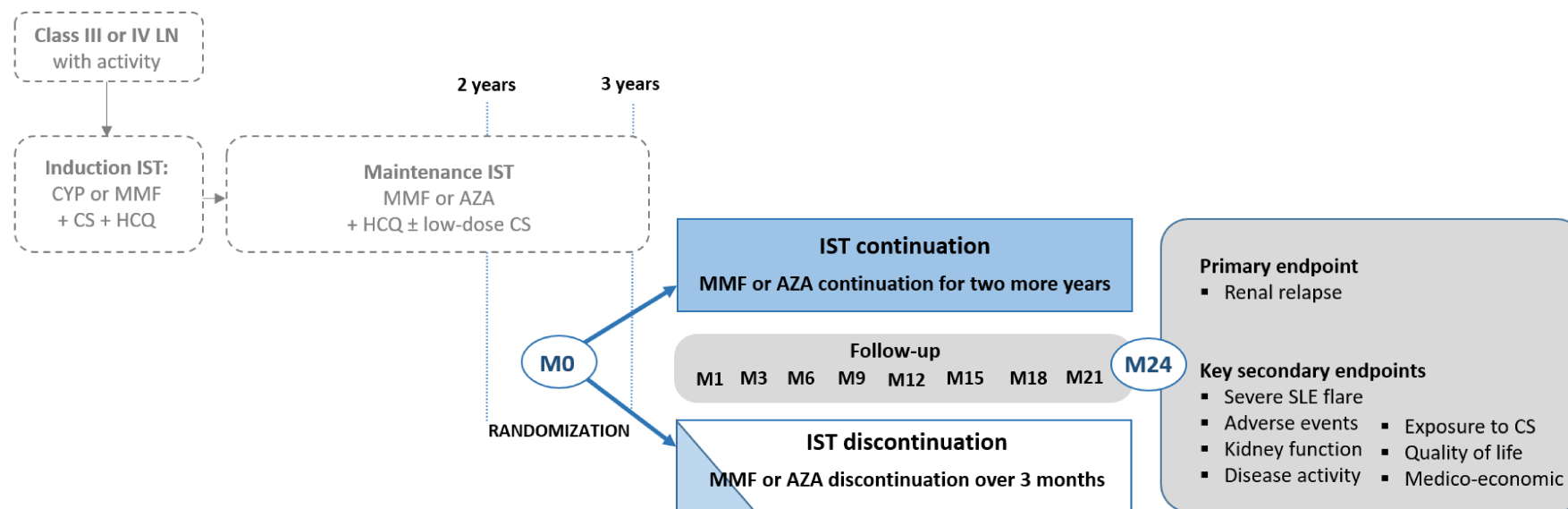


Supplementary Figure 1. WIN-Lupus: study objectives and design

To test whether maintenance immunosuppressive therapy (IST) discontinuation after 2–3 years is non-inferior to IST continuation for two more years.

