SUPPLEMENTARY MATERIAL

Sifalimumab, an anti-interferon-alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus

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EXCLUSION CRITERIA

Patients were excluded from the study if they had: active systemic lupus erythematosus (SLE)-driven renal disease; active severe or unstable neuropsychiatric SLE; overlap syndromes; non-SLE-driven inflammatory joint or skin diseases; positive tuberculosis test (unless prophylactic treatment had been initiated prior to study drug); recent live or attenuated virus vaccination; ongoing or chronic serious infections; antibiotics or hospitalisation for treatment of infection within 4 weeks of baseline; history of severe *Herpes* infections; *Herpes zoster* infection within 3 months of screening; hepatitis B positivity (unless it was isolated core positive); hepatitis C positivity; history of HIV; or history of cancer (except basal cell or cervical cancer cured ≥1 year before baseline).

METHODS

Up to three protocol-defined oral corticosteroid burst and tapers at 28-day intervals were permitted for increased SLE disease activity between Day 1 and Day 127 (Week 0 and Week 18). For burst and taper increase in prednisone (or equivalent) up to 40 mg/day was permitted, but the dosage had to be tapered to baseline oral corticosteroid dosage within 14 days. From Day 85 (Week 12) onwards, oral corticosteroid reduction below baseline was permitted. Intramuscular (80 mg or 160 mg methylprednisolone) or intra-articular injections (up to 20 mg triamcinolone acetonide per joint in a maximum of two joints) was permitted in lieu of oral corticosteroids. Intravenous corticosteroids were not permitted.

Oral corticosteroid tapering in patients meeting pre-defined clinical response criteria was optional, and the final decision to taper was at the discretion of the treating physician. To be eligible for tapering, patients had to have a 6-point improvement in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI–2K) or a 6-point improvement in Clinical SLEDAI, and a Physician's Global Assessment (PGA) of <0.5 at the current and prior visit, and no increase in disease activity that required the administration of any intramuscular methylprednisone, initiation of oral corticosteroids, or an increase in existing oral corticosteroid therapy above baseline for a minimum of 12 weeks prior to the current visit. Tapering was permitted on Days 85 (Week 12) and 113 (Week 16), and then from Days 169 to 281 (Week 24 to Week 40). Oral corticosteroid tapering was only permitted once every 4 weeks, and could not occur until after all assessments for a particular visit were completed. An External Adjudication Group confirmed that patients qualified for tapering at each potential tapering visit after reviewing the patients' SLEDAI–2K, Clinical SLEDAI, PGA, and oral corticosteroid burst and taper history. Patients with a 6-point improvement in Clinical SLEDAI were eligible for tapering without waiting for SLEDAI–2K laboratory data to be analysed.

