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Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I)

Eric F Morand, Edward M Vital, Michelle Petri, Ronald van Vollenhoven, Daniel J Wallace, Marta Mosca, Richard A Furie, Maria E Silk, Christina L Dickson, Gabriella Meszaros, Bochao Jia, Brenda Crowe, Inmaculada de la Torre, Thomas Dörner

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Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II)

Michelle Petri, Ian N Bruce, Thomas Dörner, Yoshiya Tanaka, Eric F Morand, Kenneth C Kalunian, Mario H Cardiel, Maria E Silk, Christina L Dickson, Gabriella Meszaros, Lu Zhang, Bochao Jia, Youna Zhao, Conor J McVeigh, Marta Mosca

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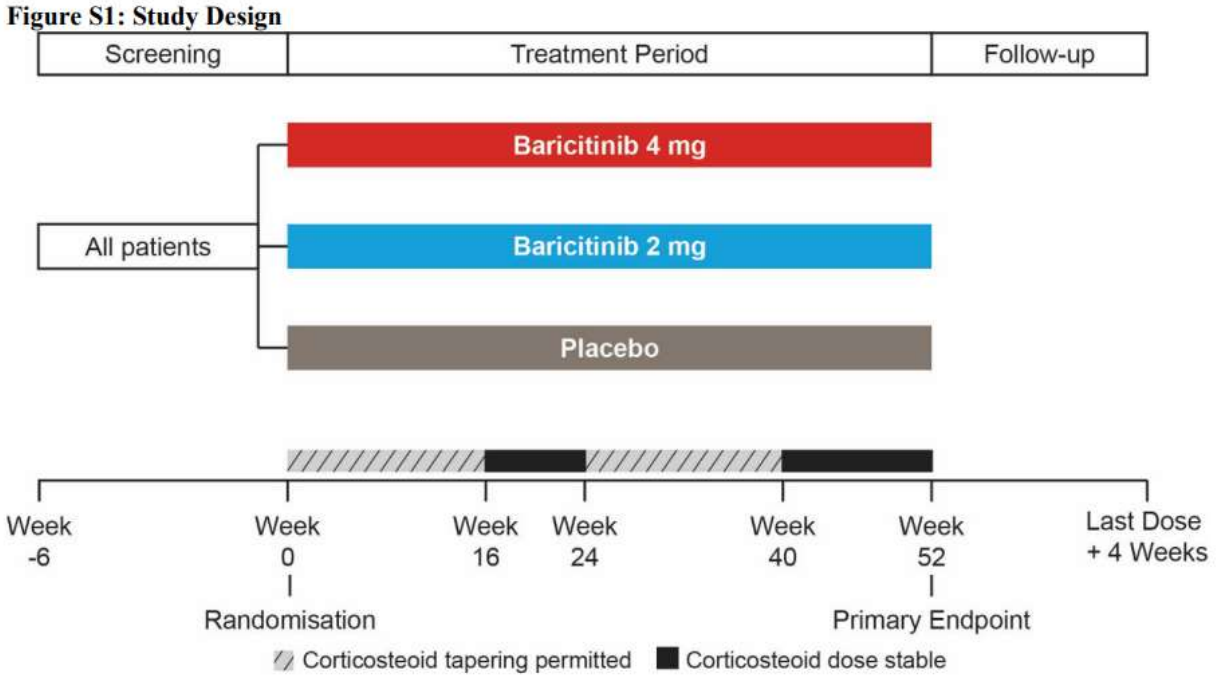
PICOもスタディデザインも同じ２つのRCT

P: moderate – severe activityの成人SLE患者
I: Baricitinib 2 or 4mg/日 p.o
C: Placebo
O: SRI-4 response at week 52

BRAVE-Iは1° endpointを達成し
BRAVE-IIは達成できなかった



Eric F Morandというひと

- オーストラリア、Monash University教授
- LLDASの提唱者（2016年ARD）
- Asia Pacific Lupus Collaboration cohortの立ち上げ
- 多くのSLE治験責任者（Anifrolumab, Baricitinib、Deucravacitinibなど）

主なInclusion Criteria

- 18歳以上の1997 ACR分類基準を満たすSLE
- スクリーニング時点でANA 80倍以上、抗DNA抗体、抗Sm抗体のいずれかが陽性
- SLEDAI ≧ 6　かつ　BILAG A 1つ以上 or BILAG B 2つ以上

主なExclusion Criteria

- Severe active lupus nephritis と severe active CNS lupus

Procedure

- 背景治療として、抗マラリア薬1種類、免疫抑制薬 (IS) 1種類、グルココルチコイド(GC)はPSL 40mg/日以下で安定して使用されて許容される（Belimumab、Anifrolumabは併用不可）
- GC、ISはそれぞれスクリーニング前2週間、8週間は追加、用量変更不可。
- GC減量は0～16週の間、24～40週の間に減量し、40週までにPSL 7.5mg以下にするよう“encouraged but not required”されている

Outcome

- **Primary Endpoint**

  SRI-4 response at 52wk (Bari 4mg vs Placebo)

- **Secondly Endpoints**

  SRI-4 response at 52wk (Bari 2mg vs Placebo)

  SRI-4 response at 24wk

  LLDAS response at 52wk

  PSL>7.5mg/d服用中の患者がPSL 25%以上減量かつPSL≦7.5 mg/dとなり40-52wkで維持されている患者の割合

  first severe flareまでの期間

  Worst Pain Numeric Rating Scaleの変化

  FACIT-Fatigue total Score

- **Exploratory Endpoints**

  SLEDAI-2K organ system domainとBILAG organ domainの改善

背景比較(1)

BRAVE-I

	Placebo (n=253)	Baricitinib 2 mg (n=255)	Baricitinib 4 mg (n=252)
Mean age, years	42·0 (12·0)	42·9 (12·4)	41·5 (12·9)
Mean time since onset of SLE, years	9·4 (7·5)	9·2 (7·7)	8·8 (8·2)
Female	237 (94%)	238 (93%)	237 (94%)
Race	250	251	248
America Indian or Alaska Native	12 (5%)	15 (6%)	7 (3%)
Asian	33 (13%)	39 (16%)	34 (14%)
Black or African American	36 (14%)	23 (9%)	30 (12%)
White	168 (67%)	172 (69%)	177 (71%)
Multiple	1 (0%)	2 (1%)	0
Ethnicity (USA only)	47	49	50
Hispanic or Latino	4 (9%)	13 (27%)	11 (22%)
Not Hispanic or Latino	42 (89%)	35 (71%)	38 (76%)
Not reported	1 (2%)	1 (2%)	1 (2%)
Region	253	255	252
Asia	31 (12%)	32 (13%)	31 (12%)
Central America, South America, and Mexico	74 (29%)	73 (29%)	72 (29%)
Europe	64 (25%)	64 (25%)	63 (25%)
North America	47 (19%)	49 (19%)	50 (20%)
Rest of world	37 (15%)	37 (15%)	36 (14%)