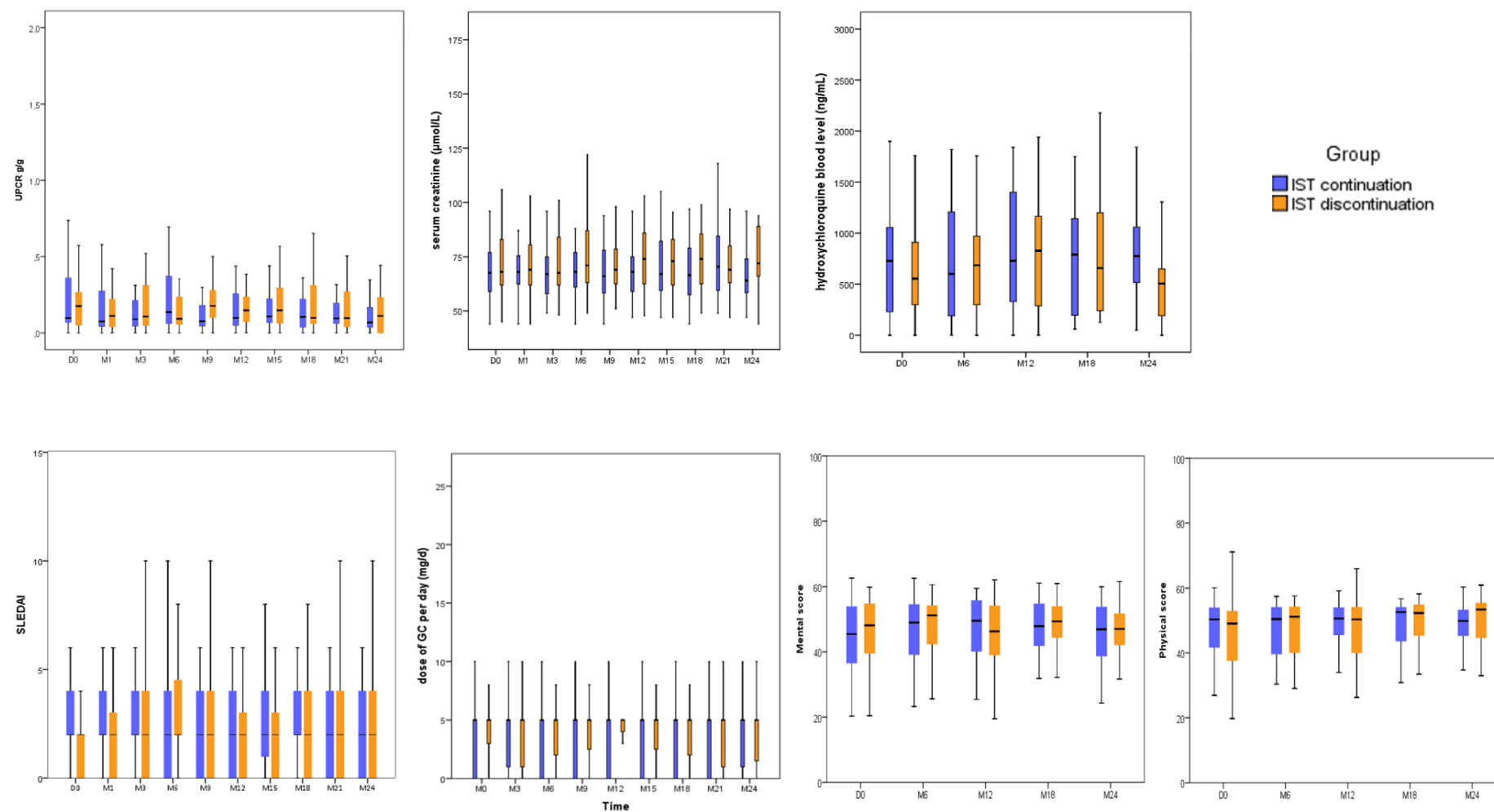


Key eligibility criteria:

- ≥ 18-years-old
- On maintenance IST for 2–3 years
- On HCQ
- Stable in remission

■ Maintenance IST with MMF or AZA after randomisation

CS: corticosteroids; CYP: cyclophosphamide; IST: immunosuppressive therapy; LN: lupus nephritis; MMF: mycophenolate mofetil; AZA azathioprine; SLE: systemic lupus erythematosus; HCQ: hydroxychloroquine



Supplementary Figure 2. Evolution of key secondary criteria in patients with IST continuation (blue) and in patients with IST discontinuation (orange).

UPCR: urinary protein to creatinine ratio; SLEDAI: systemic lupus erythematosus disease activity index; CS: corticosteroids; SF-36: short-form 36 health survey.

Supplementary Table 1. Baseline characteristics of the patients at randomization (intent to treat population)

