Concordance and Discordance in SLE Clinical Trial Outcome Measures: Analysis of Three Anifrolumab Phase 2/3 Trials

Ian N. Bruce,[1] Richard A. Furie,[2] Eric F. Morand,[3] Susan Manzi,[4] Yoshiya Tanaka,[5] Kenneth Kalunian,[6] Joan T. Merrill,[7] Patricia Puzio,[8] Emmanuelle Maho,[9] Christi Kleoudis,[10] Marius Albulescu,[9] Micki Hultquist,[8] Raj Tummala[8]

[1]Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal & Dermatological Sciences, The University of Manchester and NIHR Manchester Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom; ORCID ID: 0000-0003-3047-500X

[2]Division of Rheumatology, Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, United States;

[3]Centre for Inflammatory Disease, Monash University, Melbourne, VIC, Australia;

[4]Department of Medicine, Lupus Center of Excellence, Autoimmunity Institute, Allegheny Health Network, Pittsburgh, PA, United States;

[5]First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan;

[6]Division of Rheumatology, Allergy, and Immunology, University of California San Diego, La Jolla, CA, United States;

[7]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States;

[8]BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, United States;

[9]BioPharmaceuticals R&D, AstraZeneca, Cambridge, United Kingdom;

[10]BioPharmaceuticals R&D, AstraZeneca, Durham, NC, United States

Bruce IN, *et al. Ann Rheum Dis* 2022;0:1–8. doi: 10.1136/annrheumdis-2021-221847

Target journal: *Annals of the Rheumatic Diseases*

FUNDING

This study was supported by AstraZeneca (Gaithersburg, MD, USA).

Corresponding author:

Raj Tummala, MD, MS, MBA

Global Clinical Head

BioPharmaceuticals R&D

One MedImmune Way

Gaithersburg, MD 20878

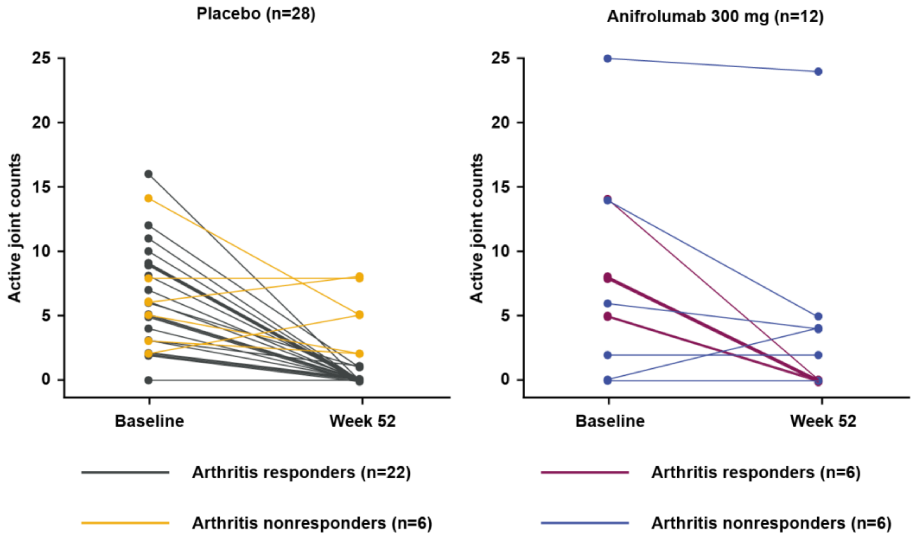
Phone: 301-398-0548

Email: Raj.Tummala@astrazeneca.com

ORCID ID: 0000-0002-0533-7185

SUPPLEMENTARY FIGURE

Figure S1. Change in active joint counts from baseline to Week 52 among patients in the TULIP-1 BICLA nonresponder/SRI(4) responder subgroup



Active joints were both swollen and tender. Points are staggered to avoid overlap in cases where patients had identical counts at baseline and/or Week 52.

