

1 **Supplement to:**

2 **Lupus Low Disease Activity State Attainment in the Phase 3 TULIP Trials of**

3 **Anifrolumab in Active Systemic Lupus Erythematosus**

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23 SUPPLEMENTARY FIGURES

24 **Figure S1.** Percentage of patients meeting the composite definition of lupus low disease
 25 activity state responder and each individual component of this definition by timepoint for
 26 each treatment group

		Weeks												
LLDAS Components		4	8	12	16	20	24	28	32	36	40	44	48	52
Anifrolumab (300 mg)	LLDAS response	0.0	2.5	6.7	13.6	18.9	23.1	25.6	25.0	27.2	29.2	29.4	30.8	30.0
	SLEDAI-2K score ≤ 4	3.1	13.3	23.3	33.1	40.0	44.7	48.1	48.1	49.7	53.9	53.6	57.5	59.2
	No activity in any SLEDAI-2K major organ ^a	78.6	84.2	88.6	88.6	88.3	89.4	90.6	90.6	90.0	91.4	92.5	93.1	93.6
	No fever	98.1	99.4	99.2	99.7	99.2	99.4	98.9	99.4	99.2	99.4	99.4	99.7	99.7
	No new lupus disease activity ^b	84.2	86.4	84.7	80.6	81.7	81.7	84.2	83.9	80.3	81.4	84.7	85.3	83.6
	PGA VAS ≤ 1	15.0	32.2	43.3	51.7	57.2	61.7	64.2	63.6	66.4	66.9	73.6	73.9	74.4
	GC dose ≤ 7.5 mg/day ^c	44.2	45.8	54.2	60.6	66.9	72.8	78.1	80.3	81.9	82.8	84.2	83.3	83.9
	No use of restricted medication ^d	97.5	96.1	95.0	93.6	92.5	91.7	91.4	90.6	88.9	88.3	87.8	85.0	81.9
	No discontinuation of IP	96.9	95.0	94.7	92.8	93.1	93.3	93.1	91.9	92.8	93.1	93.1	94.2	94.4

		Weeks												
LLDAS Components		4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	LLDAS response	0.3	1.4	4.1	7.1	9.3	11.2	13.7	15.8	16.7	15.6	17.8	16.1	19.7
	SLEDAI-2K score ≤ 4	2.7	9.8	18.0	23.2	27.0	30.6	35.0	41.3	42.3	44.3	48.9	51.1	55.2
	No activity in any SLEDAI-2K major organ ^a	76.2	77.3	78.7	80.6	84.2	85.5	85.0	85.8	86.1	86.9	91.0	91.0	91.0
	No fever	96.7	98.9	98.6	98.6	98.4	98.6	98.9	98.6	99.2	99.5	99.5	98.9	98.9
	No new lupus disease activity ^b	84.4	76.8	79.0	77.3	79.0	80.3	78.7	78.4	82.0	81.4	83.1	82.8	83.6
	PGA VAS ≤ 1	12.3	24.9	31.1	38.0	43.7	46.4	52.5	53.8	57.9	59.8	61.5	63.7	65.0
	GC dose ≤ 7.5 mg/day ^c	46.7	48.4	53.8	56.3	60.1	64.5	65.0	68.3	71.9	74.3	74.9	76.8	77.3
	No use of restricted medication ^d	98.1	96.2	94.0	89.6	88.5	87.2	85.2	83.3	82.5	80.3	79.5	78.1	76.5
	No discontinuation of IP	96.4	94.8	93.4	91.8	90.7	88.8	89.1	88.3	88.0	88.5	89.6	90.7	92.3

^aCNS, vascular, renal, cardiovascular and respiratory.

^bNo new lupus disease activity compared with the previous assessment: no present activity (item score >0) in any new SLEDAI-2K item (irrespective of organ system) compared with the previous visit.

^cNo prednisone equivalent dose ≤ 7.5 mg/day taken on any day of the period starting on the day after the previous scheduled visit and ending on the day of the visit.

^dRestricted medications as defined in TULIP-2, Morand et al, 2019.