BRAVE-Iはやや白人が多く、アジア人が少ない

BRAVE-II

	Placebo (n=256)	Baricitinib 2 mg (n=261)	Baricitinib 4 mg (n=258)
Baseline characteristics			
Mean age, years	43·5 (13·5)	42·8 (13·0)	42·2 (12·1)
Mean time since onset of SLE, years	9·0 (8·3)	8·7 (7·7)	8·5 (7·7)
Sex			
Female	241 (94%)	246 (94%)	245 (95%)
Male	15 (6%)	15 (6%)	13 (5%)
Race	252	257	254
America Indian or Alaska Native	14 (6%)	12 (5%)	13 (5%)
Asian	71 (28%)	66 (26%)	70 (28%)
Black or African American	17 (7%)	23 (9%)	26 (10%)
Native Hawaiian or other Pacific Islander	0	0	1 (0%)
White	145 (58%)	152 (59%)	140 (55%)
Multiple	5 (2%)	4 (2%)	4 (2%)
Ethnicity (USA only)	50	50	49
Hispanic or Latino	9 (18%)	11 (22%)	8 (16%)
Not Hispanic or Latino	40 (80%)	38 (76%)	40 (82%)
Not reported	1 (2%)	1 (2%)	1 (2%)
Region	256	261	258
North America	50 (20%)	50 (19%)	49 (19%)
Asia	31 (12%)	33 (13%)	31 (12%)
Europe	55 (22%)	57 (22%)	57 (22%)
Central America, South America, and Mexico	59 (23%)	58 (22%)	57 (22%)
Rest of world	61 (24%)	63 (24%)	64 (25%)

背景比較(2)

BRAVE-I

	Placebo (n=253)	Baricitinib 2 mg (n=255)	Baricitinib 4 mg (n=252)
Disease characteristics			
Antinuclear antibodies titre ≥1:80	223 (92%) of 243	214 (87%) of 245	224 (91%) of 246
Mean anti-dsDNA, IU/mL	98·34 (485·43)	68·45 (325·54)	100·02 (522·03)
Mean C3, g/L	1·03 (0·32)	1·07 (0·30)	1·06 (0·32)
Mean C4, g/L	0·18 (0·10)	0·18 (0·090)	0·19 (0·096)
Mean urine protein:creatinine ratio, mg/mmol	21·86 (29·93)	23·10 (24·72)	24·45 (39·87)
<50 mg/mmol urine protein:creatinine ratio	235 (94%)	228 (89%)	227 (90%)
≥50 mg/mmol	16 (6%)	27 (11%)	25 (10%)
Mean eGFR, mL per min per 1·73m²	93·58 (25·09)	94·04 (24·70)	97·17 (26·70)
Concomitant medications			
Glucocorticoids	195 (77%)	194 (76%)	187 (74%)
Mean prednisone dose (or equivalent), mg/day	9·8 (5)	10·4 (7)	10·1 (6)
Prednisone dose (or equivalent) ≥10 mg/day	112 (44%)	102 (40%)	105 (42%)
Antimalarials	213 (84%)	189 (74%)	206 (82%)
Immunosuppressants	150 (59%)	152 (60%)	141 (56%)
Methotrexate	60 (24%)	51 (20%)	52 (21%)
Azathioprine	38 (15%)	54 (21%)	42 (17%)
Mycophenolate mofetil	39 (15%)	39 (15%)	34 (14%)
Non-steroidal anti-inflammatory drug	63 (25%)	67 (26%)	68 (27%)
Mean SLEDAI-2K score	10·1 (3)	10·3 (3)	10·0 (3)

免疫学的指標や背景治療はほぼ同様

BRAVE-II

	Placebo (n=256)	Baricitinib 2 mg (n=261)	Baricitinib 4 mg (n=258)
Disease characteristics			
Antinuclear antibodies titre ≥1:80	231 (95%) of 244	242 (95%) of 255	241 (96%) of 250
Mean anti-dsDNA, IU/mL	67·3 (263·9)	142·8 (692·8)	143·9 (590·7)
Anti-dsDNA ≥15 IU/mL	97 (38%)	111 (43%)	97 (38%)
Mean C3, g/L	1·08 (0·33)	1·05 (0·32)	1·07 (0·33)
C3 <90·0 mg/dL	84 (33%)	86 (33%)	79 (31%)
Mean C4, g/L	0·19 (0·10)	0·18 (0·10)	0·19 (0·10)
C4 <10·0 mg/dL	51 (20%)	57 (22%)	56 (22%)
Mean urine protein:creatinine ratio, mg/mmol	25·05 (41·58)	24·30 (30·09)	20·72 (24·94)
Urine protein:creatinine ratio <50 mg/mmol	232 (91%)	234 (90%)	242 (94%)
Urine protein:creatinine ratio ≥50 mg/mmol	24 (9%)	27 (10%)	16 (6%)
Mean eGFR, mL per min per 1·73m²	95·8 (29·3)	94·0 (25·7)	99·1 (30·9)
Concomitant medications			
Glucocorticoids	207 (81%)	210 (80%)	207 (80%)
Mean prednisone dose (or equivalent), mg/day	8·8 (5·0)	9·6 (5·9)	9·8 (5·7)
Prednisone dose (or equivalent) ≥10 mg/day	101 (39%)	113 (43%)	104 (40%)
Antimalarials	209 (82%)	213 (82%)	213 (83%)
Immunosuppressants	140 (55%)	133 (51%)	133 (52%)
Methotrexate	49 (19%)	52 (20%)	60 (23%)
Azathioprine	47 (18%)	48 (18%)	33 (13%)
Mycophenolate mofetil	29 (11%)	25 (10%)	25 (10%)
Non-steroidal anti-inflammatory drug	51 (20%)	64 (25%)	70 (27%)
Mean SLEDAI-2K score	10·1 (3·2)	10·1 (3·4)	10·1 (3·0)
SLEDAI-2K score ≥10	147 (57%)	149 (57%)	144 (56%)

背景比較(3)

