time vs placebo from Week 4. Time to CRR was shorter in the 180 mg group (17.3 weeks) vs placebo (20.4 weeks). The 180 mg group also showed improvement vs placebo in total SLEDAI (SELENA) and its subscores.

The unexpected high placebo response prompted a post hoc analysis evaluating confirmed CRR (cCRR), whereby confirmation of the endpoint was required at both Weeks 46 (penultimate visit on treatment) and 52. A 15.2% higher cCRR in the 180 mg group (44.3%) vs placebo (29.1%) was observed ($p=0.26$).

While based on a small sample size, there were more reports of infection-related severe and serious adverse events and neutropenia in the 240 mg group compared with placebo. Of note, in those who experienced neutropenia, a clinical impact (e.g. increase in infections) was not established. Aside from these observations, safety data were comparable across treatment groups.

Larger decreases from baseline were observed in the percentage of CD27-IgD-CD95+, CD27-IgD+CD95+, CD27+IgD+CD95+ and CD27+IgD-CD95+ B-cell subsets in the 180 and 240 mg groups compared with placebo.

Treatment-emergent anti-drug antibodies (ADAs) were detected in five patients treated with BI 655054, all at low titre, and in one who received placebo; ADAs had no impact on pharmacokinetics or safety.

Conclusion: The trial did not meet its primary CRR endpoint. However, when confirmation of CRR was required at both Weeks 46 and 52, the resultant decrease in the placebo response generated an effect size of 15.2% and 9.1% in favour of 180 mg and 240 mg BI 655064, respectively.

Table 1. Efficacy endpoints at Week 52

	Placebo (n=40)	BI 655064		
		120 mg (n=21)	180 mg (n=20)	240 mg (n=40)
Observed CRR, n	20	8	9	18
Adjusted* CRR, %	48.3	38.3	45	44.6
Observed cCRR, n	13	5	9	16
Adjusted* cCRR, %	29.1	22.5	44.3	38.2
Mean change from baseline in SLEDAI				
Total score	-6.5	-6.1	-9.7	-8.2
Non-renal score	-1.4	-3.0	-2.8	-3.1
Renal score	-5.1	-3.7	-6.8	-5.0
Clinical score	-5.7	-3.9	-7.9	-6.5

CRR based on 24 h proteinuria; cCRR based on UP/UC (spot urine) at Weeks 46 and 52.

*Logistic regression model including treatment and the covariates race and proteinuria at screening.

Disclosure of Interests: David Jayne Consultant of: DRJ has received consulting fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline Research & Development Ltd, Novartis, and Roche, Juergen Steffgen Employee of: JS is employed by Boehringer Ingelheim, Juanita Romero-Diaz Consultant of: JRD has received research consulting fees from Boehringer Ingelheim, Hirofumi Amano Grant/research support from: HA has received research grants from Boehringer Ingelheim, Kajohnsak Noppakun Consultant of: KN has received honoraria from Boehringer Ingelheim, Novartis, Roche, Jansen, AstraZeneca, Otsuka Pharmaceuticals, Astellas Pharma, Abbott, Sanofi and Novo Nordisk, Grant/research support from: KN has received research grants from Boehringer Ingelheim, GlaxoSmithKline Research & Development Ltd, Visterra Inc., Kalbe Genexine Biologics, Aurinia Pharmaceuticals Inc., and Omeros Corporation., Harold Michael Gomez Speakers bureau: HMG has received speaker's fees for Pfizer, MSD, Unilab, Astellas Pharma, AstraZeneca, GlaxoSmithKline Research & Development Ltd, and Aurinia Pharmaceuticals Inc., Rhona Recto: None declared, Valérie Belsack Employee of: Boehringer Ingelheim, Nora Fagan Employee of: Boehringer Ingelheim, Steven Padula Employee of: Boehringer Ingelheim, Ivette Revollo Employee of: Boehringer Ingelheim, Jing Wu Employee of: Boehringer Ingelheim, Sudha Visvanathan Employee of: Boehringer Ingelheim, Richard Furie Consultant of: RF has received research consulting fees, Grant/research support from: RF has received clinical trial support

