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

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

[1]The healthcare business of Merck KGaA, Darmstadt, Germany

[2]Cedars-Sinai Medical Center, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

[3]Division of Immunology and Rheumatology, Stanford University, Palo Alto, CA, USA

[4]Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

[5]EMD Serono, Billerica, MA, USA

[6]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain

*Affiliation at the time the research was conducted

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Disclosures

Hans Guehring is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany.

Daniel Wallace has received consultant fees from Amgen, Eli Lilly, EMD Serono, **Merck KGaA, Darmstadt, Germany**, Celgene and Janssen.

Mark C Genovese has received personal compensation from AbbVie, Astellas, **EMD Serono**, Galapagos, Genentech/Roche, Gilead, Incyte, Eli Lilly, Pfizer, Sanofi and Vertex.

Davorka Tomic 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.

Dana Parsons-Rich was an employee of EMD Serono at the time the research was conducted, is an employee of Pfizer and has received stock or an ownership interest from Pfizer.

Claire Le Bolay is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany.

Amy Kao is an employee of EMD Serono and has received stock or an ownership interest from EMD Serono.

Xavier Montalban has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Alexion, Biogen, Celgene/Receptos, F. Hoffmann-La Roche Ltd., Genzyme, Medday, **Merck KGaA, Darmstadt, Germany, EMD Serono**, NervGen, Novartis, TG Therapeutics and Sanofi-Genzyme; his institution has received compensation for consultancy for Biogen, F. Hoffmann-La Roche Ltd., Medday, **Merck KGaA, Darmstadt, Germany, EMD Serono** and Novartis, and research support from Abbvie, Biogen, F. Hoffmann-La Roche Ltd., Medday, **Merck KGaA, Darmstadt, Germany,** Novartis, Sanofi and Teva.

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Introduction

Evobrutinib	• Highly selective, orally administered, covalent BTK inhibitor[1-2] • Low potential for off-target related adverse effects[1,2]

Phase II RCTs:	• **Evobrutinib was well tolerated** in all three Phase II trials[3–5]
Patients with MS (NCT02975349) **Patients with RA** (NCT03233230) **Patients with SLE** (NCT02975336)	○ 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]

Rationale	• Given the ongoing clinical development of evobrutinib in MS, there is a rationale to characterize the overall safety profile of evobrutinib

BTK, Bruton's tyrosine kinase; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **RCT**, randomized controlled trial; **SLE**, systemic lupus erythematosus

1. Haselmayer P, et al. *J Immunol*. 2019;202(10):2888–906; 2. Caldwell RD, et al. *J Med Chem*. 2019;62(17):7643–55; 3. Montalban X, et al. *N Engl J Med*. 2019;380(25):2406–17; 4. Peterfy C, et al. *Arthritis Rheumatol*. 2020;72(Suppl. 10):RA2012 (Abstract); 5. Wallace DJ, et al. *Arthritis Rheumatol.* 2020;72(Suppl. 10):SLE0865 (Abstract); 6. Montalban X, et al. *Mult Scler*. 2020;26(Suppl. 3):233 (Abstract P0235)

Objective

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
AE, adverse event; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus

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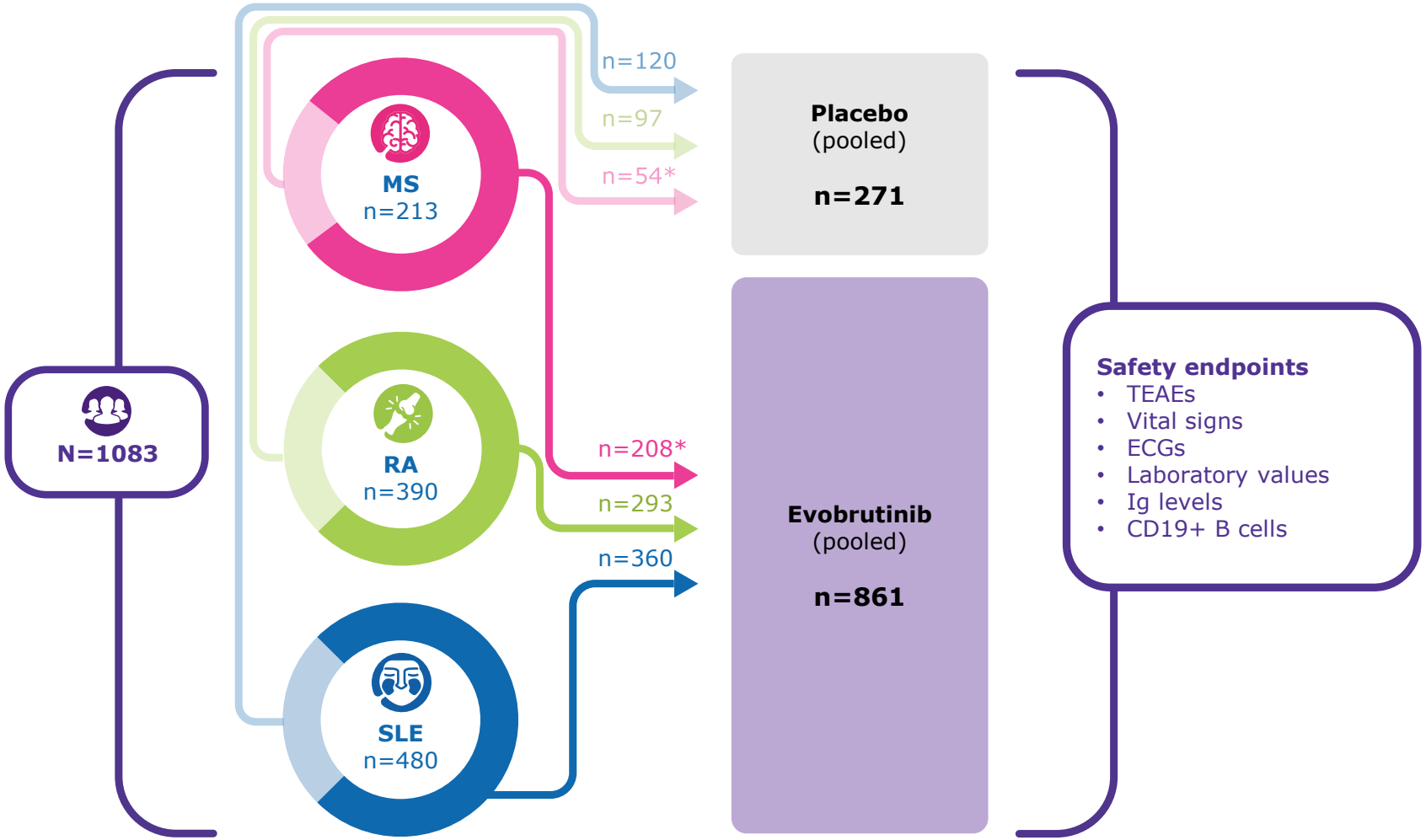
Methods