BRAVE-I

	Placebo (N=253)	Baricitinib 2 mg (N=255)	Baricitinib 4 mg (N=252)
(Continued from previous page)			
SLEDAI-2K score ≥10	144 (57%)	152 (60%)	146 (58%)
SLEDAI-2K organ system involvement			
CNS	0	0	0
Vascular	15 (6%)	15 (6%)	10 (4%)
Musculoskeletal	247 (98%)	250 (98%)	247 (98%)
Renal	15 (6%)	24 (9%)	17 (7%)
Mucocutaneous	244 (96%)	246 (97%)	241 (96%)
Cardiovascular and respiratory	10 (4%)	6 (2%)	8 (3%)
Immunological	134 (53%)	131 (51%)	137 (54%)
Constitutional	4 (2%)	3 (1%)	2 (1%)
Haematological	13 (5%)	13 (5%)	21 (8%)
≥1 BILAG A scores, n (%)	154 (61%)	173 (68%)	154 (61%)
≥2 BILAG B scores, n (%)	81 (32%)	69 (27%)	85 (34%)
Mean Physician's Global Assessment score	1·8 (0·5)	1·8 (0·4)	1·8 (0·5)
Mean CLASI activity score	6·3 (6·2)	6·5 (7·0)	6·1 (5·6)
Mean tender joint count	10·0 (7·0)	10·3 (6·5)	10·9 (7·0)
Mean swollen joint count	7·1 (5·6)	6·9 (5·1)	6·9 (5·4)
Mean SLICC/ACR Damage Index score	0·6 (1·0)	0·6 (1·0)	0·6 (1·0)

BRAVE-II

	Placebo (N=256)	Baricitinib 2 mg (N=261)	Baricitinib 4 mg (N=258)
(Continued from previous page)			
SLEDAI-2K organ system involvement			
CNS	0	0	0
Vascular	12 (5%)	11 (4%)	14 (5%)
Musculoskeletal	252 (98%)	253 (97%)	251 (97%)
Renal	18 (7%)	22 (8%)	10 (4%)
Mucocutaneous	243 (95%)	252 (97%)	251 (97%)
Cardiovascular and respiratory	4 (2%)	6 (2%)	9 (3%)
Immunological	138 (54%)	143 (55%)	132 (51%)
Constitutional	8 (3%)	10 (4%)	11 (4%)
Haematological	20 (8%)	19 (7%)	17 (7%)
≥1 BILAG A scores	172 (67%)	188 (72%)	172 (67%)
≥2 BILAG B scores	73 (29%)	64 (25%)	76 (29%)
Mean Physician's Global Assessment score	60·0 (14·6)	61·0 (12·5)	58·8 (14·6)
Mean CLASI activity score	6·8 (6·1)	6·6 (6·6)	6·7 (5·8)
Mean tender joint count	10·6 (7·1)	10·3 (6·8)	10·6 (7·1)
Mean swollen joint count	6·41 (5·4)	6·64 (5·1)	6·68 (5·0)
Mean SLICC/ACR Damage Index score	0·66 (1·1)	0·68 (1·1)	0·60 (1·0)

罹患臓器や疾患活動性はほぼ変わらない

結果比較(1)

BRAVE-I

	Placebo (n=253)	Baricitinib 2 mg (n=255)	Baricitinib 2 mg odds ratio (95% CI); difference with placebo (95% CI); p value	Baricitinib 4 mg (n=252)	Baricitinib 4 mg odds ratio (95% CI); difference with placebo (95% CI); p value
Primary outcome					
SRI-4*†	116 (46%)	126 (50%)	1·14 (0·79 to 1·65); 3·9 (−4·9 to 12·6); 0·47	142 (57%)	1·57 (1·09 to 2·27); 10·8 (2·0 to 19·6); 0·016
Reduction of ≥4 points from baseline in SLEDAI-2K score*†	117 (47%)	128 (50%)	1·14 (0·80 to 1·64); 0·47	146 (58%)	1·62 (1·12 to 2·34); 0·010
No new BILAG A and no more than one new BILAB B disease activity score*†	182 (72%)	196 (77%)	1·25 (0·83 to 1·88); 0·29	200 (80%)	1·49 (0·98 to 2·29); 0·065
No worsening (defined as an increase of ≥0·3 points [10 mm] from baseline) in the PGA*†	183 (73%)	197 (77%)	1·25 (0·83 to 1·89); 0·29	197 (79%)	1·37 (0·90 to 2·09); 0·14
Major secondary outcomes					
SRI-4 (week 24)*†	99 (39%)	114 (45%)	1·25 (0·87 to 1·81); 5·7 (−2·9 to 14·3); 0·23	117 (47%)	1·37 (0·95 to 1·99); 7·4 (−1·3 to 16·1); 0·094
Participants with ≥1 severe flare‡	38 (15%)	34 (13%)	0·83 (0·52 to 1·32); 0·44	26 (10%)	0·65 (0·40 to 1·08); 0·094
Median time to first severe flare (95% CI)	NA	NA	..	NA	..
Glucocorticoid sparing†§	36/117 (31%)	31/106 (29%)	0·94 (0·53 to 1·66); −1·5 (−13·3 to 10·5); 0·82	36/106 (34%)	1·18 (0·67 to 2·08); 3·2 (−9·0 to 15·3); 0·57
LLDAS*†	66 (26%)	65 (26%)	0·96 (0·63 to 1·45); −0·5 (−8·1 to 7·2); 0·84	74 (30%)	1·19 (0·80 to 1·79); 3·5 (−4·3 to 11·4); 0·39
Worst Pain NRS¶	−1·62 (0·15)	−1·73 (0·15)	−0·11 (−0·52 to 0·30); 0·60	−1·71 (0·15)	−0·09 (−0·50 to 0·32); 0·67
FACIT-Fatigue total score¶	7·4 (0·6)	7·5 (0·6)	0·02 (−1·65 to 1·70); 0·98	7·1 (0·6)	−0·36 (−2·03 to 1·32); 0·68
BICLA response	106 (42%)	108 (43%)	1·02 (0·71 to 1·46); 0·8 (−7·9 to 9·4); 0·92	126 (50%)	1·39 (0·97 to 1·98); 8·2 (−0·6 to 16·9); 0·072
Other secondary outcomes					
SLEDAI-2K¶	−4·4 (0·2)	−4·7 (0·2)	−0·26 (−0·92 to 0·40); 0·43	−5·3 (0·2)	−0·84 (−1·50 to −0·17); 0·014
SLEDAI-2K remission of arthritis or rash	121 (48%)	126 (49%)	1·04 (0·73 to 1·48); 1·4 (−7·3 to 10·0); 0·83	147 (59%)	1·53 (1·07 to 2·19); 10·5 (1·8 to 19·0); 0·019
PGA¶	−32·1 (1·3)	−35·1 (1·3)	−3·02 (−6·58 to 0·53); 0·095	−37·1 (1·3)	−4·93 (−8·50 to −1·36); 0·0069
≥50% reduction in CLASI activity score†‖	24/49 (49%)	25/46 (54%)	1·02 (0·43 to 2·42); 5·4 (−14·2 to 24·4); 0·97	24/43 (56%)	1·22 (0·51 to 2·92); 6·8 (−13·2 to 26·0); 0·66
28-tender joint count¶	−7·5 (0·3)	−7·3 (0·3)	0·24 (−0·61 to 1·08); 0·58	−7·9 (0·3)	−0·44 (−1·29 to 0·41); 0·31
28-swollen joint count¶	−5·4 (0·2)	−5·7 (0·2)	−0·29 (−0·84 to 0·25); 0·29	−5·8 (0·2)	−0·44 (−0·99 to 0·11); 0·11
Worst Joint Pain NRS¶	−1·7 (0·2)	−1·8 (0·2)	−0·17 (−0·59 to 0·24); 0·42	−1·8 (0·2)	−0·12 (−0·54 to 0·29); 0·57