Characteristics	IST continuation	IST discontinuation
	(N=48)	(N=48)
	Mean (SD)	Mean (SD)
	N (%)	N (%)
Age, years	37.9 ± 14.4	36.2 ± (12.9)
Sex, female	38 (79.2%)	41 (85.4%)
Ethnicity		
Caucasian	34 (70.8%)	29 (60.4%)
Black	10 (20.8%)	15 (31.3%)
Asian	4 (8.3%)	4 (8.3%)
SLE disease duration, years	9.4 ± 10	7.3 ± 6
Antiphospholipid syndrome	7 (14.6%)	7 (14.6%)
Menopause	8/36 (22.2%)	10/42 (23.8%)
Obesity (body mass index ≥30)	5 (10.4%)	6 (12.5%)
Systolic blood pressure, mmHg	122 (13)	117 (14)
Diastolic blood pressure, mmHg	74 (11)	73 (10)
First flare of proliferative LN	37 (77.1%)	36 (75.0%)
Induction therapy		
Low-dose IV cyclophosphamide	31 (64.6%)	28 (58.3%)
Mycophenolate mofetil	17 (35.4%)	20 (41.7%)
Maintenance IST		
Duration, years	2.8 (0.86)	2.8 (0.66)
Mycophenolate mofetil	38 (79.2%)	40 (83.3%)
Azathioprine	10 (20.8%)	8 (16.7%)
Doses prescribed, mg/day		
Mycophenolate mofetil	1581 (664)	1340 (748)
Azathioprine	82.5 (29)	81.2 (39)
Corticosteroids	4.1 (2.8)	4.3 (2.8)
Hydroxychloroquine	354 (111)	335 (140)
Hydroxychloroquine serum level, ng/L	791 (688)	641 (427)
Serum creatinine, μmol/L	68.8 (14.8)	72.9 (16.7)
Estimated GFR, mL/min/1.73 m ²	99.9 (26.8)	94.7 (25.5)
Chronic kidney disease stage		
Stage 1	31 (64.6%)	28 (58.3%)
Stage 2	16 (33.3%)	15 (31.3%)
Stage 3	1 (2.1%)	5 (10.4%)
Urinary protein/creatinine ratio, g/g	0.288 (0.399)	0.208 (0.269)
Urinary protein/creatinine ratio ≤0.2 g/g	32 (66.7%)	32 (66.7%)
Urinary protein/creatinine ratio ≤0.5 g/g	40 (83.3%)	46 (95.8%)
Urinary protein/creatinine ratio ≤0.7 g/g	41 (85.4%)	47 (97.9%)
Serum albumin, g/dL	4.1 (0.5)	4.2 (0.4)
Hemoglobin, g/dL	13.1 (1.7)	12.9 (1.3)
Leukocytes, G/L	5.89 (2.04)	5.61 (2.32)
Lymphocytes, G/L	1.48 (0.63)	1.36 (0.57)
Platelets, G/L	257 (87)	240 (77)
Low C3	7/46 (15.2%)	6/46 (13.0%)
Low C4	7/46 (15.2%)	5/46 (10.9%)
Positive anti-dsDNA	31/46 (67.4%)	25/48 (52.1%)
SLEDAI score	2.4 (1.8)	1.5 (1.7)

Data are expressed as Mean (SD), number (%), or number/number available (%).

IST: immunosuppressive therapy; SLE: systemic lupus erythematosus; LN: lupus nephritis; GFR: glomerular filtration rate; SLEDAI: SLE disease activity index.

Supplementary Table 2: Baseline individual characteristics of the 17 patients who presented a renal relapse, and renal presentation and pathology at the time of LN relapse.

