobrutinib

OBJECTIVES

To analyze the integrated safety profile, including drug class-related AEs, of evobrutinib using pooled data from Phase II trials in MS*, RA and SLE

*48-week data from the double-blind period

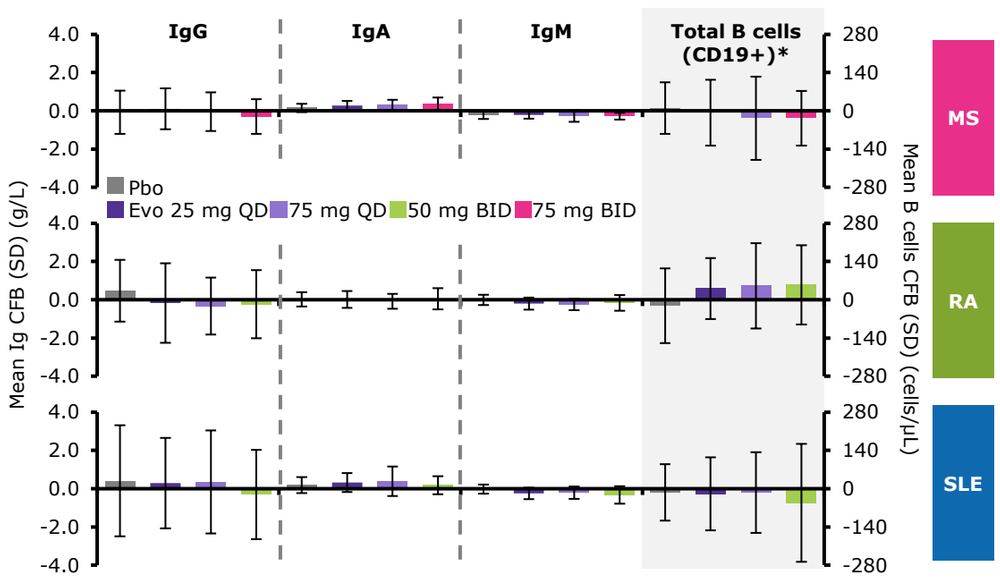
METHODS



*The placebo group switched to evobrutinib 25 mg QD at Week 24 so, data from Weeks 0–24 are included for the placebo group (n=54) and data from Weeks 25–48 for the evobrutinib group (n=49)

Additional details of the individual trials can be found in Table S1

Ig and B cell levels remained within normal ranges across indications



MS (48 weeks) Ig: pbo n=46, evo 25 mg QD n=43, evo 75 mg QD n=47, evo 75 mg BID n=48; **MS B cells:** pbo n=39, evo 25 mg QD n=37, evo 75 mg QD n=36, evo 75 mg BID n=42; **RA (12 weeks) Ig:** pbo n=83, evo 25 mg QD n=89, evo 75 mg QD n=81, evo 50 mg BID n=88; **RA B cells:** pbo n=82, evo 25 mg QD n=85, evo 75 mg QD n=77, evo 50 mg BID n=83; **SLE (52 weeks) Ig:** pbo n=78, evo 25 mg QD n=83, evo 75 mg QD n=85 (IgM n=84), evo 50 mg BID n=76; **SLE B cells:** pbo n=57, evo 25 mg QD n=60, evo 75 mg QD n=63, evo 50 mg BID n=60
*B cell levels for the SLE trial are total B cell levels; the other trials are CD19+ B cell levels

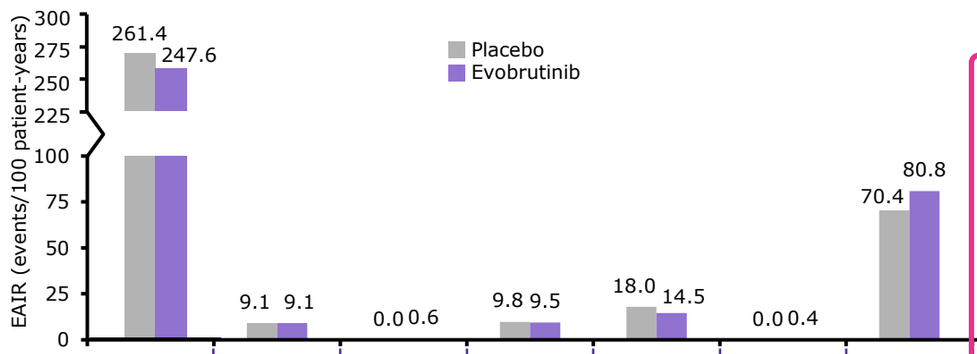
RESULTS

Concomitant medications

Patients, n (%) ATC Class Level 2	MS		RA		SLE	
	Pbo (n=54)	Evo (n=208)	Pbo (n=97)	Evo (n=293)	Pbo (n=120)	Evo (n=360)
Analgesics	15 (27.8)	48 (23.1)	18 (18.6)	71 (24.2)	52 (43.3)	165 (45.8)
Immunosuppressants	0 (0.0)	0 (0.0)	95 (97.9)	291 (99.3)	105 (87.5)	316 (87.8)
Corticosteroids	8 (14.8)	33 (15.9)	63 (64.9)	177 (60.4)	108 (90.0)	325 (90.3)

