

SUPPLEMENT

eTable 1: Most frequently used concomitant medications

Patients, n (%) ACT 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)
Paracetamol	3 (5.6)	17 (8.2)	8 (8.2)	35 (11.9)	26 (21.7)	88 (24.4)
Acetylsalicylic acid	1 (1.9)	7 (3.4)	2 (2.1)	9 (3.1)	14 (11.7)	32 (8.9)
Tramadol	–	1 (0.5)	1 (1.0)	5 (1.7)	5 (4.2)	22 (6.1)
Gabapentin	2 (3.7)	3 (1.4)	–	2 (0.7)	7 (5.8)	13 (3.6)
Duloxetine hydrochloride	1 (1.9)	–	–	2 (0.7)	6 (5.0)	13 (3.6)
Paracetamol; tramadol hydrochloride	1 (1.9)	2 (1.0)	2 (2.1)	6 (2.0)	2 (1.7)	7 (1.9)
Pregabalin	1 (1.9)	2 (1.0)	–	3 (1.0)	1 (0.8)	12 (3.3)
Amitriptyline	–	1 (0.5)	1 (1.0)	2 (0.7)	1 (0.8)	10 (2.8)
Metamizole sodium	1 (1.9)	5 (2.4)	1 (1.0)	2 (0.7)	1 (0.8)	1 (0.3)
Immunosuppressants	–	–	95 (97.9)	291 (99.3)	108 (90.0)	325 (90.3)
Methotrexate	–	–	87 (89.7)	265 (90.4)	13 (10.8)	47 (13.1)
Hydroxychloroquine	–	–	2 (2.1)	18 (6.1)	57 (47.5)	186 (51.7)
Azathioprine	–	–	–	–	22 (18.3)	62 (17.2)
Mycophenolate mofetil	–	–	–	–	16 (13.3)	48 (13.3)

Chloroquine	–	–	2 (2.1)	2 (0.7)	13 (10.8)	31 (8.6)
Methotrexate sodium	–	–	8 (8.2)	25 (8.5)	2 (1.7)	5 (1.4)
Chloroquine phosphate	–	–	1 (1.0)	3 (1.0)	7 (5.8)	25 (6.9)
Hydroxychloroquine sulfate	–	–	–	1 (0.3)	10 (8.3)	21 (5.8)
Leflunomide	–	–	–	5 (1.7)	–	5 (1.4)
Mycophenolate sodium	–	–	–	–	–	3 (0.8)
Corticosteroids	8 (14.8)	33 (15.9)	63 (64.9)	177 (60.4)	105 (87.5)	316 (87.8)
Prednisone	1 (1.9)	4 (1.9)	16 (16.5)	67 (22.9)	55 (45.8)	154 (42.8)
Methylprednisolone	6 (11.1)	18 (8.7)	30 (30.9)	65 (22.2)	19 (15.8)	74 (20.6)
Prednisolone	–	–	9 (9.3)	31 (10.6)	22 (18.3)	60 (16.7)
Meprednisone	–	–	6 (6.2)	10 (3.4)	2 (1.7)	12 (3.3)
Deflazacort	–	–	1 (1.0)	3 (1.0)	8 (6.7)	13 (3.6)
Methylprednisolone sodium succinate	1 (1.9)	11 (5.3)	–	–	1 (0.8)	1 (0.3)
Hydrocortisone	–	–	1 (1.0)	2 (0.7)	2 (1.7)	5 (1.4)
Dexamethasone	–	1 (0.5)	1 (1.0)	–	–	4 (1.1)
Betamethasone	–	1 (0.5)	–	2 (0.7)	–	1 (0.3)
Betamethasone dipropionate	–	–	–	2 (0.7)	–	2 (0.6)

MS, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus.

eTable 2: EAIRs of BTK inhibitor or concomitant drug class-associated TEAEs by preferred term

	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
Cardiac disorders																
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
Coronary artery disease	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
Hemorrhage-related TEAEs																
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
Vascular disorders																
Hypertension	0 (0.0)	–	1 (0.5)	0.7	1 (1.0)	4.9	5 (1.7)	7.7	0 (0.0)	–	13 (3.6)	4.4	1 (0.4)	0.7	19 (2.2)	3.7
Neoplasms																
Neoplasms benign, malignant and unspecified (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

Anogenital warts	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.8)	1.0	2 (0.6)	0.7	1 (0.4)	0.7	2 (0.2)	0.4
Fibrous histiocytoma	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.8)	1.0	0 (0.0)	–	1 (0.4)	0.7	0 (0.0)	–
Lipoma	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.8)	1.0	0 (0.0)	–	1 (0.4)	0.7	0 (0.0)	–
Lung neoplasm	1 (1.9)	4.2	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.4)	0.7	0 (0.0)	–
Oral papilloma	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
Papillary thyroid cancer	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.8)	1.0	0 (0.0)	–	1 (0.4)	0.7	0 (0.0)	–
Skin papilloma	0 (0.0)	–	1 (0.5)	0.7	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.1)	0.2
Thyroid adenoma	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
Uterine leiomyoma	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
Infections																
Serious infections and infestations	1 (1.9)	4.2	0 (0.0)	–	0 (0.0)	–	2 (0.7)	3.1	2 (1.7)	2.0	12 (3.3)	4.0	3 (1.1)	2.1	14 (1.6)	2.7
Herpes zoster	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	3 (2.5)	3.0	9 (2.5)	3.0	3 (1.1)	2.1	9 (1.0)	1.8
Immune system disorders																
Hypersensitivity	0 (0.0)	–	1 (0.5)	0.7	0 (0.0)	–	1 (0.3)	1.5	1 (0.8)	1.0	1 (0.3)	0.3	1 (0.4)	0.7	3 (0.3)	0.6
Musculoskeletal and connective tissue disorders																

Osteonecrosis	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	1 (0.8)	1.0	3 (0.8)	1.0	1 (0.4)	0.7	3 (0.3)	0.6
Liver-related TEAEs																
ALT increase*	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 increase*	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
Pancreas-related TEAEs																
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
Leucopenia-related TEAEs																
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
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-related TEAEs																
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

*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.

AESI, adverse event of special interest; **EAIR**, exposure-adjusted incidence rates; **MS**, multiple sclerosis; **RA**, rheumatoid arthritis; **SLE**, systemic lupus erythematosus; **SOC**, system organ class; **TEAEs**, treatment-emergent adverse events.