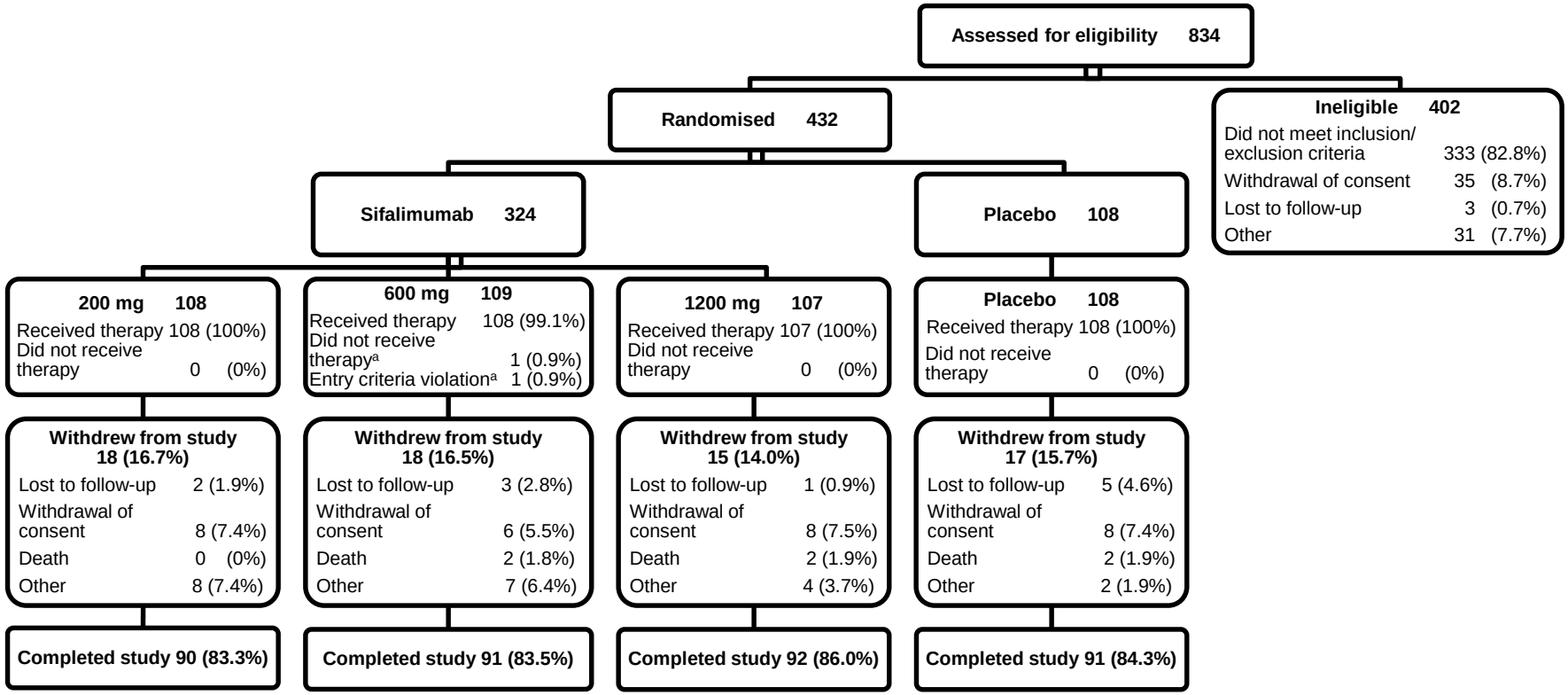
RANDOMISATION AND MASKING

An interactive voice response system (IVRS)/interactive web response system (IWRS) was used for randomisation to a treatment arm and assignment of blinded investigational product kit numbers. A patient was considered randomised into the study when the investigator or delegated site personnel notified the IVRS/IWRS that the patient met eligibility criteria and the IVRS/IWRS provided the assignment of blinded investigational product kit numbers to the patient. The randomisation procedure for IVRS/IWRS is as follows:

- Prior to Day 1, Asuragen (MedImmune's diagnostic partner) contacted the IVRS/IWRS and provided the patient's results (high versus low) of the type I IFN signature in whole blood using the four-gene diagnostic. Notification of this activity was sent to the investigational site but not the result
- Prior to Day 1, the External Adjudication Group contacted the IVRS/IWRS to confirm eligibility based on the patient's screening SLEDAI–2K (and/or "Clinical" SLEDAI–2K), BILAG–2004, and PGA assessments; notification of this activity was sent to the investigational site