IST Group	Sex	Age	Ethnicity	1st flare of LN	Initial LN ISN/RSP	M0 Low C3	M0 SLEDAI	M0 eGFR	M0 UPCR	Timing of LN relapse	LN Relapse eGFR	LN Relapse UPCR	LN Relapse ISN/RSP
Continuation	Female	26	Caucasian	No	IV-S-A/C (A 90%, C 5%)	No	2	124	0.47	M12	103	1.44	IV-G-A/C (A 78%, C 33%)
Continuation	Female	33	Asian	Yes	IV-S-A/C + V (A 90%, C 10%)	Yes	8*	98	1.04	M5	95	1.72	III-A/C + V (A 30%, C 30%)
Continuation	Female	22	Caucasian	Yes	III-A (A 45%)	Yes	6**	111	1.13	M9	74	4.95	IV-G-A/C (A 60%, C 15%)
Continuation	Female	20	Caucasian	Yes	IV-G-A (A 100%)	No	2	137	0.74	M21	107	2.21	III-A/C + V (A 15%, C 30%)
Continuation	Female	46	Caucasian	Yes	III-A/C (A 7%, C 20%)	NA	2	104	1.72	M6	80	2.89	IV-S-A/C (A 55%, C 20%)
Discontinuation	Female	22	Caucasian	Yes	IV-G-A (A 100%)	Yes	4	108	0.05	M9	116	0.83	III-S-A/C (A 25% C 25%)
Discontinuation	Female	41	Asian	No	III-A/C (A 44%, C 37%)	No	8	92	0.2	M5	68	3.71	IV-G-A/C (A 73%, C 33%)
Discontinuation	Female	30	Asian	Yes	IV-G-A (A 100%)	Yes	4	118	0.15	M21	112	0.48	IV-S-A/C (A 63%, C 11%)
Discontinuation	Female	41	Caucasian	No	IV-G-A (A 100%)	No	0	60	0.44	M3	43	6.88	IV-G-A/C (A 77%, C 27%)
Discontinuation	Female	18	Black	Yes	III-A (A 35%)	Yes	4	142	0.08	M15	156	0.80	III-A (A 37%)
Discontinuation	Female	31	Caucasian	Yes	IV-S-A/C A 100%, C 3%	No	0	95	0.26	M8	48	6.6	#
Discontinuation	Female	48	Black	No	IV-G-A/C (A 100%, C 8%)	No	0	89	0.41	M6	130	0.54	III-A/C (A 25%, C 16%)
Discontinuation	Female	24	Black	Yes	IV-G-A/C (A 95%, C 15%)	No	2	124	0.27	M9	82	0.96	IV-G-A/C (A 91%, C 21%)
Discontinuation	Female	32	Caucasian	Yes	IV-G-A (A 100%)	No	4	93	0.06	M21	100	1.37	III-A (A 30%)
Discontinuation	Female	19	Black	No	IV-S-A + V (A 80%)	No	0	146	1.77	M6	159	2.42	IV-S-A/C + V (A 10%, C 50%)
Discontinuation	Female	37	Black	Yes	IV-S-A/C (A 87%, C 47%)	Yes	4	116	0.17	M9	78	0.76	IV-S-A/C + V (A 5%, C 72%)
Discontinuation	Female	59	Caucasian	Yes	III-A/C (A 20%, C 10%)	No	2	66	0.35	M6	61	1.52	IV-S-A/C + V (A 25%, C 25%)

*SLEDAI of this patient at inclusion comprised low C3, positive anti-dsDNA and persistent proteinuria. **SLEDAI of this patient at inclusion comprised low C3 and persistent proteinuria. # No new kidney biopsy was performed at LN relapse for this patient, who presented acute kidney injury with a nephrotic syndrome and active urinary sediment. A: activity (% of glomeruli with active lesions). C: chronicity (% of glomeruli with chronic lesions). eGFR: estimated glomerular filtration rate. ISN/RPS: International Society of Nephrology/Renal Pathology Society 2003 classification. LN: lupus nephritis. NA: not available. UPCR: urinary protein to creatinine ratio.

Supplementary Table 3. Comparison of health-related costs per patient over the follow-up period between patients with IST continuation and patients with IST discontinuation in the total per-protocol population (N=84) and according to relapse status

	Total per-protocol population (N=84)		Renal relapse (N=17)		No renal relapse (N=67)	
	Mean costs (95% CI)		Mean costs (95% CI)		Mean costs (95% CI)	
	IST continuation	IST discontinuation	IST continuation	IST discontinuation	IST continuation	IST discontinuation
Total cost (Euros)	2654** (1925–3383)	1581** (1055–2107)	4532 (0-10 554)	3394 (2235-4552)	2385** (1832-2939)	929** (505-1354)
Maintenance IST costs ^a	1750** (1300–2200)	296** (86–507)	530 (0-1211)	245 (36-454)	1924** (1440-2408)	335** (31-637)
Antimalarial drug costs ^b	184 (165–203)	159 (132–186)	85 (4-166)	74 (45-104)	198 (183-214)	198 (170-226)
Corticosteroid costs ^c	42 (32–52)	31 (24–38)	45 (0-103)	16 (8-24)	41 (32-51)	37 (29-46)
Inpatient care costs ^d	678* (23–1333)	1095* (588–1602)	3873 (0-9263)	3059 (1928-4190)	222 (0-543)	359 (42-676)

95%CI: 95% confidence interval; IST: immunosuppressive therapy.