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28 CNS, central nervous system; GC, glucocorticoid; IP, investigational product; LLDAS,

29 Lupus Low Disease Activity State; PGA, physician global assessment; SLEDAI-2K,

30 Systemic Lupus Erythematosus Disease Activity Index 2000, TULIP, Treatment of

31 Uncontrolled Lupus via the Interferon Pathway; VAS, visual analogue scale.

32 SUPPLEMENTARY TABLES

33 **Table S1.** Baseline patient demographics and disease characteristics in pooled TULIP data

	Pooled TULIP	
	Anifrolumab 300 mg (n=360)	Placebo (n=366)
Age, mean (SD), years	42.6 (12.0)	41.0 (11.9)
Female, n (%)	333 (92.5)	341 (93.2)
Race, ^a n (%)		
White	235 (65.3)	244 (66.7)
Asian	41 (11.4)	35 (9.6)
Black/African American	46 (12.8)	48 (13.1)
Other	30 (8.3)	31 (8.5)
Time from SLE diagnosis to randomisation, median (range), months	91.0 (0–555)	78.5 (4–503)
IFNGS status at screening, n (%)		
High	298 (82.8)	302 (82.5)
Low	62 (17.2)	64 (17.5)
≥1 BILAG-2004 A, n (%)	174 (48.3)	179 (48.9)
No BILAG-2004 A and ≥2 BILAG-2004 B, n (%)	170 (47.2)	162 (44.3)
SLEDAI-2K global score, mean (SD)	11.4 (3.8)	11.5 (3.7)

SLEDAI-2K ≥ 10, n (%)	254 (70.6)	266 (72.7)
PGA score, mean (SD)	1.8 (0.4)	1.8 (0.4)
CLASI activity score, mean (SD)	8.4 (7.6)	7.8 (7.2)
Swollen joint count,^b mean (SD)	6.8 (5.8)	7.2 (5.7)
Tender joint count,^b mean (SD)	10.3 (7.4)	10.8 (7.5)
SDI score, mean (SD)	0.6 (1.0)	0.6 (0.9)
SLE treatments at baseline, n (%)		
Glucocorticoid^c	291 (80.8)	304 (83.1)
Glucocorticoid ≥ 10 mg/day	190 (52.8)	185 (50.5)
Antimalarials	243 (67.5)	267 (73.0)
Immunosuppressants^d	173 (48.1)	177 (48.4)

34 ^aRace data were missing for 16 patients in TULIP-2 (8 each in the anifrolumab and placebo groups). ^bJoint counts are based on 28 joints.

35 ^cGlucocorticoids include prednisone or equivalent. ^dAzathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine.

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37 BILAG-2004, British Isles Lupus Assessment Group-2004; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS,

38 type I interferon gene signature; PGA, Physician's Global Assessment; SD, standard deviation; SDI, Systemic Lupus International Collaborating

39 Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index

40 2000; TULIP, Treatment of Uncontrolled Lupus via the Interferon Pathway.

41 **Table S2.** LLDAS response rate by timepoint and BICLA response status from Week 4 to Week 52, analysed using a stratified Cochran–
 42 Mantel–Haenszel approach
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Timepoint	BICLA responder status at Week 52 ^b	Number of patients, n (%) ^a			Comparison between groups ^a		
		LLDAS Responder	LLDAS Nonresponder	95% CI response rate	Difference in response rates	95% CI difference	P-value ^c
Week 4	Responder	0	318 (100)	0.0, 1.8	-0.2	-2.4, 2.1	0.8665
	Nonresponder	1 (0.2)	500 (99.8)	0.0, 1.5			
Week 8	Responder	10 (3.2)	308 (96.8)	0.6, 5.7	1.8	-1.2, 4.8	0.2424
	Nonresponder	7 (1.4)	494 (98.6)	0.0, 3.0			
Week 12	Responder	27 (8.5)	291 (91.5)	5.2, 11.8	5.5	1.7, 9.3	0.0044
	Nonresponder	15 (3.0)	486 (97.0)	1.1, 4.9			
Week 16	Responder	61 (19.4)	257 (80.6)	15.2, 23.6	14.6	9.8, 19.3	<0.0001
	Nonresponder	24 (4.8)	477 (95.2)	2.6, 7.0			
Week 20	Responder	89 (28.1)	229 (71.9)	23.4, 32.9	22.1	16.8, 27.4	<0.0001