SUPPLEMENTARY TABLES

Table S1. Patient baseline demographics and clinical characteristics in the MUSE, TULIP-1, and TULIP-2 trials

	TULIP-1		**TULIP-2**		**MUSE**	
	Placebo (n=184)	**Anifrolumab 300 mg (n=180)**	**Placebo (n=182)**	**Anifrolumab 300 mg (n=180)**	**Placebo (n=102)**	**Anifrolumab 300 mg (n=99)**
Age, mean (SD), years	41.0 (12.3)	42.0 (12.0)	41.1 (11.5)	43.1 (12.0)	39.3 (12.9)	39.1 (11.9)
Female, n (%)	171 (92.9)	165 (91.7)	170 (93.4)	168 (93.3)	93 (91.2)	93 (93.9)
Race, n (%)						
White	137 (74.5)	125 (69.4)	107 (58.8)	110 (61.1)	41 (40.2)	35 (35.4)
Black/African American	23 (12.5)	29 (16.1)	25 (13.7)	17 (9.4)	12 (11.8)	19 (19.2)
Asian	5 (2.7)	11 (6.1)	30 (16.5)	30 (16.7)	13 (12.7)	3 (3.0)
Other	19 (10.3)	15 (8.3)	12 (6.6)	15 (8.3)	36 (35.3)	38 (38.4)
Time from SLE diagnosis to randomization, median (range), months	79.5 (4–503)	88.0 (0–450)	78.0 (6–494)	94.5 (6–555)	65.8 (6.9–404)	71.4 (7.1–361)

IFNGS status at screening, n (%)						
High	151 (82.1)	148 (82.2)	151 (83.0)	150 (83.3)	76 (74.5)	75 (75.8)
Low	33 (17.9)	32 (17.8)	31 (17.0)	30 (16.7)	26 (25.5)	24 (24.2)
≥1 BILAG-2004 A, n (%)	84 (45.7)	93 (51.7)	95 (52.2)	81 (45.0)	49 (48.0)	52 (52.5)
No BILAG-2004 A and ≥2 BILAG-2004 B, n (%)	84 (45.7)	79 (43.9)	78 (42.9)	91 (50.6)	48 (47.1)	41 (41.4)
SLEDAI-2K global score, mean (SD)	11.5 (3.5)	11.3 (4.0)	11.5 (3.9)	11.4 (3.6)	11.1 (4.4)	10.7 (3.7)
SLEDAI-2K ≥10, n (%)	135 (73.4)	125 (69.4)	131 (72.0)	129 (71.7)	61 (59.8)	59 (59.6)
PGA score, mean (SD)	1.8 (0.4)	1.9 (0.4)	1.8 (0.4)	1.7 (0.4)	1.8 (0.4)	1.9 (0.4)
CLASI activity score, mean (SD)	8.1 (6.7)	8.5 (7.3)	7.6 (7.8)	8.3 (7.9)	6.7 (5.1)	7.5 (6.3)

Swollen joint count,[a] mean (SD)	7.0 (4.8)	7.4 (5.8)	7.4 (6.6)	6.2 (5.7)	8.3 (6.4)	8.6 (6.0)
Tender joint count,[a] mean (SD)	10.6 (7.2)	11.7 (7.5)	11.0 (7.9)	9.0 (7.1)	10.5 (7.4)	12.2 (7.1)
SDI score, mean (SD)	0.6 (1.0)	0.7 (1.2)	0.5 (0.8)	0.5 (0.9)	0.7 (1.2)	0.7 (1.0)
SLE treatments at baseline, n (%)						
GC[b]	153 (83.2)	150 (83.3)	151 (83.0)	141 (78.3)	88 (86.3)	79 (79.8)
GC ≥10 mg/day	102 (55.4)	103 (57.2)	83 (45.6)	87 (48.3)	64 (62.7)	55 (55.6)
Antimalarials	134 (72.8)	124 (68.9)	133 (73.1)	119 (66.1)	75 (73.5)	76 (76.8)
Immuno-suppressants[c]	91 (49.5)	85 (47.2)	86 (47.3)	88 (48.9)	46 (45.1)	53 (53.5)

BILAG-2004, British Isles Lupus Assessment Group-2004; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; GC, glucocorticoid; IFNGS, interferon gene signature; PGA, Physician's Global Assessment; SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

[a]Joint count was based on 28 joints. [b]Prednisone or equivalent. [c]Immunosuppressants: azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine.