BRAVE-II

	Placebo (N=256)	Baricitinib 2 mg (N=261)	Baricitinib 2 mg odds ratio (95% CI); difference with placebo (95% CI); p value	Baricitinib 4 mg (N=258)	Baricitinib 4 mg odds ratio (95% CI); difference with placebo (95% CI); p value
Primary outcome					
SRI-4*†‡	116 (46%)	120 (46%)	1·05 (0·73, 1·50); 0·8 (−7·9 to 9·4); 0·79	121 (47%)	1·07 (0·75 to 1·53); 1·5 (−7·1 to 10·2); 0·71
Reduction of ≥4 points from baseline in SLEDAI-2K score*†‡	116 (46%)	124 (48%)	1·10 (0·77 to 1·57); 1·8 (−6·8 to 10·5); 0·61	123 (48%)	1·09 (0·76 to 1·56); 2·0 (−6·6 to 10·6); 0·63
No new BILAG A and no more than one new BILAG B disease activity score*†‡	196 (77%)	195 (75%)	0·92 (0·61 to 1·38); −1·7 (−9·2 to 5·7); 0·69	188 (73%)	0·82 (0·55 to 1·23); −3·8 (−11·3 to 3·8); 0·33
No worsening (defined as an increase of ≥0·3 points [10 mm] from baseline) in the PGA*‡	198 (78%)	197 (76%)	0·91 (0·60 to 1·39); −1·8 (−9·3 to 5·7); 0·67	191 (74%)	0·83 (0·55 to 1·26); −3·3 (−10·8 to 4·2); 0·39
Major secondary outcomes n (%)					
SRI-4 (week 24)*†‡	98 (39%)	104 (40%)	1·08 (0·75 to 1·57); 1·3 (−7·2 to 9·9); 0·68	108 (42%)	1·18 (0·81 to 1·71); 3·5 (−5·2 to 12·1); 0·39
Participants with ≥1 severe flare‡	26 (10%)	29 (11%)	1·11 (0·65 to 1·89); 0·70	29 (11%)	1·15 (0·67 to 1·94); 0·62
Glucocorticoid sparing*†§	33/104 (32%)	34/114 (30%)	0·91 (0·51 to 1·64); −1·9 (−14·1 to 10·2); 0·76	36/105 (34%)	1·17 (0·65 to 2·10); 2·6 (−10·1 to 15·1); 0·61
LLDAS*†‡	59 (23%)	62 (24%)	1·10 (0·72 to 1·68); 0·8 (−6·6 to 8·2); 0·67	65 (25%)	1·15 (0·75 to 1·75); 2·2 (−5·2 to 9·6); 0·52
Worst Pain NRS¶	−1·37 (0·14)	−1·45 (0·14)	−0·08 (−0·47 to 0·32); 0·70	−1·44 (0·14)	−0·07 (−0·46 to 0·33); 0·74
FACIT-Fatigue total score¶	7·26 (0·60)	6·9 (0·60)	−0·36 (−2·00 to 1·28); 0·67	6·96 (0·61)	−0·30 (−1·95 to 1·35); 0·72
Other secondary outcomes					
BICLA	110 (43%)	120 (46%)	1·15 (0·80 to 1·64); 3·0 (−5·6 to 11·7); 0·45	114 (44%)	1·04 (0·73 to 1·49); 1·1 (−7·5 to 9·7); 0·82
SLEDAI-2K¶‖	−4·14 (0·26)	−4·12 (0·26)	0·02 (−0·70 to 0·73); 0·96	−4·46 (0·26)	−0·32 (−1·04 to 0·40); 0·39
SLEDAI-2K remission of arthritis or rash	130 (51%)	131 (51%)	1·01 (0·71 to 1·44); −0·2 (−8·8 to 8·4); 0·95	133 (52%)	1·04 (0·73 to 1·48); 0·8 (−7·8 to 9·3); 0·84
PGA¶‖	−33·74 (1·29)	−34·46 (1·30)	−0·72 (−4·29 to 2·86); 0·70	−36·70 (1·32)	−2·96 (−6·57 to 0·64); 0·11
≥50% reduction in CLASI activity score*†**	39/59 (66%)	29/51 (57%)	0·69 (0·31 to 1·55); −9·2 (−26·6 to 8·7); 0·37	29/50 (58%)	0·78 (0·34 to 1·78); −8·1 (−25·6 to 9·8); 0·56
28-tender joint count¶‖	−6·92 (0·30)	−7·40 (0·30)	−0·48(−1·31 to 0·34) 0·25	−7·83 (0·31)	−0·91 (−1·74 to −0·07) 0·033*
28-swollen joint count¶‖	−4·79 (0·20)	−5·10 (0·20)	−0·30 (−0·86 to 0·25); 0·28	−5·31 (0·21)	−0·52 (−1·08 to 0·04); 0·069
Worst Joint Pain NRS¶‖	−1·43 (0·14)	−1·52 (0·14)	−0·09 (−0·48 to 0·30); 0·65	−1·47 (0·14)	−0·04 (−0·44 to 0·36); 0·84

1º outcomeのSRI4達成(52w)はBRAVE-I ○ BRAVE-II ×。その要因はBari 4mgの有効性がBRAVE-IIで低かった
すべての2º outcomeはBRAVE-Iでも×。　BRAVE-IIはBICLA達成で評価しても有意差は認めず。