^a included mycophenolate mofetil (CELLCEPT®)/mycophenolic acid (MYFORTIC®) and azathioprine (IMUREL®);

^b included hydroxychloroquine (PLAQUENIL®);

^c included prednisone (CORTANCYL®), prednisolone (SOLUPRED®) and methylprednisolone (SOLUMEDROL®) ;

^d included hospitalizations during follow-up and relapse care (including a biopsy for confirmation and hospital length of stay according to disease severity) (only 25 patients underwent inpatient care (n=17 (38.6%) vs. 8 (20%) in the IST discontinuation and IST continuation group, respectively).

*p<0.05, **p<0.01 for the comparison between IST continuation and IST discontinuation (independent-samples, Student's t-test).

Supplementary Table 4. Risk factors for severe flare of SLE at inclusion (per-protocol population)

	Severe flare (N=19)	No severe flare (N=65)	p
	Mean (SD)	Mean (SD)	
	N (%)	N (%)	
Age, years	31.7 (11.3)	38.7 (13.8)	0.047
Sex, female	19 (100.0%)	52 (80.0%)	0.034
Ethnicity			0.450
Caucasian	10 (52.6%)	43 (66.2%)	-
Black	6 (31.6%)	17 (26.2%)	-
Asian	3 (15.8%)	5 (7.7%)	-
SLE disease duration	8.1 (5.6)	8.7 (9.0)	0.786
Associated antiphospholipid syndrome	5 (26.3%)	6 (9.2%)	0.114
Menopause	1 (5.3%)	15/50 (30.0%)	0.052
Obesity	3 (15.8%)	8 (12.3%)	0.706
First flare of proliferative LN	13 (68.4%)	51 (78.5%)	0.373
Induction therapy			0.869
Intravenous cyclophosphamide	11 (57.9%)	39 (60.0%)	-
Mycophenolate mofetil	8 (42.1%)	26 (40.0%)	-
Maintenance IST duration at M0, years	2.7 (1.0)	2.9 (0.7)	0.433
Maintenance IST			0.540
Mycophenolate mofetil	14 (73.7%)	52 (80.0%)	-
Azathioprine	5 (26.3%)	13 (20.0%)	-
Dose prescribed at M0, mg/day			
Mycophenolate mofetil	1392.9 (684.4)	1510.2 (639.3)	0.553
Azathioprine	80.0 (27.4)	82.7 (35.9)	0.882
Corticosteroids	4.9 (3.2)	4.1 (2.6)	0.279
Hydroxychloroquine	331.6 (142.6)	353.8 (104.7)	0.455
Serum hydroxychloroquine levels, ng/L	758 (485)	729 (604)	0.857
Serum hydroxychloroquine <200 ng/L	3 (17.6%)	11 (21.6%)	1.00
Serum creatinine, µmol/L	62.8 (10.5)	72.4 (16.9)	0.025
Estimated GFR, mL/min/1.73 m²	109.9 (25.8)	94.6 (26.5)	0.029
Chronic kidney disease stage			0.067
Stage 1	16 (84.2%)	36 (55.4%)	-
Stage 2	2 (10.5%)	24 (36.9%)	-
Stage 3	1 (5.3%)	5 (7.7%)	-
Urinary protein/creatinine ratio, g/g	0.50 (0.54)	0.17 (0.19)	0.017
Urinary protein/creatinine ratio ≤0.2 g/g	7 (36.8%)	48 (73.8%)	0.003
Urinary protein/creatinine ratio ≤0.5 g/g	14 (73.7%)	62 (95.4%)	0.013
Urinary protein/creatinine ratio ≤0.7 g/g	14 (73.7%)	64 (98.5%)	0.002
Serum albumin, g/dL	3.9 (0.3)	4.3 (0.4)	0.002
Hemoglobin level, g/dL	12.0 (1.3)	13.2 (1.4)	0.001
Leukocyte count, G/L	4.7 (2.4)	5.9 (1.9)	0.037
Lymphocyte count, G/L	1.1 (0.5)	1.5 (0.6)	0.012
Basophil count, G/L	0.01 (0.01)	0.02 (0.02)	0.075
Eosinophil count, G/L	0.04 (0.04)	0.11 (0.14)	0.069
Platelet count, G/L	285 (129)	237 (63)	0.137
Low C3	6/18 (33.3%)	4/62 (6.5%)	0.007
Low C4	3/18 (16.7%)	5/62 (8.1%)	0.370
Positive anti-dsDNA	15 (78.9%)	34 (52.4%)	0.039
SLEDAI score	3 (2.4)	1.6 (1.4)	0.023