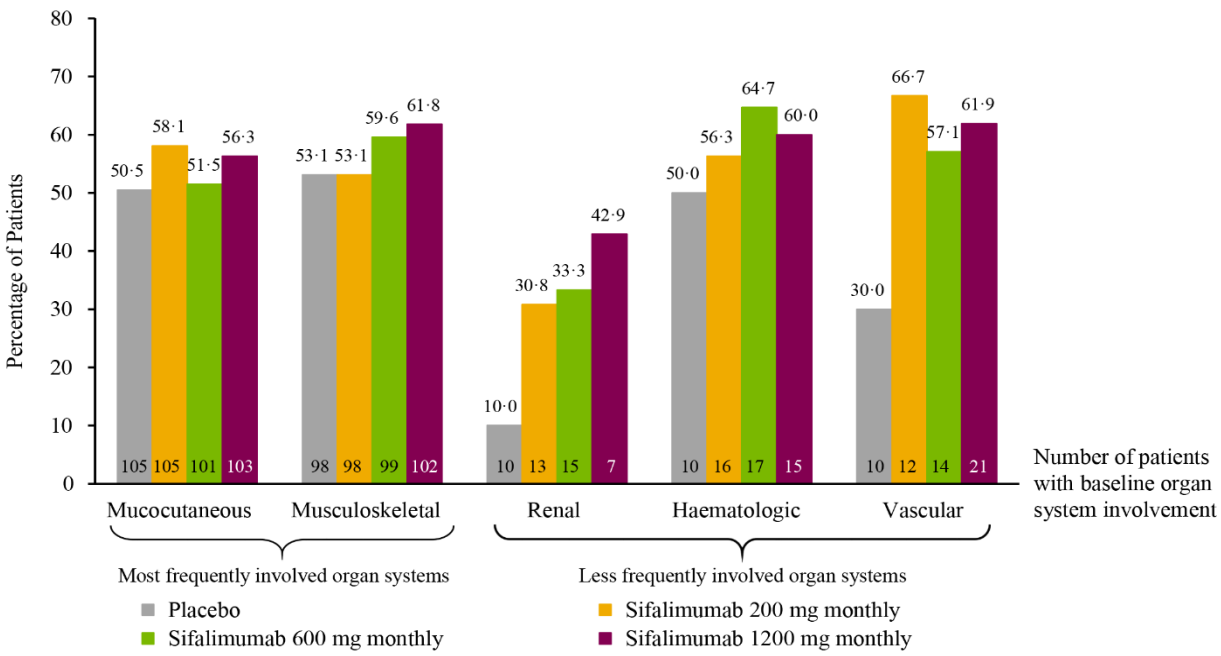
- On Day 1, investigator confirmed that “Clinical” SLEDAI–2K numerical score was ≥ the “Clinical” SLEDAI–2K numerical score completed at the initiation of screening period
- On Day 1, the investigator or designee contacted the IVRS/IWRS and provided the patient identification number and patient’s baseline characteristic(s), including the confirmatory “Clinical” SLEDAI–2K numerical score, to verify patient identity
- The IVRS/IWRS assigned a treatment arm and investigational product kit number(s) to the patient