結果比較　SRI-4達成率

BRAVE-I

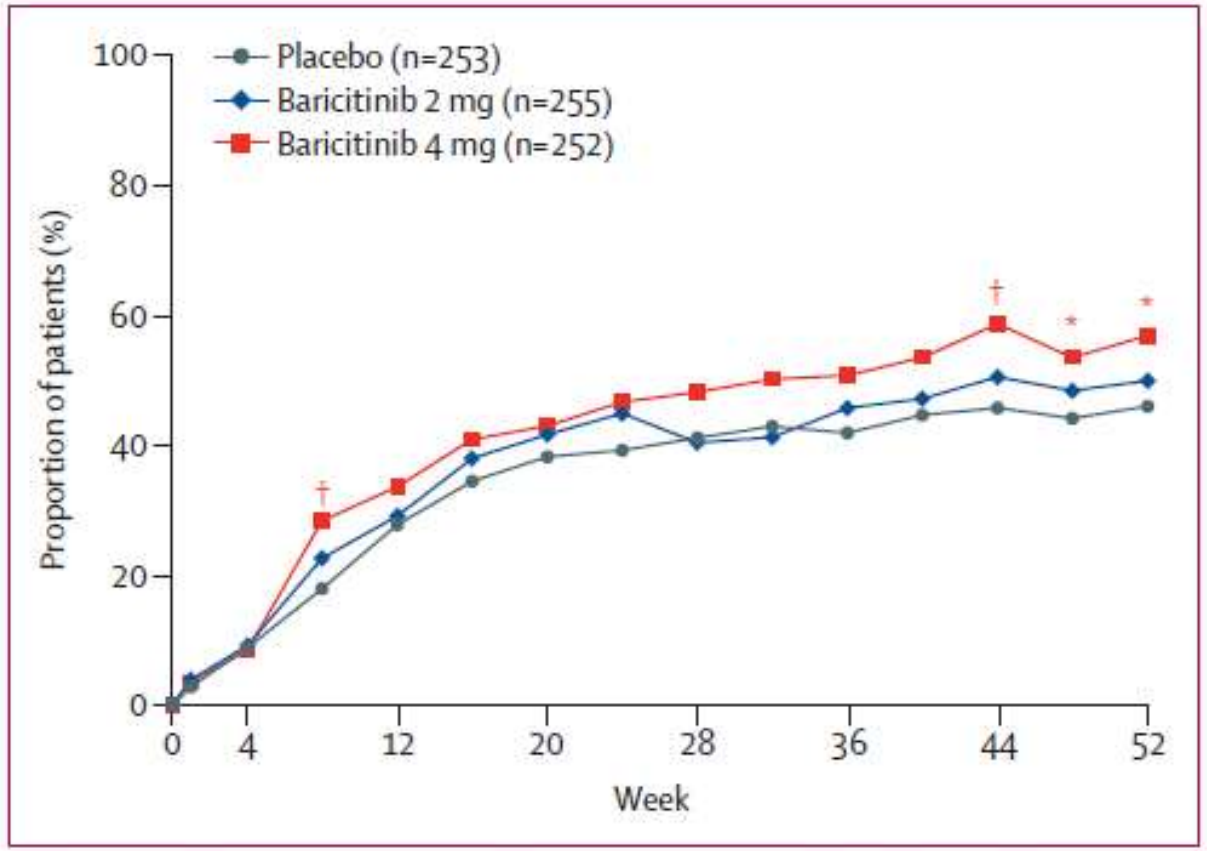


Figure 2: SRI-4 response through 52 weeks in overall study population

BRAVE-II

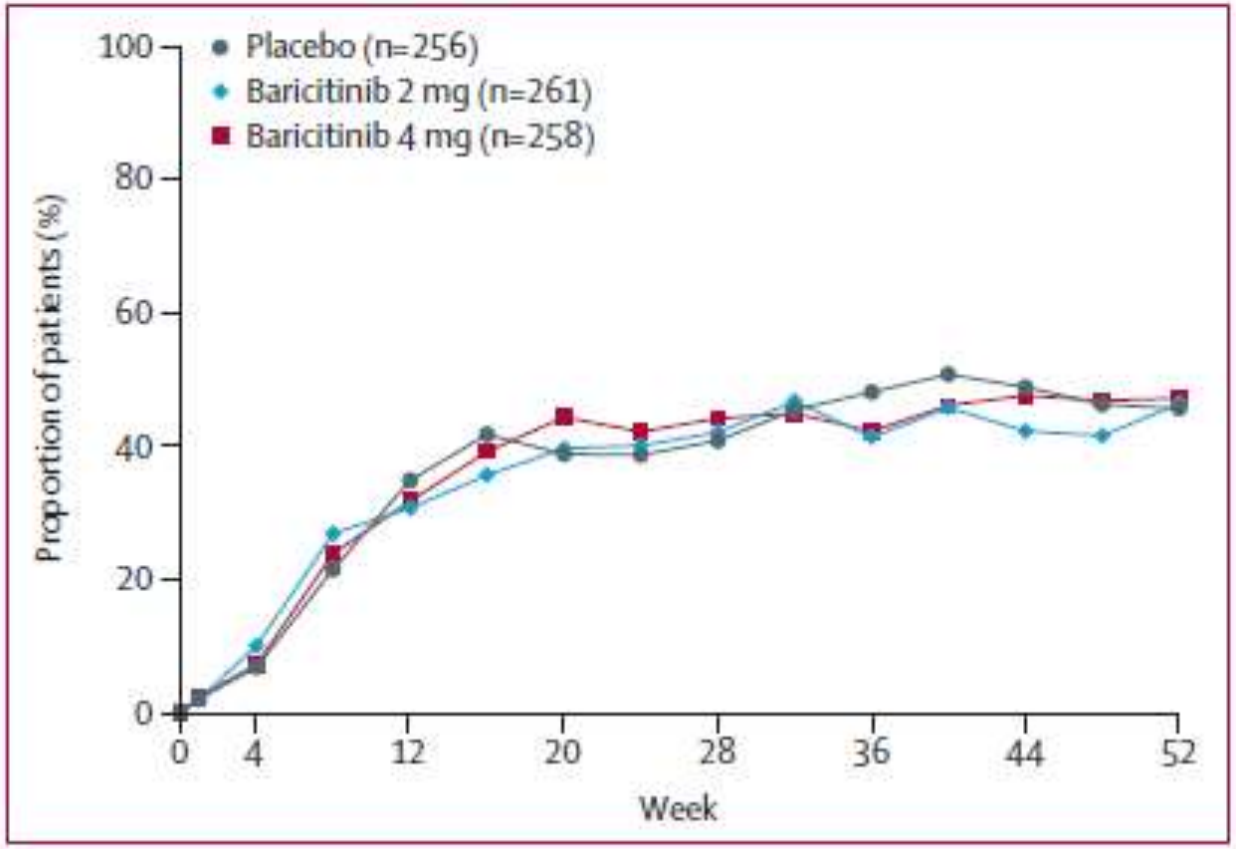


Figure 2: SRI-4 response through 52 weeks in overall study population

有効性評価（ドメイン別）

BRAVE-I