Data are expressed as % or mean (SD). In the case of missing data, the number/number available (%) is indicated.

IST: immunosuppressive therapy; SLE: systemic lupus erythematosus; LN: lupus nephritis; GFR: glomerular filtration rate; SLEDAI: SLE disease activity index.

Supplemental Table 5. Risk factors for renal relapse after IST discontinuation (patients randomized in the IST discontinuation group, per-protocol population)

	Relapse (N=12)	No relapse (N=32)	p
	Mean (SD) N (%)	Mean (SD) N (%)	
Age, years	33.7 (12.4)	37.8 (13.6)	0.368
Sex, female	12 (100.0%)	26 (81.3%)	0.167
Ethnicity			0.302
Caucasian	5 (41.7%)	21 (65.6%)	
Black	5 (41.7%)	9 (28.1%)	
Asian	2 (16.7%)	2 (6.3%)	
SLE disease duration, years	6.9 (5.2)	7.9 (6.6)	0.638
Antiphospholipid syndrome	3 (25.0%)	3 (9.4%)	0.321
Menopause	1 (8.3%)	9/26 (34.6%)	0.131
Obesity	2 (16.7%)	4 (12.5%)	0.658
First flare of proliferative LN	8 (66.7%)	24 (75.0%)	0.707
Induction therapy with			0.711
Intravenous cyclophosphamide	6 (50.0%)	18 (56.3%)	
Mycophenolate mofetil	6 (50.0%)	14 (43.7%)	
Maintenance IST duration at M0	2.7 (1.1)	2.9 (0.4)	0.359
Maintenance IST			0.413
Mycophenolate mofetil	11 (91.7%)	25 (78.1%)	
Azathioprine	1 (8.3)	7 (21.9%)	
Serum [HCQ] levels, ng/L	851 (435)	562 (404)	0.057
Serum [HCQ] levels < 200 ng/L	0 (0.0%)	7 (25.0%)	0.159
Serum creatinine μ mol/L	66.3 (10.6)	75.0 (18.6)	0.151
Estimated GFR mL/min/1.73 m ²	104.2 (26.7)	91.4 (25.0)	0.146
Chronic kidney disease stage			0.413
Stage 1	9 (75.0%)	17 (53.1%)	
Stage 2	2 (16.7%)	11 (34.4%)	
Stage 3	1 (8.3%)	4 (12.5%)	
Urinary protein/creatinine ratio, g/g	0.35 (0.47)	0.16 (0.14)	0.193
Urinary protein/creatinine ratio \leq 0.2 g/g	5 (41.7%)	24 (75.0%)	0.071
Urinary protein/creatinine ratio \leq 0.5 g/g	11 (91.7%)	31 (96.9%)	0.476
Urinary protein/creatinine ratio \leq 0.7 g/g	11 (91.7%)	32 (100.0%)	0.273
Serum albumin, g/dL	3.9 (0.4)	4.3 (0.3)	0.005
Hemoglobin, g/dL	12.1 (1.4)	13.1 (1.1)	0.011
Leukocytes, G/L	4.8 (2.9)	5.9 (2.2)	0.197
Lymphocytes, G/L	1.1 (0.4)	1.5 (0.6)	0.039
Basophils, G/L	0.01 (0.01)	0.02 (0.02)	0.081
Eosinophils, G/L	0.05 (0.04)	0.1 (0.1)	0.116
Platelets, G/L	271 (124)	229 (55)	0.137
Low C3	4 (33.3%)	1/30 (3.3%)	0.018
Low C4	2 (16.7%)	2/30 (6.7%)	0.565
Positive anti-dsDNA	8 (66.7%)	16 (50.0%)	0.323
SLEDAI score at M0	2.5 (2.4)	1.25 (1.3)	0.114

Data are expressed as number (%) or mean (SD). IST: immunosuppressive therapy; SLE: systemic lupus erythematosus; LN: lupus nephritis; GFR: glomerular filtration rate.