- Confirmation of this information was sent to the investigator/designee, who dispensed the investigational product to the patient as per the communication, and recorded the appropriate information in the patient’s medical records and investigational product accountability log.

Figure S1 Patient Disposition.



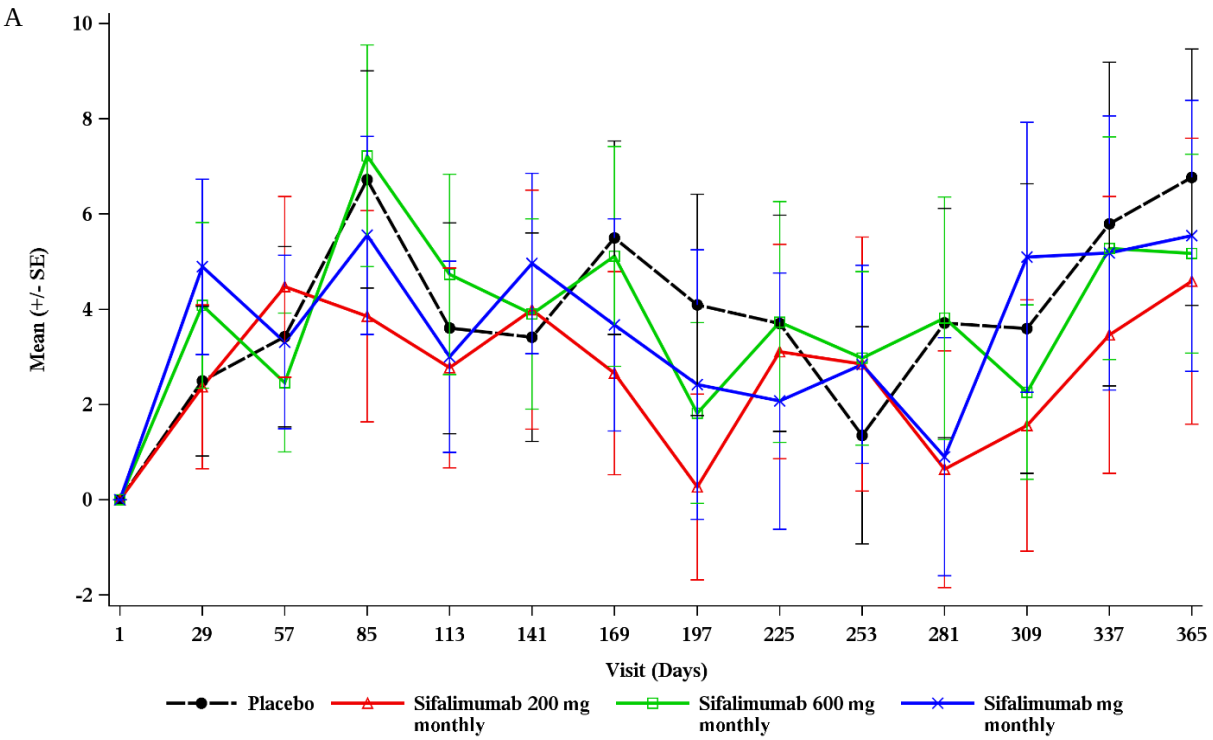
a. The entry criteria violation and non-receipt of therapy were reported for the same patient.
Treatment was administered on Days 1, 15, and 29, and then every 28 days thereafter.