Per the RA and SLE trial designs, concomitant immunosuppressants/immunomodulators (RA: methotrexate; SLE: azathioprine, 6-mercaptopurine, mycophenolate, methotrexate, sulfasalazine and leflunomide), non-steroidal anti-inflammatory drugs and corticosteroids were permitted

No imbalance in the rate of TEAEs between evobrutinib and placebo



EAIR (events/100 patient-years)

MS*	148.3	119.7	8.3	6.6	0.0	0.0	8.4	5.3	20.8	11.1	0.0	0.0	59.9	35.7	4.2	0.0
RA	306.8	331.8	4.9	4.6	0.0	0.0	9.7	7.7	28.9	16.8	0.0	0.0	61.4	63.1	0.0	3.1
SLE	302.1	343.0	10.2	11.4	0.0	1.0	10.1	12.1	15.1	15.7	0.0	0.7†	76.1	121.4	2.0	4.0

*MS trial: patients were treated with placebo between Weeks 0–24 after which they switched to evobrutinib 25 mg QD; †Two TEAEs in the evobrutinib treatment group from the SLE trial were fatal. One of these events was considered to be treatment related by the investigator

Generally well balanced rates of other potential class-associated TEAEs between evobrutinib and placebo (see Table S2 for details by indication)

	Total			
	Pbo (n=271)		Evo (n=861)	
	n (%)	EAIR	n (%)	EAIR
ALT increased*	4 (1.5)	2.8	25 (2.9)	4.8
AST increased*	1 (0.4)	0.7	18 (2.1)	3.5
Tachycardia	0 (0.0)	–	1 (0.1)	0.2
Ventricular arrhythmia	0 (0.0)	–	1 (0.1)	0.2
Bleeding†	7 (2.6)	2.4	13 (1.5)	0.6
Bruising‡	1 (0.4)	0.7	5 (0.6)	0.5
Neoplasms (SOC)	5 (1.8)	3.5	7 (0.8)	1.4
Infections and infestations (SOC)	78 (28.8)	70.4	294 (34.1)	80.8
Amylase increase	10 (3.7)	7.0	26 (3.0)	5.1
Lipase increase*	4 (1.5)	2.8	17 (2.0)	4.0
Neutropenia*	6 (2.2)	4.2	10 (1.2)	1.9
Thrombocytopenia*	0 (0.0)	–	2 (0.2)	0.4
Lymphopenia*	10 (3.7)	7.2	16 (1.9)	3.1

Liver-related TEAEs
- Higher EAIR of ALT/AST increases with evobrutinib versus placebo
- Asymptomatic and reversible on treatment withdrawal

Bleeding events
- No increased EAIR observed with evobrutinib

*The event with the highest severity for a patient during the treatment period and meeting the AESI definition was included in the summary; †Defined by medical concept as epistaxis, hematoma, hematoma muscle, hemorrhagic diathesis; ‡Defined by medical concept as ecchymosis and petechiae

Abbreviations: AEs, adverse events; **AESI**, AE of special interest; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ATC**, anatomical therapeutic chemical; **BID**, twice daily; **BTK,** Bruton's tyrosine kinase; **CFB**, change from baseline; **EAIR**, exposure-adjusted incidence rate; **ECG**, electrocardiogram; **evo**, evobrutinib; **Ig**, immunoglobulin; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **pbo**, placebo; **QD**, once daily; **RA**, rheumatoid arthritis; **SD**, standard deviation; **SLE**, systemic lupus erythematosus; **SOC**, system organ class; **TEAE**, treatment-emergent AE

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. Montalban X, et al. *N Engl J Med.* 2019;380(25):2406–2417; 4. Peterfy C, et al. *Arthritis Rheumatol.* 2020;72(10)RA2012 (Abstract); 5. Wallace DJ, et al. *Arthritis Rheumatol.* 2020;72(10)SLE0865 (Abstract); 6. Montalban X, et al. *Mult Scler.* 2020;26(S3):233 (Abstract P0235).

The authors thank the patients and their families, as well as the investigators, co-investigators and the study teams at each of the participating centers; Emily Martin, Daniela Sera (EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA) and Karin Broeder (Merck Healthcare KGaA, Darmstadt, Germany) for providing assistance with the statistical analyses. Merck Healthcare KGaA was involved in the study design, collection, analysis and interpretation of the data, and the development of this presentation. Medical writing assistance was provided by Bioscript Stirling Ltd, Macclesfield, UK and supported by Merck Healthcare KGaA (CrossRef Funder ID: 10.13039/100009945).