Table S2. Patient baseline demographics in TULIP-1, overall and stratified by BICLA/SRI(4) concordance

	Concordant outcomes				Discordant outcomes				All patients	
	BICLA−/SRI(4)−		BICLA+/SRI(4)+		BICLA+/SRI(4)−		BICLA−/SRI(4)+			
	Placebo (n=101)	Anifrolumab 300 mg (n=83)	Placebo (n=51)	Anifrolumab 300 mg (n=76)	Placebo (n=4)	Anifrolumab 300 mg (n=9)	Placebo (n=28)	Anifrolumab 300 mg (n=12)	Placebo (n=184)	Anifrolumab 300 mg (n=180)
Mean age, years (SD)	39.1 (12.5)	41.8 (11.2)	43.5 (11.2)	41.7 (12.3)	31.8 (14.8)	50.4 (12.8)	44.3 (11.8)	38.9 (13.7)	41.0 (12.3)	42.0 (12.0)
Female, n (%)	92 (91.1)	75 (90.4)	47 (92.2)	71 (93.4)	4 (100)	8 (88.9)	28 (100)	11 (91.7)	171 (92.9)	165 (91.7)
Race										
White	72 (71.3)	56 (67.5)	41 (80.4)	55 (72.4)	2 (50.0)	6 (66.7)	22 (78.6)	8 (66.7)	137 (74.5)	125 (69.4)
Black/ African American	13 (12.9)	15 (18.1)	6 (11.8)	11 (14.5)	1 (25.0)	2 (22.2)	3 (10.7)	1 (8.3)	23 (12.5)	29 (16.1)
Asian	3 (3.0)	6 (7.2)	1 (2.0)	4 (5.3)	0	1 (11.1)	1 (3.6)	0	5 (2.7)	11 (6.1)
Other	12 (11.9)	6 (7.2)	3 (5.9)	6 (7.9)	1 (25.0)	0	2 (7.1)	3 (25.0)	18 (9.8)	15 (8.3)
Region										
Asia Pacific	3 (3.0)	6 (7.2)	2 (3.9)	4 (5.3)	0	1 (11.1)	1 (3.6)	0	6 (3.3)	11 (6.1)
Europe	35 (34.7)	22 (26.5)	26 (51.0)	38 (50.0)	0	1 (11.1)	15 (53.6)	3 (25.0)	76 (41.3)	64 (35.6)
Eastern Europe	31 (30.7)	15 (18.1)	24 (47.1)	33 (43.4)	0	1 (11.1)	15 (53.6)	3 (25.0)	70 (38.0)	52 (28.9)
Western Europe	4 (4.0)	7 (8.4)	2 (3.9)	5 (6.6)	0	0	0	0	6 (3.3)	12 (6.7)

	Concordant outcomes				Discordant outcomes				All patients	
	BICLA−/SRI(4)−		BICLA+/SRI(4)+		BICLA+/SRI(4)−		BICLA−/SRI(4)+			
	Placebo (n=101)	Anifrolumab 300 mg (n=83)	Placebo (n=51)	Anifrolumab 300 mg (n=76)	Placebo (n=4)	Anifrolumab 300 mg (n=9)	Placebo (n=28)	Anifrolumab 300 mg (n=12)	Placebo (n=184)	Anifrolumab 300 mg (n=180)
Latin America	13 (12.9)	6 (7.2)	8 (15.7)	12 (15.8)	1 (25.0)	2 (22.2)	3 (10.7)	4 (33.3)	25 (13.6)	24 (13.3)
USA/ Canada	47 (46.5)	46 (55.4)	13 (25.5)	20 (26.3)	3 (75.0)	5 (55.6)	9 (32.1)	4 (33.3)	72 (39.1)	75 (41.7)
Rest of world	3 (3.0)	3 (3.6)	2 (3.9)	2 (2.6)	0	0	0	1 (8.3)	5 (2.7)	6 (3.3)

BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; BICLA+, a responder on BICLA; n, number of patients in analysis; SD, standard deviation; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥4.