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		Number of patients, n (%) ^a			Comparison between groups ^a		
Timepoint	BICLA responder status at Week 52 ^b	LLDAS Responder	LLDAS Nonresponder	95% CI response rate	Difference in response rates	95% CI difference	P-value ^c
	Nonresponder	30 (6.1)	471 (93.9)	3.7, 8.4			
Week 24	Responder	109 (34.5)	209 (65.5)	29.4, 39.5	28.4	22.8, 34.0	<0.0001
	Nonresponder	31 (6.1)	470 (93.9)	3.7, 8.4			
Week 28	Responder	117 (36.8)	201 (63.2)	31.7, 41.8	28.4	22.7, 34.2	<0.0001
	Nonresponder	42 (8.3)	459 (91.7)	5.7, 10.9			
Week 32	Responder	125 (39.2)	193 (60.8)	34.0, 44.4	31.8	26.0, 37.6	<0.0001
	Nonresponder	37 (7.4)	464 (92.6)	4.9, 9.9			
Week 36	Responder	139 (43.6)	179 (56.4)	38.3, 49.0	36.1	30.2, 42.0	<0.0001
	Nonresponder	38 (7.5)	463 (92.5)	5.0, 10.0			
Week 40	Responder	150 (47.2)	168 (52.8)	41.8, 52.6	41.2	35.3, 47.1	<0.0001
	Nonresponder	30 (6.0)	471 (94.0)	3.7, 8.4			
Week 44	Responder	153 (47.9)	165 (52.1)	42.6, 53.3	40.8	34.8, 46.7	<0.0001

Timepoint	BICLA responder status at Week 52 ^b	Number of patients, n (%) ^a			Comparison between groups ^a		
		LLDAS Responder	LLDAS Nonresponder	95% CI response rate	Difference in response rates	95% CI difference	<i>P</i> -value ^c
	Nonresponder	36 (7.2)	465 (92.8)	4.7, 9.7			
Week 48	Responder	168 (52.9)	150 (47.1)	47.5, 58.3	48.3	42.4, 54.1	<0.0001
	Nonresponder	23 (4.6)	478 (95.4)	2.4, 6.7			
Week 52	Responder	186 (58.4)	132 (41.6)	53.1, 63.7	54.7	49.0, 60.3	<0.0001
	Nonresponder	19 (3.8)	482 (96.2)	1.7, 5.8			

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45 ^aResponder rates were calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors of SLEDAI-2K at screening,
 46 Day 1 glucocorticoid dose, type I IFN gene signature at screening, and study. Nominal *P*-values were calculated using logistic regression with
 47 the same stratification factors. ^bThe number of patients analysed at each timepoint was the same; n=318 responders and n=501 nonresponders.

48 ^cUnadjusted *P*-values are presented.

49 BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; CI, confidence interval; IFN, interferon; LLDAS, Lupus
 50 Low Disease Activity State; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

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51 **Table S3. LLDAS response rate by timepoint and SRI(4) response status from Week 4 to week 52, analysed using a stratified Cochran–**
 52 **Mantel–Haenszel approach**

Timepoint	SRI(4) responder status at Week 52 ^b	Number of patients, n (%) ^a			Comparison between groups ^a		
		LLDAS Responder	LLDAS Nonresponder	95% CI response rate	Difference in response rates	95% CI difference	P-value ^c
Week 4	Responder	0	380 (100)	0.0, 1.6	−0.2	−2.4, 1.9	0.8231
	Nonresponder	1 (0.2)	438 (99.8)	0.0, 1.7			
Week 8	Responder	10 (2.7)	370 (97.3)	0.5, 4.9	1.1	−1.7, 3.9	0.4448
	Nonresponder	7 (1.6)	432 (98.4)	0.0, 3.3			
Week 12	Responder	30 (8.1)	350 (91.9)	5.1, 11.1	5.3	1.8, 8.9	0.0035
	Nonresponder	12 (2.7)	427 (97.3)	0.8, 4.7			
Week 16	Responder	66 (17.5)	314 (82.5)	13.8, 21.3	13.3	8.9, 17.6	<0.0001
	Nonresponder	19 (4.3)	420 (95.7)	2.0, 6.5			
Week 20	Responder	99 (26.4)	281 (73.6)	22.1, 30.7	22.0	17.2, 26.8	<0.0001
	Nonresponder	20 (4.4)	419 (95.6)	2.2, 6.6			

