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

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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

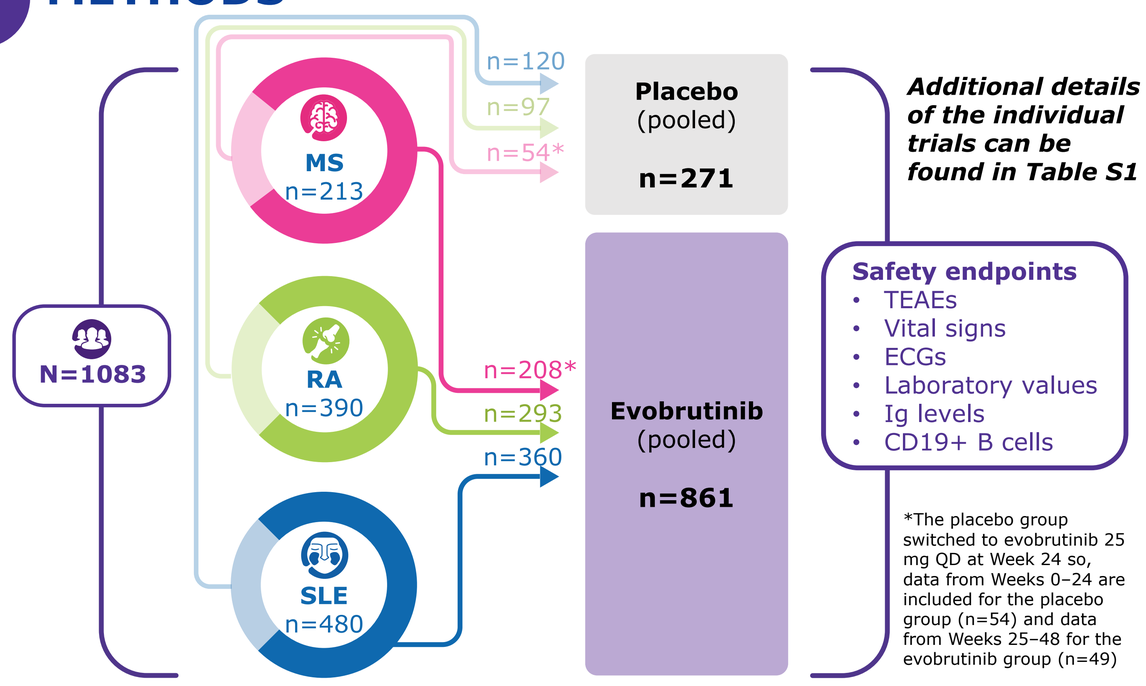
- Evobrutinib is a highly selective, orally administered, covalent BTK inhibitor, with a low potential for off-target related adverse effects[1,2]
- Evobrutinib has been investigated in patients with MS, RA and SLE in Phase II trials:
  - **Evobrutinib was well tolerated** in all three Phase II trials[3–5]
    - 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

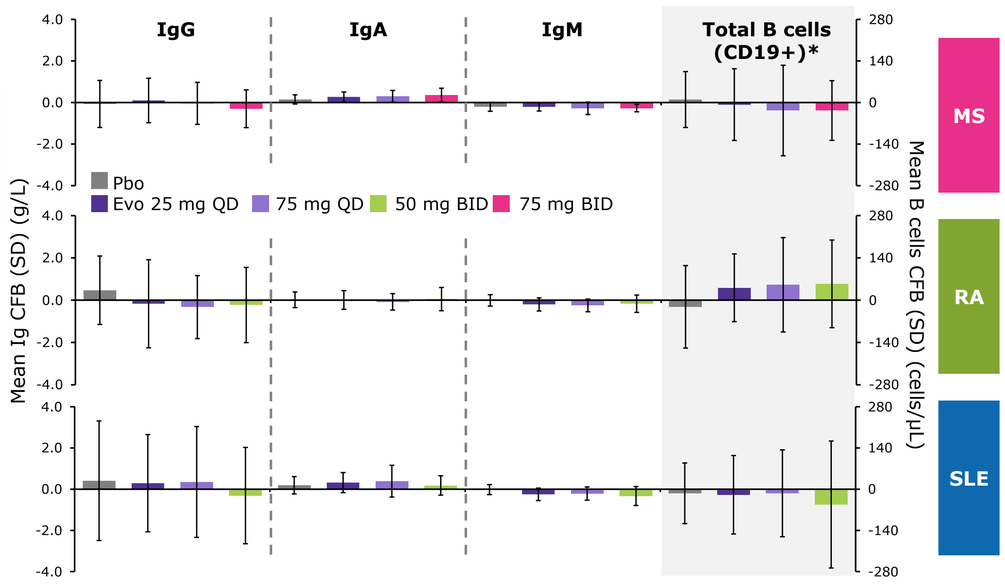
*48-week data from the double-blind period

METHODS



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

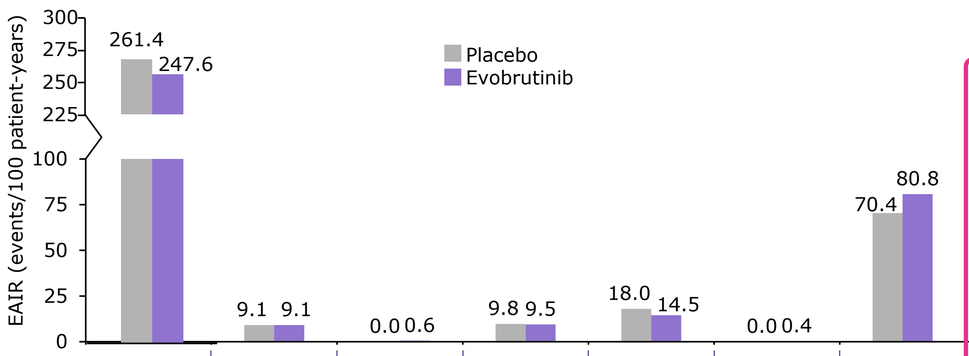
RESULTS

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: AE, adverse event; **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

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