BICLA– and SRI(4)– refer to nonresponders; BICLA+ and SRI(4)+ refer to responders.

Table S3. Disease activity and glucocorticoid use at baseline in TULIP-2 stratified by BICLA/SRI(4) response

	Concordant outcomes				Discordant outcomes			
Baseline disease characteristic	**BICLA−/SRI(4)−**		**BICLA+/SRI(4)+**		**BICLA+/SRI(4)−**		**BICLA−/SRI(4)+**	
	Placebo (n=105)	**Anifrolumab 300 mg (n=72)**	**Placebo (n=48)**	**Anifrolumab 300 mg (n=78)**	**Placebo (n=9)**	**Anifrolumab 300 mg (n=8)**	**Placebo (n=20)**	**Anifrolumab 300 mg (n=22)**
SLEDAI-2K								
Mean (SD)	11.6 (4.21)	11.6 (3.79)	11.2 (3.3)	11.1 (3.5)	8.9 (2.47)	9.3 (1.39)	13.1 (3.65)	13.0 (3.83)
≥10 points, n (%)	76 (72.4)	50 (69.4)	33 (68.8)	57 (73.1)	3 (33.3)	3 (37.5)	19 (86.4)	19 (95.0)
BILAG-2004								
Global score, mean (SD)	19.0 (5.32)	18.9 (4.18)	19.2 (4.49)	18.9 (5.33)	16.7 (4.92)	17.9 (7.36)	19.6 (4.49)	17.1 (2.35)
≥1 A, n (%)	54 (51.4)	28 (38.9)	25 (52.1)	41 (52.6)	7 (77.8)	4 (50.0)	9 (45.0)	8 (36.4)
No A and ≥2 B, n (%)	46 (43.8)	43 (59.7)	20 (41.7)	31 (39.7)	1 (11.1)	3 (37.5)	11 (55.0)	14 (63.6)
Mean PGA score (SD)	1.80 (0.38)	1.71 (0.38)	1.69 (0.46)	1.65 (0.46)	1.70 (0.38)	1.81 (0.34)	1.76 (0.33)	1.70 (0.37)
Active joint count,[a,b] mean (SD)	7.5 (6.85)	7.0 (6.78)	6.9 (6.19)	4.6 (4.37)	7.4 (7.14)	8.1 (6.31)	5.3 (4.85)	4.0 (3.31)
Swollen joint count,[a] mean (SD)	7.9 (6.93)	7.6 (6.71)	7.2 (6.16)	5.1 (4.50)	7.8 (7.50)	8.6 (6.70)	5.5 (4.84)	4.9 (3.94)
Tender joint count,[a] mean (SD)	11.7 (8.25)	10.5 (7.59)	9.9 (7.24)	7.6 (6.18)	13.4 (8.25)	15.7 (8.40)	8.1 (5.98)	7.0 (6.53)

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG-2004, British Isles Lupus Assessment Group-2004; PGA, Physician's Global Assessment; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥4.

BICLA– and SRI(4)– refer to nonresponders; BICLA+ and SRI(4)+ refer to responders.

[a]Joint count was based on 28 joints. [b]Prednisone or equivalent.

Table S4. Baseline organ involvement in TULIP-1, overall and stratified by BICLA/SRI(4) response