Timepoint	SRI(4) responder status at Week 52 ^b	Number of patients, n (%) ^a			Comparison between groups ^a		
		LLDAS Responder	LLDAS Nonresponder	95% CI response rate	Difference in response rates	95% CI difference	P-value ^c
Week 24	Responder	118 (31.2)	262 (68.8)	26.6, 35.8	26.4	21.2, 31.5	<0.0001
	Nonresponder	22 (4.9)	417 (95.1)	2.6, 7.1			
Week 28	Responder	127 (33.9)	253 (66.1)	29.3, 38.5	26.7	21.4, 32.0	<0.0001
	Nonresponder	32 (7.2)	407 (92.8)	4.5, 9.8			
Week 32	Responder	134 (35.6)	246 (64.4)	30.9, 40.3	29.4	24.1, 34.7	<0.0001
	Nonresponder	28 (6.2)	411 (93.8)	3.7, 8.7			
Week 36	Responder	153 (40.7)	227 (59.3)	35.9, 45.6	35.5	30.1, 40.8	<0.0001
	Nonresponder	24 (5.3)	415 (94.7)	2.9, 7.6			
Week 40	Responder	165 (43.9)	215 (56.1)	39.0, 48.8	40.5	35.3, 45.8	<0.0001
	Nonresponder	15 (3.3)	424 (96.7)	1.3, 5.4			
Week 44	Responder	174 (46.4)	206 (53.6)	41.6, 51.2	43.1	37.8, 48.3	<0.0001
	Nonresponder	15 (3.3)	424 (96.7)	1.3, 5.4			

Timepoint	SRI(4) responder status at Week 52 ^b	Number of patients, n (%) ^a			Comparison between groups ^a		
		LLDAS Responder	LLDAS Nonresponder	95% CI response rate	Difference in response rates	95% CI difference	<i>P</i> -value ^c
Week 48	Responder	184 (48.9)	196 (51.1)	43.9, 53.8	47.3	42.0, 52.5	<0.0001
	Nonresponder	7 (1.6)	432 (98.4)	0.0, 3.3			
Week 52	Responder	203 (54.0)	177 (46.0)	49.1, 58.8	53.5	48.4, 58.6	<0.0001
	Nonresponder	2 (0.5)	437 (99.5)	0.0, 1.9			

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54 ^aResponder rates were calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors of SLEDAI-2K at screening,55 Day 1 glucocorticoid dose, type I IFN gene signature at screening, and study. Nominal *P*-values were calculated using logistic regression with56 the same stratification factors. ^bThe number of patients analysed at each timepoint was the same; n=380 responders and n=439 nonresponders.57 ^cUnadjusted *P*-values are presented.

58 CI, confidence interval; IFN, interferon; LLDAS, Lupus Low Disease Activity State; SLEDAI-2K, Systemic Lupus Erythematosus Disease

59 Activity Index 2000; SRI(4), SLE Responder Index-4; SLE, systemic lupus erythematosus.

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61 **Table S4.** LupusQoL responses (change from baseline) by LLDAS attainment at Week 52,
 62 analysed using summary statistics

LupusQoL change from baseline to Week 52 by domain, median (IQR)	LLDAS responder (n=205)	LLDAS nonresponder (n=614)
Physical health	9.38 (0, 25.00)	3.13 (-3.13, 18.75)
Pain	8.34 (0, 33.33)	8.33 (0, 25.00)
Planning	8.33 (0, 33.33)	0 (-8.33, 16.67)
Intimate relationships	0 (0, 25.00)	0 (0, 12.50)
Burden to others	8.33 (0, 33.33)	0 (-8.33, 25.00)
Emotional health	4.17 (0, 16.67)	4.16 (-4.17, 16.66)
Body image	7.50 (0, 25.00)	5.00 (-5.00, 20.83)
Fatigue	12.50 (0, 31.25)	6.25 (-6.25, 18.75)

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64 IQR, interquartile range; LLDAS, Lupus Low Disease Activity State; LupusQoL, Lupus

65 Quality of Life.