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SUPPLEMENTARY MATERIAL

Table S1. Individual trial details

Indication	Treatment	N	Duration (weeks)
MS[1]	Placebo (24 weeks)*	54	48
	Evobrutinib 25 mg QD	52	
	Evobrutinib 75 mg QD	53	
	Evobrutinib 75 mg BID	54	
RA[2]	Placebo	97	12
	Evobrutinib 25 mg QD	98	
	Evobrutinib 75 mg QD	96	
	Evobrutinib 50 mg BID	99	
SLE[3]	Placebo	117	52
	Evobrutinib 25 mg QD	118	
	Evobrutinib 75 mg QD	117	
	Evobrutinib 50 mg BID	117	

*The placebo group switched to evobrutinib 25 mg QD at Week 24

Table S2. Generally well balanced rates of other potential class-associated TEAEs between evobrutinib and placebo

	MS				RA				SLE				Total			
	Placebo (n=54)		Evobrutinib (n=208)		Placebo (n=97)		Evobrutinib (n=293)		Placebo (n=120)		Evobrutinib (n=360)		Placebo (n=271)		Evobrutinib (n=861)	
	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR
ALT increased*	2 (3.7)	8.4	10 (4.8)	6.6	1 (1.0)	4.8	3 (1.0)	4.6	1 (0.8)	1.0	12 (3.3)	4.0	4 (1.5)	2.8	25 (2.9)	4.8
AST increased*	0 (0.0)	–	7 (3.4)	4.6	0 (0.0)	–	3 (1.0)	4.6	1 (0.8)	1.0	8 (2.2)	2.7	1 (0.4)	0.7	18 (2.1)	3.5
Tachycardia	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.3)	0.3	0 (0.0)	–	1 (0.1)	0.2
Ventricular arrhythmia	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.3)	1.5	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.1)	0.2
Bleeding†	0 (0.0)	–	1 (0.5)	2.3	1 (1.0)	4.8	4 (1.4)	4.6	6 (5.0)	6.2	8 (2.2)	2.0	7 (2.6)	2.4	13 (1.5)	0.6
Bruising‡	0 (0.0)	–	1 (0.5)	2.3	1 (1.0)	4.8	0 (0.0)	–	0 (0.0)	–	4 (1.1)	1.4	1 (0.4)	0.7	5 (0.6)	0.5
Neoplasms (SOC)	1 (1.9)	4.2	1 (0.5)	0.7	0 (0.0)	–	0 (0.0)	–	4 (3.3)	4.0	6 (1.7)	2.0	5 (1.8)	3.5	7 (0.8)	1.4
Infections and infestations (SOC)	13 (24.1)	59.9	47 (22.6)	35.7	12 (12.4)	61.4	38 (13.0)	63.1	53 (44.2)	76.1	209 (58.1)	121.4	78 (28.8)	70.4	294 (34.1)	80.8
Amylase increase	4 (7.4)	17.0	8 (3.8)	5.3	1 (1.0)	4.9	3 (1.0)	4.6	5 (4.2)	5.1	15 (4.2)	5.1	10 (3.7)	7.0	26 (3.0)	5.1
Lipase increase*	1 (1.9)	4.2	6 (2.9)	4.0	1 (1.0)	4.9	1 (0.3)	1.5	2 (1.7)	2.0	10 (2.8)	3.4	4 (1.5)	2.8	17 (2.0)	4.0
Neutropenia*	0 (0.0)	–	1 (0.5)	0.7	1 (1.0)	4.8	0 (0.0)	–	5 (4.2)	5.1	9 (2.5)	3.0	6 (2.2)	4.2	10 (1.2)	1.9
Thrombocytopenia*	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	2 (0.6)	0.7	0 (0.0)	–	2 (0.2)	0.4
Lymphopenia*	0 (0.0)	–	2 (1.0)	1.3	1 (1.0)	4.9	1 (0.3)	1.5	9 (7.5)	9.6	13 (3.6)	4.5	10 (3.7)	7.2	16 (1.9)	3.1

*The event with the highest severity for a patient during the treatment period and meeting the AESI definition was included in the summary.
†Defined by medical concept as epistaxis, hematoma, hematoma muscle, hemorrhagic diathesis; ‡Defined by medical concept as ecchymosis and petechiae.

Liver-related TEAEs
- Higher EAIR of ALT/AST increases with evobrutinib versus placebo
- Asymptomatic and reversible on treatment withdrawal

Bleeding events
- No increased EAIR observed with evobrutinib

Neoplasms
- Lower EAIR with evobrutinib versus placebo

Abbreviations: AESI, adverse event of special interest; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **BID**, twice daily; **EAIR**, exposure-adjusted incidence rates; **MS**, multiple sclerosis; **QD**, twice daily; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus; **SOC**, system organ class; **TEAE**, treatment-emergent adverse event.

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