DOI: 10.1136/annrheumdis-2021-eular.1401

POS0688

CHARACTERIZATION OF PK/PD OF ANIFROLUMAB IN PATIENTS WITH MODERATE TO SEVERE SLE

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Background: In the TULIP-1 and TULIP-2 trials, anifrolumab, a type I interferon (IFN) receptor antibody, at a dosage of 300 mg once every 4 weeks (Q4W),

demonstrated consistent median pharmacokinetic (PK) concentrations¹ and sustained neutralization of the pharmacodynamic (PD) 21-gene type I IFN gene signature (IFNGS)²⁻⁴ in patients with moderate to severe systemic lupus erythematosus (SLE) despite standard therapy.

Objectives: To characterize the PK/PD relationship of anifrolumab and to confirm anifrolumab 300 mg provides adequate PD neutralization in IFNGS test-high patients.

Methods: This study included IFNGS test-high patients from the phase 3 randomized, placebo-controlled, 52-week TULIP-1² (NCT02446912) and TULIP-2³ (NCT02446899) trials of intravenous anifrolumab 150 mg or 300 mg Q4W plus standard therapy. IFNGS test status (high or low) at screening was classified with an analytically validated 4-gene qPCR based test on whole blood.² PD neutralization was measured with 21-gene type I IFNGS and expressed as a percentage change from baseline.³ For the graphic PK/PD analysis, patients with ≥ 1 quantifiable serum PK sample and ≥ 1 PD measurement before discontinuation were categorized depending on C_{ave} (individual predicted average anifrolumab concentration over treatment duration) median and tertiles (T) for anifrolumab 150 mg and 300 mg, respectively. Median PD IFNGS neutralization and medium absolute deviations were compared across C_{ave} subgroups. PK/PD modeling was assessed in patients with ≥ 1 quantifiable serum PK sample and a baseline and ≥ 1 postbaseline PD measurement before discontinuation, using a nonlinear mixed-effects model (NONMEM; version 7.3; ICON) to estimate parameters and characterize the PK/PD data. The PD/efficacy analysis included patients with ≥ 1 postbaseline PD measurement before discontinuation. BILAG-based Combined Lupus Assessment (BICLA) response rates at Week (W)52 were compared across median PD neutralization quartiles (Q) for pooled anifrolumab 300 mg and 150 mg groups.

Results: The PK/PD graphic analysis included 654 IFNGS test-high patients (placebo [n=293]; anifrolumab 150 mg [n=72] or 300 mg [n=289]). C_{ave} was generally higher with anifrolumab 300 mg ($\mu\text{g/mL}$, TULIP-1: T1 <32, T2 32–<44.3, T3 ≥ 44.3 ; TULIP-2: T1 <32.4, T2 32.4–<47.9, T3 ≥ 47.9) than with anifrolumab 150 mg (median 11.5 $\mu\text{g/mL}$); overlap between anifrolumab 300 mg and 150 mg C_{ave} subgroups was small owing to nonlinearity. Anifrolumab 300 mg elicited rapid

Figure. Observed PD neutralization of the 21-gene type I IFNGS according to C_{ave} subgroup over the 52-week treatment duration in A) TULIP-1 and B) TULIP-2

C_{ave} , average anifrolumab concentration over the treatment period; IFNGS, interferon gene signature; PD, pharmacodynamic; PK, pharmacokinetic. Figure includes patients with ≥ 1 quantifiable serum PK observation and ≥ 1 PD measurement prior to discontinuation; PD collected after discontinuations were not included.