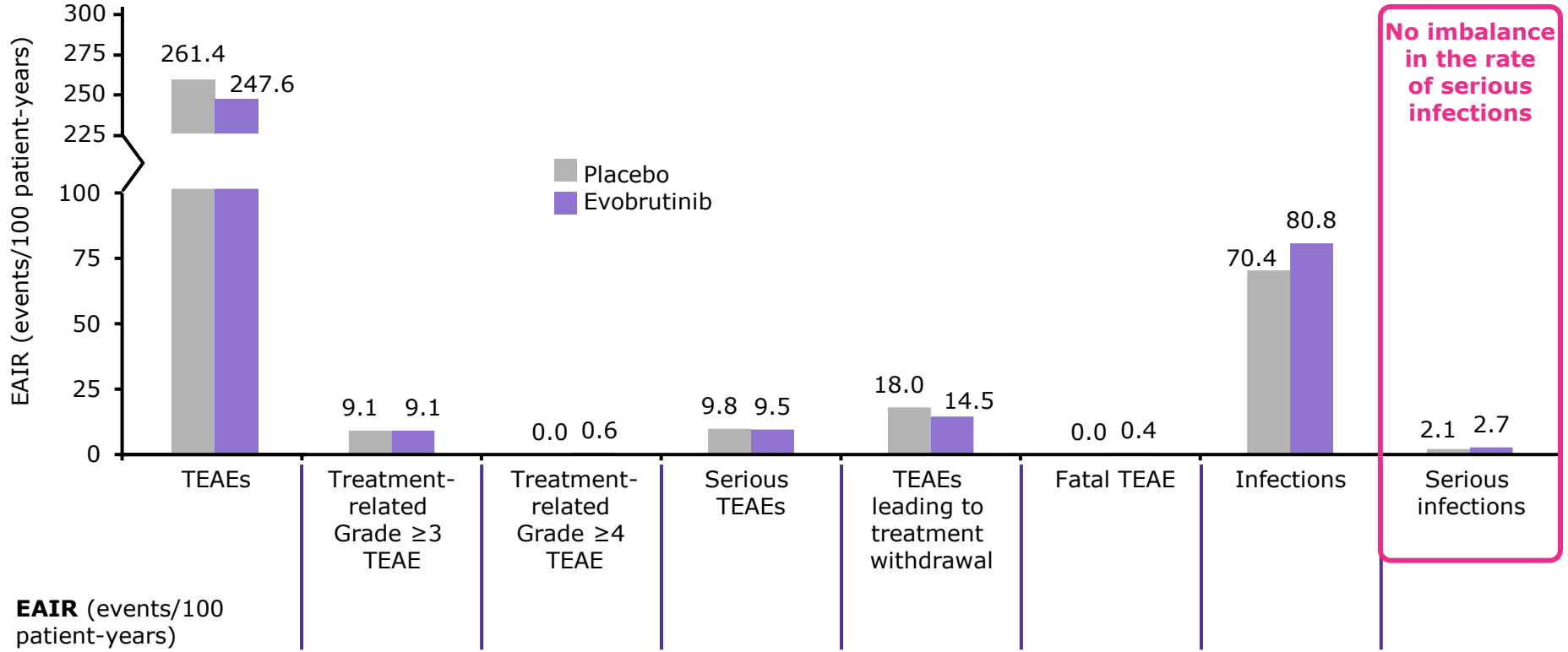
MS[1] (48 weeks): placebo (24 weeks)* n=54, evobrutinib 25 mg QD n=52, evobrutinib 75 mg QD n=53, evobrutinib 75 mg BID n=54
*The placebo group switched to evobrutinib 25 mg QD at Week 24 so, data from Weeks 0–24 are included for the placebo group (n=54) and data from Weeks 25–48 for the evobrutinib group (n=49)
RA[2] (12 weeks): placebo n=97, evobrutinib 25 mg QD n=98, evobrutinib 75 mg QD n=96, evobrutinib 50 mg BID n=99
SLE[3] (52 weeks): placebo n=117, evobrutinib 25 mg QD n=118, evobrutinib 75 mg QD n=117, evobrutinib 50 mg BID n=117
BID, twice daily; **ECG**, electrocardiogram; **Ig**, immunoglobulin; **MS**, multiple sclerosis; **QD**, once daily; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus; **TEAE**, treatment-emergent adverse event
1. Montalban X, et al. *N Engl J Med*. 2019;380(25):2406–17; 2. Peterfy C, et al. *Arthritis Rheumatol*. 2020;72(Suppl. 10):RA2012 (Abstract); 3. Wallace DJ, et al. *Arthritis Rheumatol*. 2020;72(Suppl. 10):SLE0865 (Abstract)

Concomitant medications were allowed in the Phase II trials

Patients, n (%) ATC Class Level 2	MS		RA		SLE	
	Placebo (n=54)	Evobrutinib (n=208)	Placebo (n=97)	Evobrutinib (n=293)	Placebo (n=120)	Evobrutinib (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
ATC, anatomical therapeutic chemical; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus

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
EAIR, exposure-adjusted incidence rate; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus; **TEAE**, treatment-emergent adverse event

