Supplement to:

Lupus Low Disease Activity State Attainment in the Phase 3 TULIP Trials of Anifrolumab in Active Systemic Lupus Erythematosus

Eric F. Morand[1], Gabriel Abreu[2], Richard A. Furie[3], Vera Golder[1], Raj Tummala[4]

[1]Centre for Inflammatory Diseases, Monash University, Melbourne, Victoria, Australia

[2]Biometrics, Late Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[3]Zucker School of Medicine at Hofstra/Northwell, Division of Rheumatology, Great Neck, NY, USA

[4]Clinical Development, Late Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA

Running title: LLDAS Attainment in TULIP Phase 3 Trials of Anifrolumab

Target journal: *Annals of the Rheumatic Diseases*

Corresponding author: Raj Tummala

1 MedImmune Way

Gaithersburg, MD 20878

Phone: 1-301-398-0548

Email: Raj.Tummala@astrazeneca.com

ORCID iD: 0000-0002-5506-4445

Morand EF, *et al. Ann Rheum Dis* 2023; 82:639–645. doi: 10.1136/ard-2022-222748

SUPPLEMENTARY FIGURES

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

[a]CNS, vascular, renal, cardiovascular and respiratory.
[b]No 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.
[c]No 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.
[d]Restricted medications as defined in TULIP-2, Morand et al, 2019.

CNS, central nervous system; GC, glucocorticoid; IP, investigational product; LLDAS, Lupus Low Disease Activity State; PGA, physician global assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000, TULIP, Treatment of Uncontrolled Lupus via the Interferon Pathway; VAS, visual analogue scale.

SUPPLEMENTARY TABLES

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)

[a]Race data were missing for 16 patients in TULIP-2 (8 each in the anifrolumab and placebo groups). [b]Joint counts are based on 28 joints.

[c]Glucocorticoids include prednisone or equivalent. [d]Azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine.

BILAG-2004, British Isles Lupus Assessment Group-2004; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, type I 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, SLE Disease Activity Index 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

43

		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]**
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

5

		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

		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	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			

[a]Responder rates were calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors of SLEDAI-2K at screening, Day 1 glucocorticoid dose, type I IFN gene signature at screening, and study. Nominal *P*-values were calculated using logistic regression with the same stratification factors. [b]The number of patients analysed at each timepoint was the same; n=318 responders and n=501 nonresponders. [c]Unadjusted *P*-values are presented.

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

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**

		Number of patients, n (%)[a]			Comparison between groups[a]		
Timepoint	**SRI(4) responder status at Week 52[b]**	**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			

8

		Number of patients, n (%)[a]			Comparison between groups[a]		
Timepoint	**SRI(4) responder status at Week 52[b]**	**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			

		Number of patients, n (%)[a]			Comparison between groups[a]		
Timepoint	**SRI(4) responder status at Week 52[b]**	**LLDAS Responder**	**LLDAS Nonresponder**	**95% CI response rate**	**Difference in response rates**	**95% CI difference**	***P*-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			

[a]Responder rates were calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors of SLEDAI-2K at screening, Day 1 glucocorticoid dose, type I IFN gene signature at screening, and study. Nominal *P*-values were calculated using logistic regression with the same stratification factors. [b]The number of patients analysed at each timepoint was the same; n=380 responders and n=439 nonresponders. [c]Unadjusted *P*-values are presented.

CI, confidence interval; IFN, interferon; LLDAS, Lupus Low Disease Activity State; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), SLE Responder Index-4; SLE, systemic lupus erythematosus.

Table S4. LupusQoL responses (change from baseline) by LLDAS attainment at Week 52, 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)

IQR, interquartile range; LLDAS, Lupus Low Disease Activity State; LupusQoL, Lupus Quality of Life.