Figure S2 Patients with improvements in SLEDAI–2K organ systems at Week 52.



Treatment was administered on Days 1, 15, and 29, and then every 28 days thereafter.
SLEDAI–2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Figure S3 Change from baseline in C3 (A) and C4 (B) complement for patients with abnormal levels at baseline.



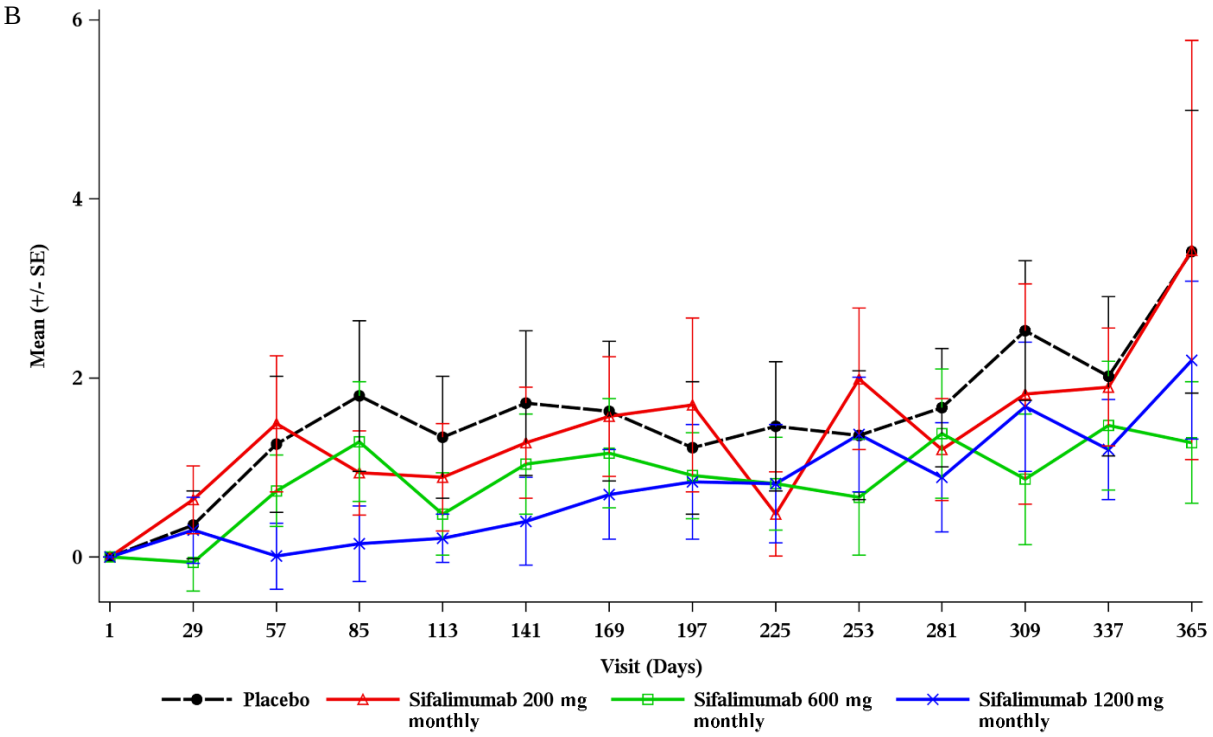
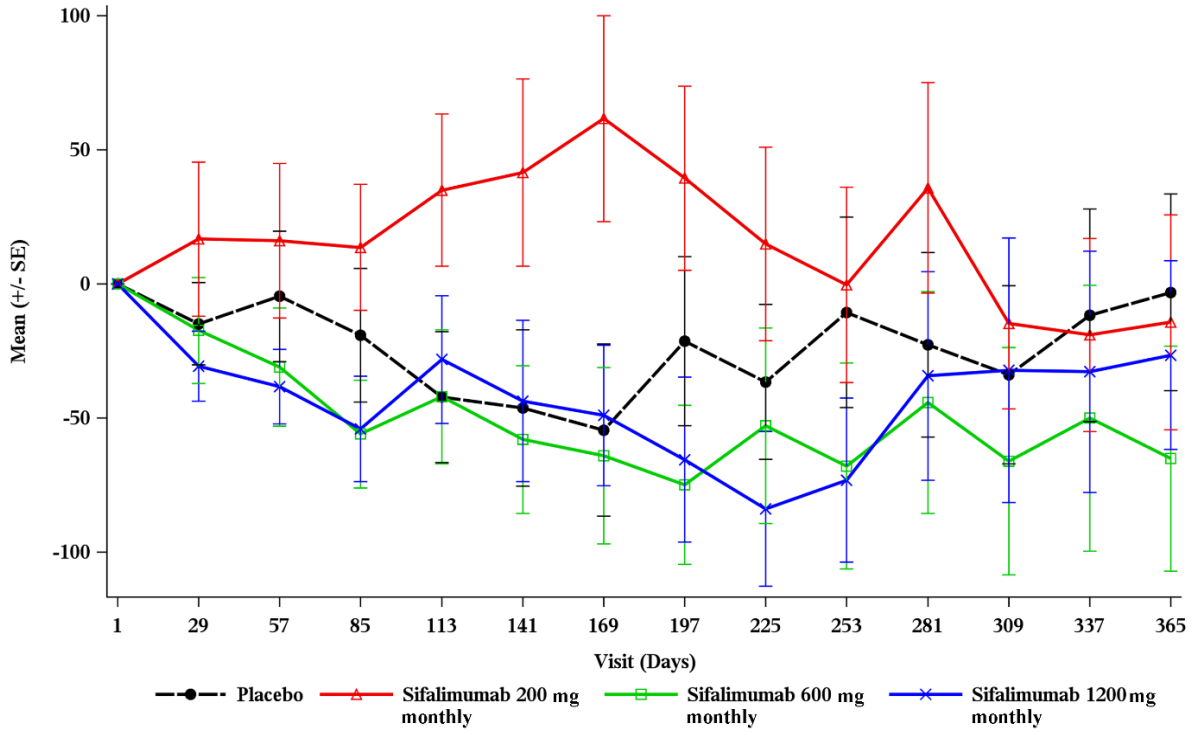
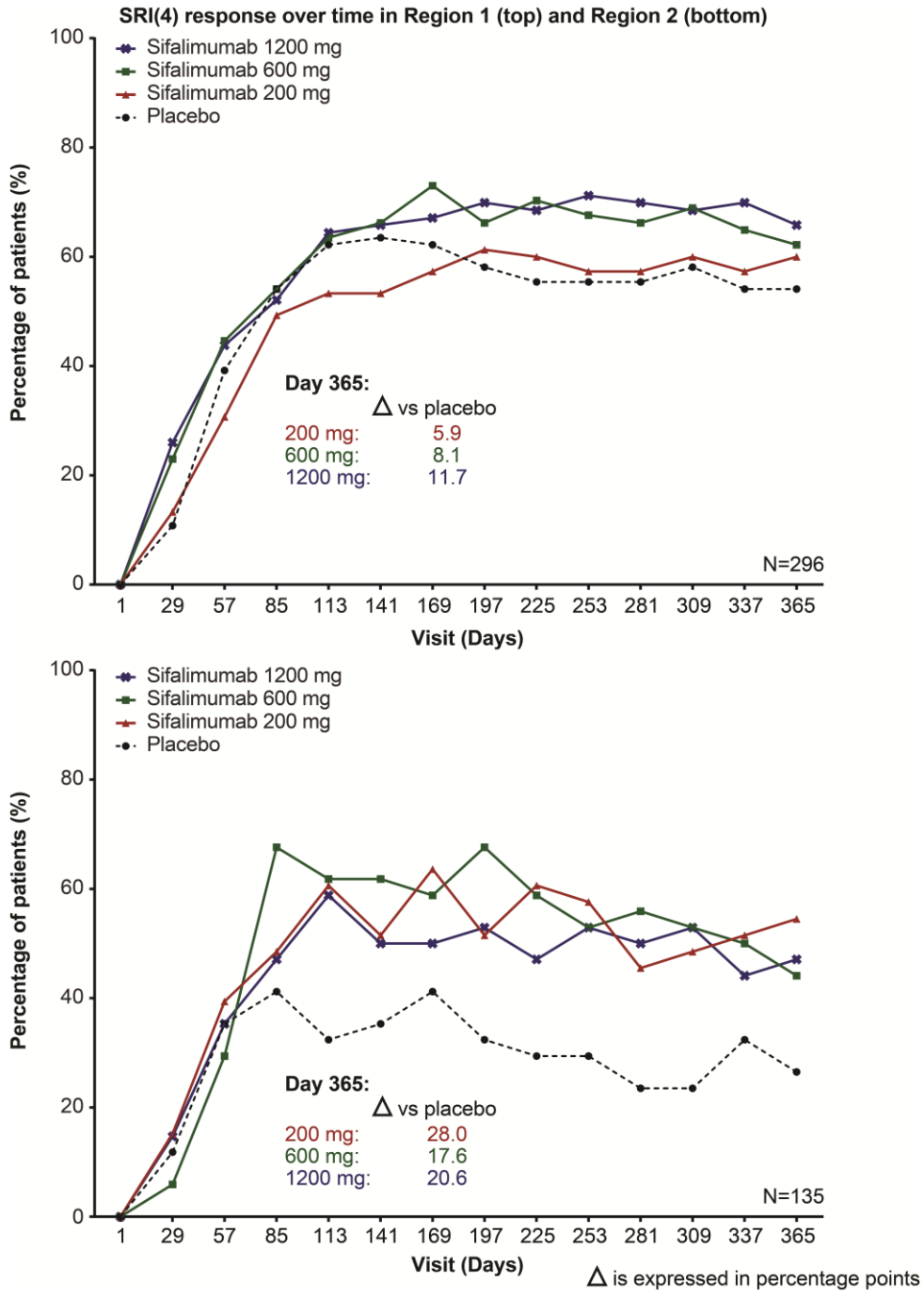