(by W4⁴) and sustained median PD neutralization >80%, vs a lower and delayed PD neutralization (median >50% at W52) with anifrolumab 150 mg, and minimal PD neutralization with placebo. The median PD neutralization increased with higher C_{ave} subgroups, plateauing at ~90% at W12–W52. All anifrolumab 300 mg C_{ave} tertiles had a median PD neutralization ~80%; however, the variability was greater in the lowest C_{ave} tertiles vs higher C_{ave} tertiles across trials (Figure 1). The PK/PD modeling, which included 646 IFNGS test–high patients (placebo [n=289], anifrolumab 150 mg [n=70] or 300 mg [n=287]), gave an IC₈₀ estimate of 3.88 µg/mL. The median W24 (study midpoint) C_{trough} was higher with anifrolumab 300 mg vs 150 mg (15.6 vs 0.2 µg/mL); thus, the W24 C_{trough} exceeded the IC₈₀ in a higher proportion of patients treated with anifrolumab 300 mg vs 150 mg (~83% vs ~27%). The PD/efficacy analysis included 341 patients who received anifrolumab. Higher median percentage PD neutralization quartiles (Q1 <51.7%, Q2 51.7%–85.3%, Q3 85.3%–92.6%, Q4 >92.6%) were associated with higher W52 BICLA response rates (Q1 37.6%, Q2 49.4%, Q3 51.8%, Q4 58.1%).

Conclusion: In TULIP-1 and TULIP-2, anifrolumab 300 mg yielded higher anifrolumab C_{ave} vs 150 mg. High C_{ave} was associated with rapid (W4⁴–W12), substantial, and sustained PD neutralization of the 21-gene IFNGS in IFNGS test–high patients, which in turn was associated with higher efficacy.

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Acknowledgements: Writing assistance by Matilda Shackley, MPhil, of JK Associates Inc., part of Fishawack Health. This study was sponsored by AstraZeneca.

Disclosure of Interests: Yen Lin Chia Employee of: AstraZeneca, Raj Tummala Employee of: AstraZeneca, Tu Mai Employee of: Genentech, Tomas Rouse Employee of: AstraZeneca, Wendy White Employee of: AstraZeneca, Eric F. Morand Speakers bureau: AstraZeneca, Consultant of: AstraZeneca, Grant/research support from: AstraZeneca, Richard Furie Consultant of: AstraZeneca, Grant/research support from: AstraZeneca
DOI: 10.1136/annrheumdis-2021-eular.1464 on 19 May 2021.

POS0689 A 6-MONTH OPEN-LABEL EXTENSION STUDY OF THE SAFETY AND EFFICACY OF INTRAVENOUS BELIMUMAB IN PATIENTS WITH LUPUS NEPHRITIS

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Background: BLISS-LN (GSK Study BEL114054; NCT01639339), the largest lupus nephritis (LN) study to date, showed that intravenous (IV) belimumab (BEL) + standard therapy (ST) improved outcomes compared with ST alone in patients (pts) with active LN.¹

Objectives: To assess additional safety and efficacy data of BEL + ST in pts with LN in a 6-month open-label (OL) phase beyond 2 years of double-blind (DB) treatment in BLISS-LN.

Methods: In this OL phase, eligible completers of the DB phase received monthly BEL 10 mg/kg IV + ST for 6 months. Endpoints: safety; Primary Efficacy Renal Response (PERR; uPCR ≤0.7; eGFR no worse than 20% below OL baseline eGFR or ≥60 ml/min/1.73 m²; no prohibited medications) and Complete Renal Response (CRR; uPCR <0.5; eGFR no worse than 10% below OL baseline eGFR or ≥90 ml/min/1.73 m²; no prohibited medications) at OL Week 28; proportion of pts with SLEDAI score <4; corticosteroid use; biomarkers. Analyses were based on observed data and summarised relative to the OL baseline (last value measured prior to the first dose of OL treatment).

Results: We enrolled 257 pts (57.4% of pts in BEL114054) and treated 255 pts. All treated pts were included in the safety population (123 pts switched from placebo [PBO] to BEL; 132 pts remained on BEL). Efficacy was assessed in the safety population, excluding 1 pt due to non-compliance (mITT population; PBO to BEL: 122 pts; BEL to BEL: 132 pts). 96.5% of pts completed the OL phase; 3.5% withdrew, mainly due to adverse events (AE; 2.0%).