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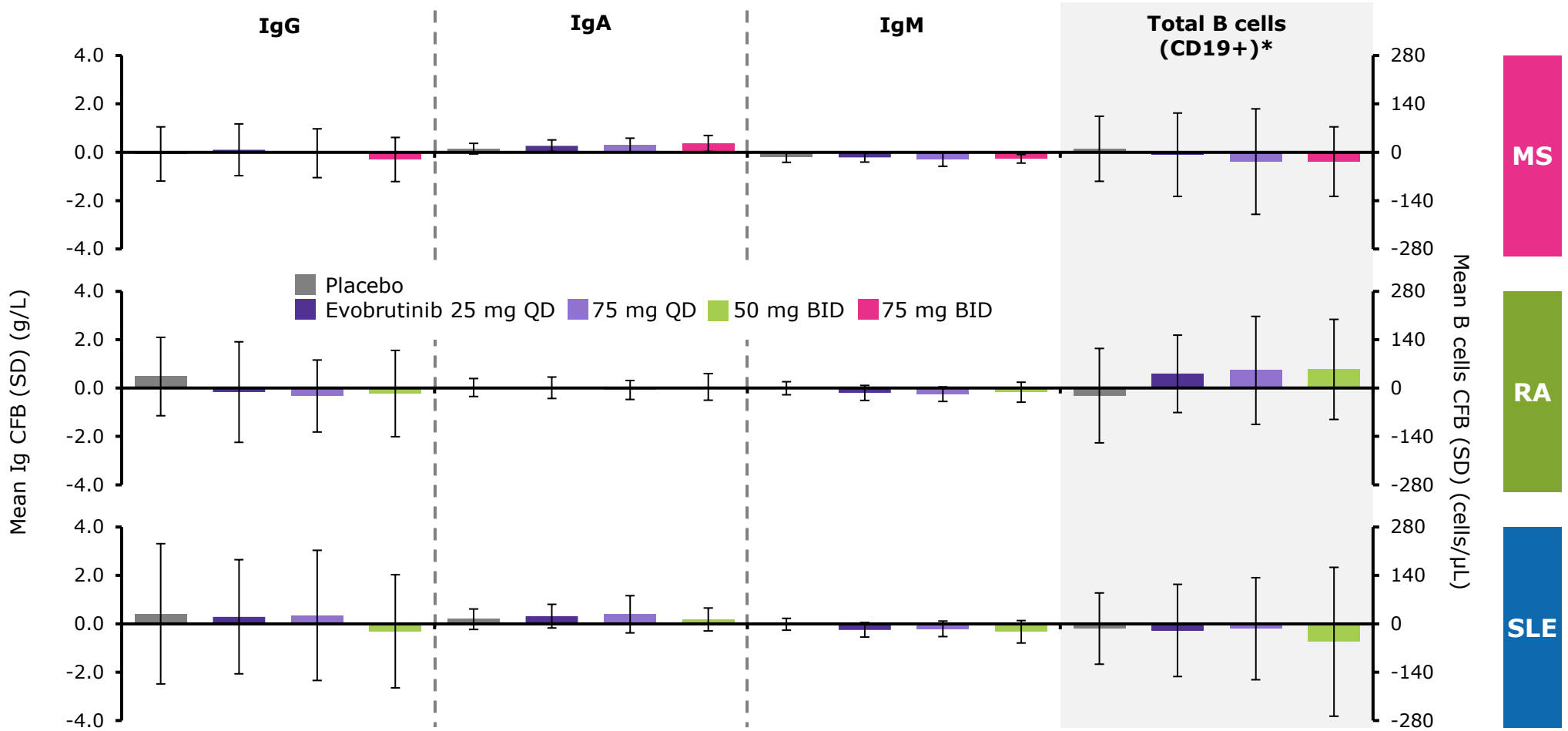
Ig and B cell levels remained within normal ranges across indications



MS (48 weeks) Ig: placebo n=47, evo 25 mg QD n=43, evo 75 mg QD n=47, evo 75 mg BID n=48; **MS B cells:** placebo n=45, evo 25 mg QD n=44, evo 75 mg QD n=47, evo 75 mg BID n=48;
RA (12 weeks) Ig: placebo n=83, evo 25 mg QD n=89, evo 75 mg QD n=81, evo 50 mg BID n=88; **RA B cells:** placebo n=82, evo 25 mg QD n=85, evo 75 mg QD n=77, evo 50 mg BID n=83;
SLE (52 weeks) Ig: placebo 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:** placebo 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
BID, twice daily; **CFB**, change from baseline; **evo**, evobrutinib; **Ig**, immunoglobulin; **MS**, multiple sclerosis; **QD**, once daily; **RA**, rheumatoid arthritis; **SD**, standard deviation; **SLE**, systemic lupus erythematosus

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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
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
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

Bleeding events
- No increased EAIR observed with evobrutinib

Neoplasms
- Lower EAIR with evobrutinib versus placebo

*Defined by medical concept as epistaxis, hematoma, hematoma muscle, hemorrhagic diathesis; †Defined by medical concept as ecchymosis and petechiae
EAIR, exposure-adjusted incidence rate; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus; **SOC**, system organ class; **TEAE**, treatment-emergent adverse event

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

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

	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
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
AESI, adverse event of special interest; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **EAIR**, exposure-adjusted incidence rate; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus; **TEAE**, treatment-emergent adverse event

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Conclusions

- 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

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **BTK**, Bruton's tyrosine kinase; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus; **TEAE**, treatment-emergent adverse event

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