Figure S4 Change from baseline in anti-dsDNA by multiplexed assay for patients with abnormal levels (≥100 IU/ml) at baseline.



dsDNA, double-stranded DNA.

Figure S5 SRI(4) response (primary endpoint) over time by geographical region.



Region 1 (high SOC response region): Central America, South America, Eastern Europe, and Asia; Region 2 (low SOC response region): North America, Western Europe, and South Africa.
SRI(4), Systemic Lupus Erythematosus Responder Index; SOC, standard-of-care.

Table S1 Baseline demographic and clinical characteristics between regions* in total sifalimumab group

Characteristic, mean (SD) [n] unless stated	Placebo (N=108)	Sifalimumab 200 mg† (N=108)	Sifalimumab 600 mg† (N=108)	Sifalimumab 1200 mg† (N=107)	Total (N=431)
Age (years)					
Region 1	35.1 (10.6) [74]	39.4 (11.5) [75]§	39.4 (12.2) [74]§	38.0 (12.2) [73]	38.0 (11.7) [296]
Region 2	45.3 (12.9) [34]	41.0 (11.2) [33]§	41.3 (9.1) [34]§	42.4 (11.5) [34]	42.5 (11.3) [135]
Weight (kg)					
Region 1	64.8 (14.4) [74]§	64.3 (12.2) [75]	63.5 (14.2) [74]	66.4 (15.8) [73]§	64.7 (14.2) [296]
Region 2	69.4 (19.3) [34]§	78.0 (22.0) [33]	73.6 (19.4) [34]	70.3 (18.5) [34]§	72.8 (19.9) [135]
Non-Hispanic/Latino, n (%)					
Region 1	38 (51.4)	42 (56.0)	36 (48.6)	34 (46.6)	150 (50.7)
Region 2	30 (88.2)	30 (90.9)	32 (94.1)	29 (85.3)	121 (89.6)
Duration of SLE‡ (months, median)					
Region 1	71.8 (61.1) [74]	91.7 (78.3) [75]	75.1 (65.6) [74]	81.7 (85.8) [73]	80.1 (73.4) [296]
Region 2	131.1 (86.3) [34]	131.5 (93.5) [33]	149.6 (93.1) [34]	141.4 (101.8) [34]	138.4 (93.1) [135]
SLEDAI–2K global score					
Region 1	11.3 (4.0) [74]	11.4 (4.3) [75]	11.6 (4.9) [74]	12.2 (5.0) [73]	11.6 (4.6) [296]
Region 2	10.7 (4.2) [34]	10.2 (3.0) [33]	10.9 (4.0) [34]	10.5 (4.0) [34]	10.6 (3.8) [135]
BILAG–2004 global score					
Region 1	18.9 (4.8) [74]	19.5 (5.3) [75]	19.5 (6.1) [7.4]	19.0 (5.9) [73]	19.2 (5.5) [296]
Region 2	18.1 (5.2) [34]	19.5 (5.3) [33]	20.5 (7.1) [34]	19.0 (5.2) [34]	19.2 (5.7) [135]
PGA					
Region 1	1.79 (0.38) [74]	1.79 (0.36) [75]	1.71 (0.37) [74]	1.74 (0.39) [73]	1.76 (0.38) [296]
Region 2	1.92 (0.39) [34]	1.87 (0.38) [33]	1.76 (0.44) [34]	1.85 (0.43) [34]	1.85 (0.41) [135]
SLICC/ACR damage index					
Region 1	0.6 (1.0) [74]	0.6 (1.0) [75]	0.6 (1.2) [73]	0.4 (0.8) [72]	0.5 (1.0) [294]
Region 2	1.2 (1.9) [34]	1.0 (1.5) [33]	0.8 (0.9) [34]	1.4 (1.3) [34]	1.1 (1.4) [135]
CLASI activity score					
Region 1	7.9 (7.7) [74]	7.7 (6.4) [75]	7.8 (6.5) [74]	6.5 (5.0) [73]	7.5 (6.5) [296]
Region 2	9.7 (10.1) [34]	8.9 (9.2) [33]	8.7 (8.7) [34]	7.4 (8.2) [34]	8.7 (9.0) [135]
IFN test, n (%)					
Region 1					
High	61 (82.4)	61 (81.3)	59 (79.7)	60 (82.2)	241 (81.4)
Low	13 (17.6)	14 (18.7)	15 (20.3)	13 (17.8)	55 (18.6)
Region 2					
High	27 (79.4)	26 (78.8)	29 (85.3)	27 (79.4)	109 (80.7)
Low	7 (20.6)	7 (21.2)	5 (14.7)	7 (20.6)	26 (19.3)
Corticosteroid use, n (%)					
Region 1	71 (95.9)	72 (96.0)	68 (91.9)	64 (87.7)§	275 (92.9)
Region 2	22 (64.7)	24 (72.7)	19 (55.9)	28 (82.4)§	93 (68.9)
Corticosteroids dosage (mg/day)					
Region 1	11.5 (5.7) [71]	11.6 (5.5) [72]	11.1 (5.8) [68]	12.7 (6.0) [64]	11.7 (5.8) [275]
Region 2	9.9 (4.6) [22]	9.0 (5.1) [24]	9.4 (4.9) [19]	8.9 (4.1) [28]	9.3 (4.6) [93]
Other immunomodulatory medication					
Antimalarial, n (%)					
Region 1	49 (66.2)	49 (65.3)	56 (75.7)	56 (76.7)	210 (70.9)
Region 2	28 (82.4)	28 (84.8)	27 (79.4)	23 (67.6)	106 (78.5)
Azathioprine, n (%)					
Region 1	26 (35.1)	22 (29.3)§	25 (33.8)	17 (23.3)	90 (30.4)
Region 2	2 (5.9)	9 (27.3)§	6 (17.6)	4 (11.8)	21 (15.6)
Methotrexate, n (%)					
Region 1	12 (16.2)	11 (14.7)	6 (8.1)	6 (8.2)	35 (11.8)
Region 2	2 (5.9)	6 (18.2)	11 (32.4)	10 (29.4)	29 (21.5)
Mycophenolate, n (%)					
Region 1	4 (5.4)	3 (4.0)	1 (1.4)	3 (4.1)	11 (3.7)
Region 2	9 (26.5)	8 (24.2)	4 (11.8)	9 (26.5)	30 (22.2)