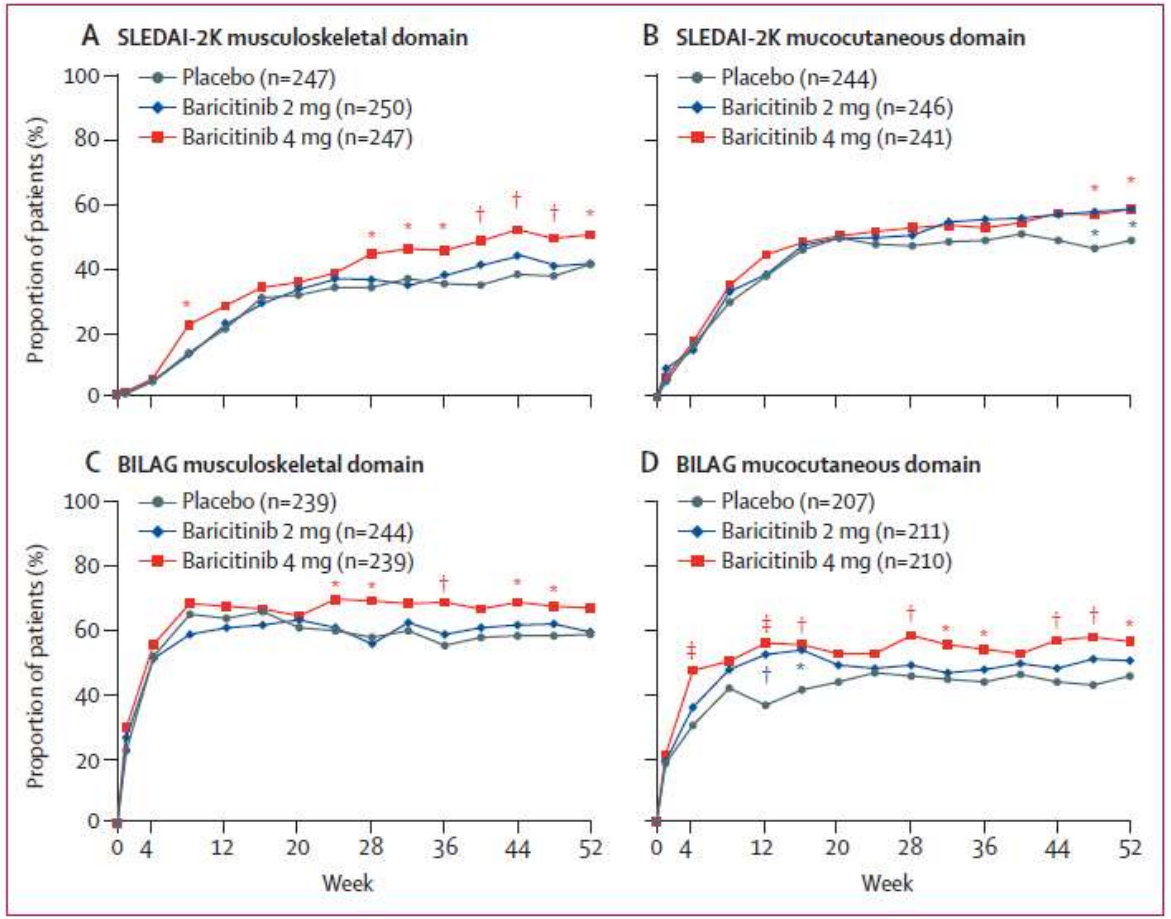


Figure 3: Improvement from baseline in SLEDAI-2K and BILAG organ systems through 52 weeks

BRAVE-II

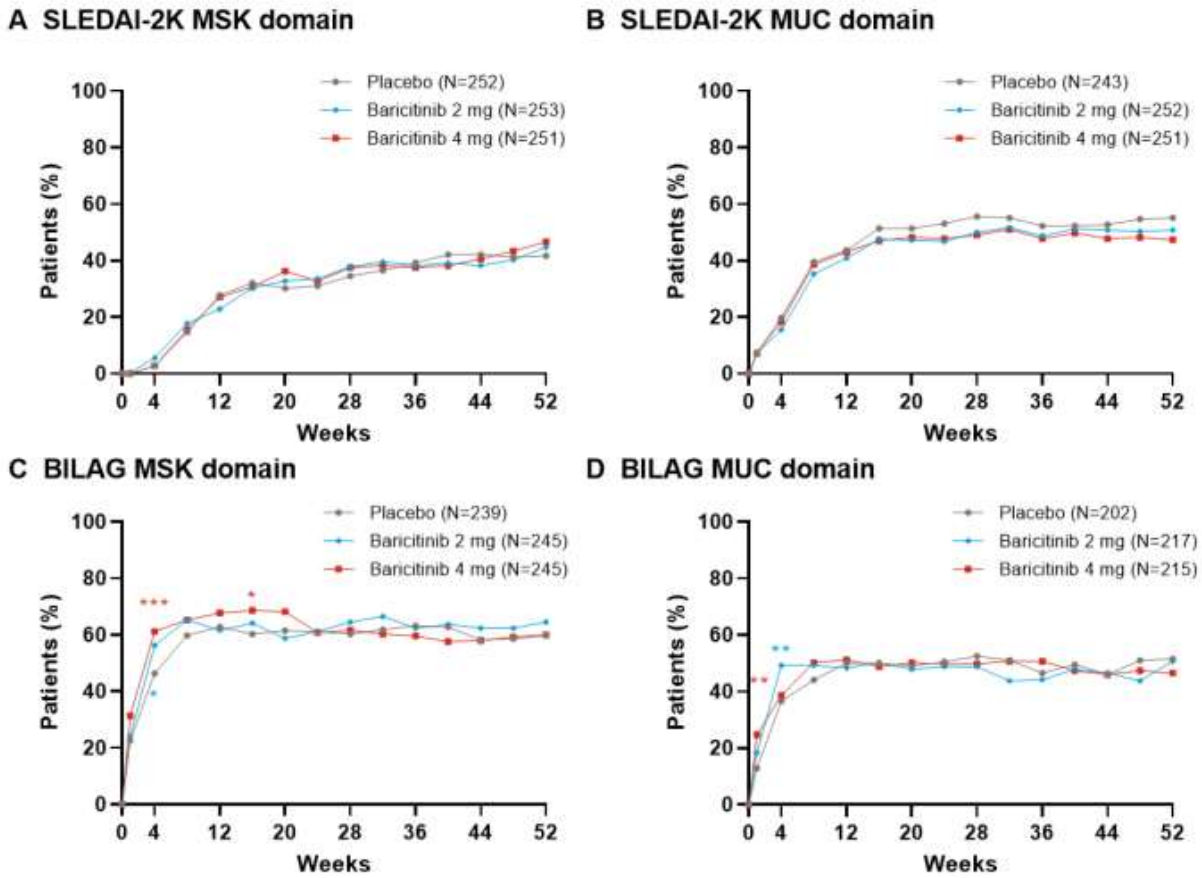


Figure S6. Improvement from baseline in SKEDAI-2K and BILAG organ systems through 52 weeks