Supplemental Table 6. Risk factors for severe SLE flare after IST discontinuation (patients randomized in the IST discontinuation group, per-protocol population).

	Relapse (N=14)	No Relapse (N=30)	p
	Mean (SD) N (%)	Mean (SD) N (%)	
Age, years	32.6 (11.8)	38.6 (13.6)	0.158
Sex, female	14 (100.0%)	24 (80.0%)	0.155
Ethnicity			0.315
Caucasian	6 (42.9%)	20 (66.7%)	
Black	6 (42.9%)	8 (26.7%)	
Asian	2 (14.3%)	2 (6.7%)	
SLE disease duration, years	7.2 (4.9)	7.9 (6.8)	0.747
Antiphospholipid syndrome	3 (21.4%)	3 (10.0%)	0.364
Menopause	1 (7.1%)	9/24 (37.5%)	0.064
Obesity	3 (21.4%)	3 (10.0%)	0.364
First flare of proliferative LN	9 (64.3%)	23 (76.7%)	0.475
Induction therapy with			0.679
Intravenous cyclophosphamide	7 (50.0%)	17 (56.7%)	
Mycophenolate mofetil	7 (50.0%)	13 (43.3%)	
Maintenance IST duration at M0	2.8 (1.1)	2.8 (0.4)	0.804
Maintenance IST			1.00
Mycophenolate mofetil	12 (85.7%)	24 (80.0%)	
Azathioprine	2 (14.3%)	6 (20.0%)	
Serum [HCQ] levels, ng/L	804 (437)	564 (409)	0.100
Serum [HCQ] levels < 200 ng/L	1 (7.7%)	6 (23.1%)	0.388
Serum creatinine $\mu\text{mol/L}$	64.5 (10.9)	76.3 (18.3)	0.013
Estimated GFR mL/min/1.73m²	108.2 (28.9)	88.6 (22.1)	0.017
Chronic kidney disease stage			0.196
Stage 1	11 (78.6%)	15 (50.0%)	
Stage 2	2 (14.3%)	11 (36.7%)	
Stage 3	1 (7.1%)	4 (13.3%)	
Urinary protein/creatinine ratio, g/g	0.32 (0.44)	0.17 (0.15)	0.098
Urinary protein/creatinine ratio ≤ 0.2 g/g	7 (50.0%)	22 (73.3%)	0.177
Urinary protein/creatinine ratio ≤ 0.5 g/g	13 (92.9%)	29 (96.7%)	0.540
Urinary protein/creatinine ratio ≤ 0.7 g/g	13 (92.9%)	30 (100.0%)	0.318
Serum albumin, g/dL	3.9 (0.3)	4.3 (0.3)	0.003
Hemoglobin, g/dL	12.1 (1.3)	13.2 (1.1)	0.008
Leukocytes, G/L	4.7 (2.8)	6.0 (2.2)	0.101
Lymphocytes, G/L	1.2 (0.6)	1.5 (0.6)	0.236
Basophils, G/L	0.01 (0.01)	0.02 (0.02)	0.045
Eosinophils, G/L	0.05 (0.05)	0.1 (0.1)	0.087
Platelets, G/L	268 (122)	228 (49)	0.130
Low C3	4 (28.6%)	1 (3.6%)	0.035
Low C4	2 (14.3%)	2/28 (7.1%)	0.59
Positive anti-dsDNA	10 (71.4%)	14 (46.7%)	0.124
SLEDAI score at M0	2.5 (2.2)	1.2 (1.3)	0.018

Data are expressed as number (%) or mean (SD).

IST: immunosuppressive therapy; SLE: systemic lupus erythematosus; LN: lupus nephritis; GFR: glomerular filtration rate; SLEDAI: SLE disease activity index.