*Region 1 (high SOC response region): Central America, South America, Eastern Europe, and Asia; Region 2 (low SOC response region): North America, Western Europe, and South Africa.
†Treatment was administered on Days 1, 15, and 29, and then every 28 days thereafter.
‡Duration from diagnosis to study entry.
§<10% difference between regions.

CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SD, standard deviation; SLE, systemic lupus erythematosus; SLICC/ACR, Systemic Lupus International Collaborating Clinic/American College of Rheumatology; SOC, standard-of-care.

Table S2 SRI(4) results at Week 52 by anti-dsDNA assay

Assay	SRI(4) responder	Placebo (N=108)	Sifalimumab 200 mg (N=108)	Sifalimumab 600 mg (N=108)	Sifalimumab 1200 mg (N=107)	Total (N=431)
Farr	Yes	49 (45.4%)	62 (57.4%)	61 (56.5%)	64 (59.8%)	236 (54.8%)
	No*	59 (54.6%)	46 (42.6%)	47 (43.5%)	43 (40.2%)	195 (45.2%)
Multiplex	Yes	49 (45.4%)	63 (58.3%)	61 (56.5%)	64 (59.8%)	237 (55.0%)
	No	59 (54.6%)	45 (41.7%)	47 (43.5%)	43 (40.2%)	194 (45.0%)

*For subjects with missing FARR results at Day 1 or Day 365, the anti-dsDNA was considered to be no change

dsDNA, double-stranded DNA; SRI(4), Systemic lupus erythematosus Responder Index;
SRI(4) responder; 4-point improvement in Systemic Lupus Erythematosus Disease Activity Index 2000; no clinically significant worsening (≥0.3) in physician global assessment; and no new British Isles Lupus Assessment Group−2004 “A” (severe) or >1 new “B” (moderate) organ system scores.

Table S3 Sensitivity analysis: patients with baseline CLASI activity score ≥10 who experienced a 50% reduction by Week 52

Treatment	Week 52	*P*-Value
Placebo	40.0 (14/35)	
Sifalimumab 200 mg	63.6 (21/33)	0.049
Sifalimumab 600 mg	54.5 (18/33)	0.240
Sifalimumab 1200 mg	65.4 (17/26)	0.050

CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index

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