BRAVE-IIは皮膚症状のみ、筋骨格系のみでもダメ

BRAVE-I　有害事象

	Placebo (N=253)	Baricitinib 2 mg (N=255)	Baricitinib 4 mg (N=252)
Treatment-emergent adverse events	210 (83%)	210 (82%)	208 (83%)
Mild	88 (35%)	92 (36%)	88 (35%)
Moderate	106 (42%)	97 (38%)	98 (39%)
Severe	16 (6%)	21 (8%)	22 (9%)
Serious adverse events	18 (7%)	24 (9%)	26 (10%)
Death	1 (0%)	1 (0%)	0
Discontinuation from study treatment because of an adverse event (including death)	21 (8%)	28 (11%)	17 (7%)
Infections	131 (52%)	141 (55%)	143 (57%)
Serious infections	3 (1%)	10 (4%)	7 (3%)
Herpes simplex	12 (5%)	9 (4%)	5 (2%)
Herpes zoster virus infection	9 (4%)	9 (4%)	17 (7%)
Opportunistic infections	14 (6%)	17 (7%)	20 (8%)
Pulmonary tuberculosis	0	0	1 (0%)
COVID-19	9 (4%)	17 (7%)	14 (6%)
Major adverse cardiovascular events*	0	0	1 (0%)
Cardiovascular death	0	0	0
Myocardial infarction	0	0	0
Stroke	0	0	1 (0%)
Arterial thromboembolic events*	0	0	0
Venous thromboembolic events*	2 (1%)	2 (1%)	1 (0%)
Deep-vein thrombosis	0	2 (1%)	0
Pulmonary embolism	0	1 (0%)	0
Other†	2 (1%)	0	1 (0%)
Malignancies			
Non-melanoma skin cancer	1 (0%)	0	0
Malignancies other than non-melanoma skin cancer	1 (0%)	2 (1%)	1 (0%)
Gastrointestinal perforations	0	1 (0%)	0
Hepatic disorders	14 (6%)	19 (8%)	12 (5%)

Data are n (%). Adverse events that occurred between baseline and week 52 and up to 28 days after treatment are shown. *Positively adjudicated by an independent external masked clinical event committee. †Other events were all classified as non-superficial below knee thrombosis.

Table 3: Bariの新たな有害事象シグナルを認めず

Discussion (BRAVE-II)

Discussion

JAK inhibitors with varied and selective inhibitory profiles have enabled a shift in the treatment of multiple autoimmune disorders.[9] JAK inhibitors suppress the intracellular signalling of multiple cytokines involved in the cause of rheumatoid arthritis, alopecia areata, and other inflammatory diseases.[9]

Baricitinib is an oral small molecule inhibitor of JAK1 and JAK2 signalling that is approved for the treatment of rheumatoid arthritis, atopic dermatitis, and alopecia areata. A considerable body of evidence supports the role of pathways targeted by baricitinib in the pathogenesis of SLE,[9] including positive results of a phase 2 study, which showed that daily oral baricitinib 4 mg in conjunction with SOC was superior to placebo plus SOC in resolving SLEDAI-2K arthritis or rash at week 24[9] and evidence from the same study showed effects on expression of JAK–STAT pathway genes, interferon responsive genes, and serum cytokines.[9,10] These data prompted and supported the investigation of baricitinib in a phase 3 trial programme.

In this study, treatment with once-daily oral baricitinib 4 mg in addition to SOC did not achieve the primary outcome of a higher proportion of patients reaching an SRI-4 response compared with placebo. There were no differences between baricitinib 4 mg or 2 mg and placebo, based on nominal *p* value, in any non-multiplicity-controlled secondary outcomes or exploratory outcomes, and analysts had not identified any subset of responders based on clinical or molecular characteristics (data not shown). These findings, despite positive results in a parallel phase 3 study that included the same primary outcome measure,[9] leave uncertainty regarding baricitinib's efficacy as a treatment for SLE. The profile of patients, including organ involvement, in this trial was similar to that of other recent late-stage clinical trials in SLE,[9] suggesting that patient selection was not a major factor.

No new safety signals were observed; safety was consistent with the known profile for baricitinib. Rates of herpes zoster infections were higher in patients given baricitinib 4 mg, which is consistent with other patient groups and typical for JAK1 inhibitors.[9] Serious infections were higher in the baricitinib 4 mg group, but within the expected range. Other treatment-emergent and serious adverse events were within the expected range, including MACE, malignancy, VTEs, and infections. Notably, there was no VTE excess within this population at high risk of VTEs.[9] Safety will be further evaluated in the integrated safety dataset, including safety data from all baricitinib studies in SLE.

Limitations of this study are similar to those of other trials in SLE, including the exclusion of patients with severe active renal and CNS disease. Additional limitations include that part of the trial occurred during the COVID-19 pandemic, and that there were high placebo rates compared with other recent SLE trials,[9] which might have partially masked the efficacy of baricitinib in SLE. Due to missing data and reduced power for the analysis in the subpopulations of participants with SLEDAI-2K score of 10 or greater and glucocorticoid dose of 10 mg or greater, caution should be taken when interpreting the analysis. Steroid tapering was not enforced as strictly as it might have been in other recent trials, which could have contributed to the high placebo response rate.

Although phase 2 data suggested baricitinib as a potential treatment for patients with SLE, in particular for patients with high disease activity in joints, the SLE-BRAVE-II phase 3 study was negative and additional studies into the efficacy of baricitinib in patients with SLE are not planned.

こんな短いDiscussion見たことない。。。

・　1º だけでなく2º outcomeもすべて有意差がなかった。これはどのような臨床的、分子的特徴のサブセットで解析しても同様だった（data not shown)。

・　罹患臓器を含めた患者profileは他のSLE治験と同様であり、患者選定の問題ではない

・　Limitationとしては、
1. 重篤な腎障害、中枢神経障害は含まれていない
2. 治験の一部がCOVID-19のpandemic最中に重なった
3. プラセボでの達成率が高い（他の治験と比較しても）
4. ステロイド減量圧力が他の治験ほど厳しくなかった

参考1: Tulip2でのプラセボ率

Table 2. Primary and Key Secondary Efficacy End Points.