	Concordant outcomes				Discordant outcomes				All patients	
	BICLA−/SRI(4)−		BICLA+/SRI(4)+		BICLA+/SRI(4)−		BICLA−/SRI(4)+			
Baseline disease characteristic	**Placebo (n=101)**	**Anifrolumab 300 mg (n=83)**	**Placebo (n=51)**	**Anifrolumab 300 mg (n=76)**	**Placebo (n=4)**	**Anifrolumab 300 mg (n=9)**	**Placebo (n=28)**	**Anifrolumab 300 mg (n=12)**	**Placebo (n=184)**	**Anifrolumab 300 mg (n=180)**
SLEDAI-2K organ domain involvement[a]										
Central nervous system	1(1.0)	1 (1.2)	0	0	0	0	0	1 (8.3)	1 (0.5)	2 (1.1)
Vascular	10 (9.9)	9 (10.8)	4 (7.8)	7 (9.2)	0	0	4 (14.3)	2 (16.7)	18 (9.8)	18 (10.0)
Musculoskeletal	98 (97.0)	78 (94.0)	49 (96.1)	70 (92.1)	3 (75.0)	8 (88.9)	28 (100)	11 (91.7)	178 (96.7)	167 (92.8)
Renal	11 (10.9)	10 (12.0)	3 (5.9)	2 (2.6)	0	0	2 (7.1)	3 (25.0)	16 (8.7)	15 (8.3)
Mucocutaneous	96 (95.0)	80 (96.4)	50 (98.0)	73 (96.1)	4 (100)	9 (100)	28 (100)	12 (100)	178 (96.7)	174 (96.7)
Cardiovascular	9 (8.9)	9 (10.8)	1 (2.0)	4 (5.3)	0	1 (11.1)	0	2 (16.7)	10 (5.4)	16 (8.9)
Immunology	68 (67.3)	47 (56.6)	32 (62.7)	49 (64.5)	1 (25.0)	5 (55.6)	17 (60.7)	9 (75.0)	118 (64.1)	110 (61.1)
Hematological and fever	17 (16.8)	12 (14.5)	5 (9.8)	6 (7.9)	0	1 (11.1)	0	1 (8.3)	22 (12.0)	20 (11.1)
BILAG-2004 organ domain involvement[a]										
Constitutional	8 (7.9)	7 (8.4)	2 (3.9)	3 (3.9)	0	0	1 (3.6)	0	11 (6.0)	10 (5.6)
Mucocutaneous	82 (81.2)	72 (86.7)	45 (88.2)	67 (88.1)	3 (75.0)	9 (100)	28 (100)	12 (100)	158 (85.9)	160 (88.9)
Neuropsychiatric	3 (3.0)	7 (8.4)	0	0	0	0	0	1 (8.3)	3 (1.6)	8 (4.4)

Musculoskeletal	91 (90.1)	76 (91.6)	47 (92.2)	66 (86.8)	3 (75.0)	7 (77.8)	26 (92.9)	10 (83.3)	167 (90.8)	159 (88.3)
Cardiorespiratory	7 (6.9)	8 (9.6)	1 (2.0)	5 (6.6)	0	1 (11.1)	1 (3.6)	2 (16.7)	9 (4.9)	16 (8.9)
Gastrointestinal	0	0	0	0	0	0	1 (3.6)	0	1 (0.5)	0
Ophthalmic	0	0	0	1 (1.3)	0	0	0	0	0	1 (0.6)
Renal	10 (9.9)	10 (12.0)	4 (7.8)	2 (2.6)	0	0	1 (3.6)	3 (25.0)	15 (8.2)	15 (8.3)
Hematological	0	1 (1.2)	1 (2.0)	0	0	0	0	0	1 (0.6)	1 (0.6)

BICLA, British Isles Lupus Assessment Group–based Combined Lupus Assessment; BILAG-2004, British Isles Lupus Assessment Group-2004; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥4.

BICLA– and SRI(4)– refer to nonresponders; BICLA+ and SRI(4)+ refer to responders.

[a]Involvement defined as an A or B score at baseline.

Table S5. SLE-related treatments at baseline in TULIP-1, stratified by BICLA/SRI(4) response