Overall, 168/255 (65.9%) pts had ≥1 AE (76/123 [61.8%] PBO to BEL pts; 92/132 [69.7%] BEL to BEL pts); 15/255 (5.9%) pts had ≥1 serious AE (5/123 [4.1%] PBO to BEL pts; 10/132 [7.6%] BEL to BEL pts); 1 (0.8%) pt died in the PBO to BEL group. Proportions of PERR and CRR responders increased from OL baseline to OL Week 28 (Table 1. below)

Proportions of pts who attained SLEDAI scores <4 increased from OL baseline to OL Week 28 in the BEL to BEL group and decreased in the PBO to BEL group. Among pts receiving average daily prednisone-equivalent doses of ≤5 mg or ≤7.5 mg dose was maintained from OL baseline to OL Week 28 (Table 1. below) In pts with autoantibodies at OL baseline, anti-dsDNA and anti-C1q levels decreased from OL baseline to OL Week 28 in both groups. Among pts with low C3/C4 levels at OL baseline, C3/C4 levels increased from OL baseline to OL Week 28 in both groups (Table 1. below)

Conclusion: In this OL phase of BLISS-LN, proportions of PERR and CRR responders increased in both the BEL-naïve and BEL-experienced groups; and no new safety signals were observed. Improvements in biomarker levels were observed, especially in pts who switched from PBO to BEL.

Table 1. Responses at OL baseline and OL Week 28 (mITT population, N=254)

	OL baseline*		OL Week 28	
	PBO to BEL (n=122)	BEL to BEL (n=132)	PBO to BEL (n=122)	BEL to BEL (n=132)
n	122	132	118	122
PERR, n (%)	73 (59.8) [†]	93 (70.5) [†]	79 (66.9)	91 (74.6)
CRR, n (%)	44 (36.1) [†]	63 (47.7) [†]	57 (48.3)	76 (62.3)
SLEDAI score <4				
n	122	132	120	122
Responders, n (%)	44 (36.1) [†]	64 (48.5) [†]	40 (33.3)	64 (52.5)
Prednisone-equivalent dose				
n	122	132	121	128
≤5 mg, n (%)	59 (48.4)	78 (59.1)	60 (49.6)	75 (58.6)
≤7.5 mg, n (%)	62 (50.8)	85 (64.4)	66 (54.5)	83 (64.8)
Anti-dsDNA (IU/ml) [‡]				
n	85	64	81	61
Median (IQR) levels	107.0 (49.0, 212.0)	65.5 (42.5, 126.5)	-	-
Median (IQR) % change from baseline	-	-	-30.2 (-46.3, -6.8)	-10.7 (-27.2, 9.1)
Anti-C1q (U/ml) [§]				
n	64	60	58	54
Median (IQR) levels	71.7 (36.6, 167.5)	47.1 (33.0, 75.7)	-	-
Median (IQR) % change from baseline	-	-	-23.0 (-41.5, 0.5)	-16.5 (-33.0, 6.1)
C3 (mg/dl)				
n	45	37	44	35
Median (IQR) levels	78.0 (72.0, 83.0)	80.0 (71.0, 84.0)	-	-
Median (IQR) % change from baseline	-	-	6.2 (-4.2, 14.6)	4.7 (-4.8, 16.9)
C4 (mg/dl)				
n	18	12	18	11
Median (IQR) levels	7.5 (6.0, 8.0)	7.0 (7.0, 8.5)	-	-
Median (IQR) % change from baseline	-	-	23.6 (11.1, 37.5)	11.1 (0.0, 57.1)

*DB Week 104 visit and the OL baseline visit were the same visit; [†]Post hoc analyses; [‡]Among anti-dsDNA positive pts at OL baseline (≥30 IU/ml); [§]Among anti-C1q positive pts at OL baseline (≥22.2 U/ml); ^{||}Among pts with low C3 (<90 mg/dl)/C4 (<10 mg/dl) levels at OL baseline.