End Point	Placebo (N=182)*	Anifrolumab, 300 mg (N=180)*
	number/total number (percent)	
Primary end point: BICLA response at wk 52‡	57/182 (31.5)	86/180 (47.8)
Key secondary end points		
BICLA response at wk 52 in patients with a high type I interferon gene signature	46/151 (30.7)	72/150 (48.0)
Glucocorticoid reduction to target dose, sustained from wk 40 to wk 52§	25/83 (30.2)	45/87 (51.5)

参考2: BLISS-52でのプラセボ率

	Belimumab 1 mg/kg (n=288)	Belimumab 10 mg/kg (n=290)	Placebo (n=287)
SRI response rate*	148 (51%)	167 (58%)	125 (44%)

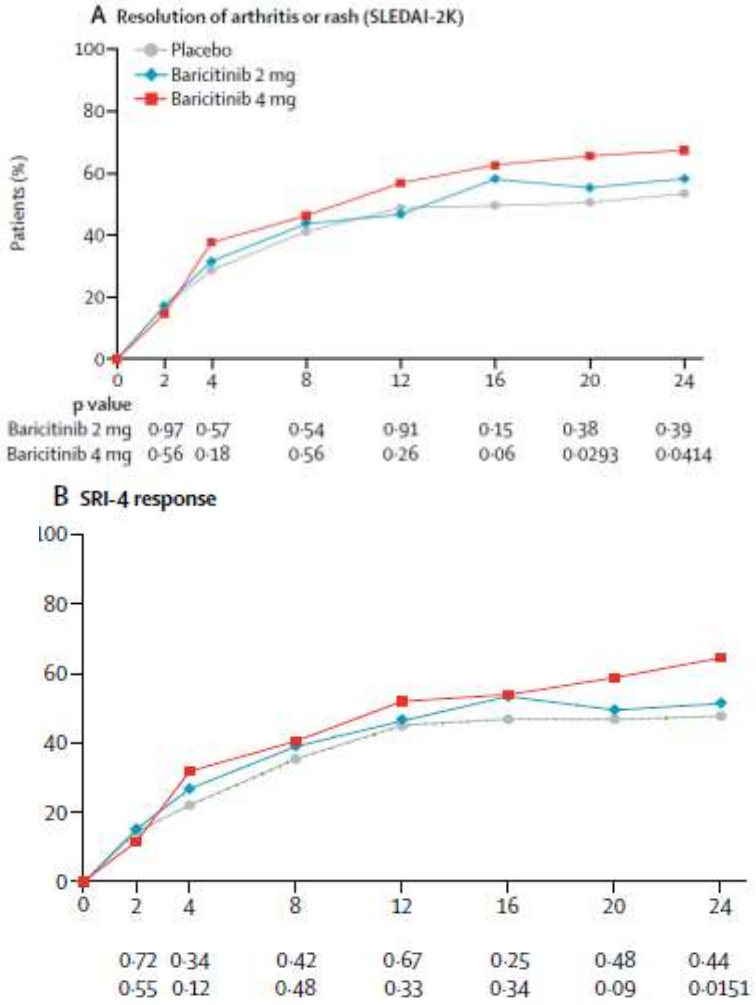
参考（P2結果）

Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial

Daniel J Wallace, Richard A Furie, Yoshiya Tanaka, Kenneth C Kalunian, Marta Mosca, Michelle A Petri, Thomas Dörner, Mario H Cardiel, Ian N Bruce, Elisa Gomez, Tara Carmack, Amy M DeLozier, Jonathan M Jones, Matthew D Linnik, Stephanie de Bono, Maria E Silk, Robert W Hoffman

***Lancet* 2018; 392: 222–31**

皮疹もしくは関節炎のあるSLEを対象にBari 4mg/2mg/placebo。
Primary Endpointは皮疹もしくは関節炎の回復率（SLEDAI)。
Primary Endpointは満たしたがギリギリ。



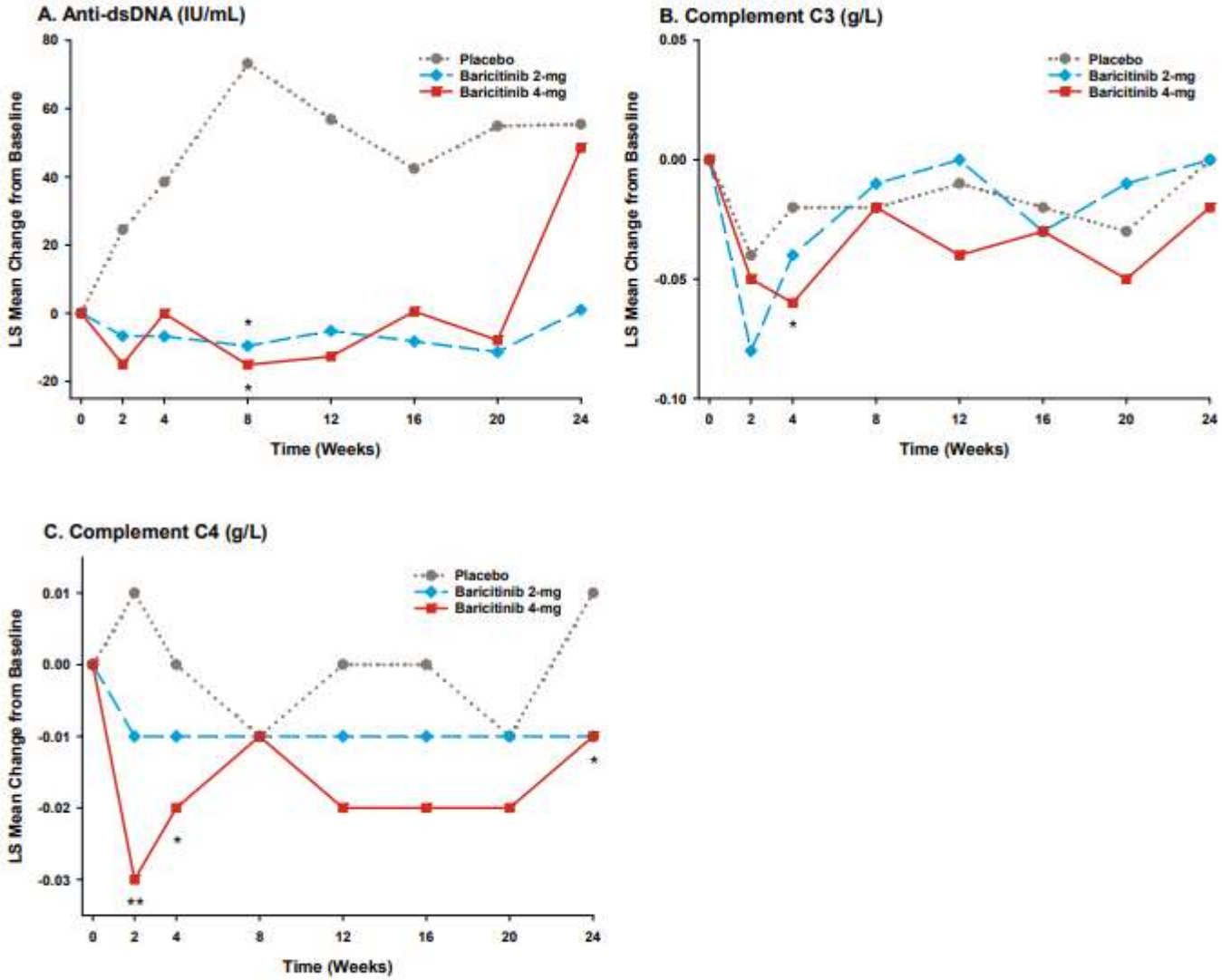


Figure S4: Biomarker Analyses, Weeks 0-24.