	Concordant outcomes				Discordant outcomes				All patients	
	BICLA−/SRI(4)−		BICLA+/SRI(4)+		BICLA+/SRI(4)−		BICLA−/SRI(4)+			
	Placebo (n=101)	Anifrolumab 300 mg (n=83)	Placebo (n=51)	Anifrolumab 300 mg (n=76)	Placebo (n=4)	Anifrolumab 300 mg (n=9)	Placebo (n=28)	Anifrolumab 300 mg (n=12)	Placebo (n=184)	Anifrolumab 300 mg (n=180)
Oral GC, n (%)	86 (85.1)	68 (81.9)	39 (76.5)	65 (85.5)	4 (100)	7 (77.8)	24 (85.7)	10 (83.3)	153 (83.2)	150 (83.3)
≥10 mg/day, n (%)	57 (56.4)	47 (56.6)	26 (51.0)	44 (57.9)	4 (100)	5 (55.6)	15 (53.6)	7 (58.3)	102 (55.4)	103 (57.2)
Dose, mean (SD), mg/day[c]	12.3 (7.7)	14.6 (16.3)	11.9 (8.3)	11.1 (6.3)	17.5 (9.6)	12.9 (7.0)	9.5 (5.8)	11.6 (5.8)	11.9 (7.7)	12.8 (12.0)
Antimalarials, n (%)	76 (75.2)	54 (65.1)	40 (78.4)	54 (71.1)	2 (50.0)	7 (77.8)	16 (57.1)	9 (75.0)	134 (72.8)	124 (68.9)
Immunosuppressants, n (%)	54 (53.5)	43 (51.8)	24 (47.1)	30 (39.5)	1 (25.0)	6 (66.7)	12 (42.9)	6 (50.0)	91 (49.5)	85 (47.2)
NSAIDs, n (%)	20 (19.8)	16 (19.3)	8 (15.7)	9 (11.8)	1 (25.0)	2 (22.2)	6 (21.4)	4 (33.3)	35 (19.0)	31 (17.2)

BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; GC, glucocorticoid; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥4.

BICLA– and SRI(4)– refer to nonresponders; BICLA+ and SRI(4)+ refer to responders.

[a]Oral GC includes prednisone or equivalent.

Table S6. SLEDAI-2K musculoskeletal domain improvement in TULIP-1, stratified by BICLA/SRI(4) response

	Concordant outcomes				Discordant outcomes			
	BICLA−/SRI(4)−		BICLA+/SRI(4)+		BICLA+/SRI(4)−		BICLA−/SRI(4)+	
	Placebo (n=101)	Anifrolumab 300 mg (n=83)	Placebo (n=51)	Anifrolumab 300 mg (n=76)	Placebo (n=4)	Anifrolumab 300 mg (n=9)	Placebo (n=28)	Anifrolumab 300 mg (n=12)
Musculoskeletal involvement at baseline[a]	98	78	48	70	3	8	28	11
Musculoskeletal improvement at Week 52[b]	8 (8.2)	4 (5.1)	47 (97.9)	68 (97.1)	0	1 (12.5)	22 (78.6)	6 (54.5)

BICLA, British Isles Lupus Assessment Group–based Combined Lupus Assessment; BILAG-2004, British Isles Lupus Assessment Group-2004; SLEDAI 2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥4.

[a]Defined as a SLEDAI-2K score in the musculoskeletal domain of >0.

[b]Improvement is a SLEDAI-2K organ system score less than the corresponding score at baseline. Patients treated with restricted medication beyond protocol allowed threshold and those who discontinued investigational product were regarded as nonresponders with respect to improvement in SLEDAI-2K organ systems.

Table S7. Reasons for BICLA nonresponse at Week 52 in TULIP-1 among BICLA nonresponders/SRI(4) responders

	BICLA nonresponders/SRI(4) responders in TULIP-1	
BICLA nonresponse (no improvement in BILAG-2004 A or B items), n (%)	**Placebo (n=28)**	**Anifrolumab 300 mg (n=12)**
Arthritis	2 (7.1)	2 (16.7)
Arthritis only	2 (7.1)	2 (16.7)
Arthritis + other items	0	0
Rash	24 (85.7)	8 (66.7)
Rash only	15 (53.6)	5 (41.7)
Rash + other items	9 (32.1)	3 (25.0)
Cognitive dysfunction	0	1 (8.3)
Pleurisy/pericarditis	0	1 (8.3)
Lupus hepatitis	1 (3.6)	0
Interstitial alveolitis/pneumonitis	1 (3.6)	0

BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; BILAG-2004, British Isles Lupus Assessment Group-2004; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥4.