Background: Baricitinib (BARI), an oral, selective Janus kinase (JAK)1 and JAK2 inhibitor, improved disease severity in adults with systemic lupus erythematosus (SLE) receiving standard background therapy in a phase 2 trial¹. There were no meaningful reductions in least squares mean change from baseline (BL) in levels of serologic biomarkers for SLE with BARI treatment, including anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies and complement component (C)3 and C4¹.

Objectives: Evaluate the median change from BL in serologic biomarkers in subgroups and the overall population of BARI-treated SLE patients, in addition to the Systemic Lupus Erythematosus Responder Index-4 (SRI-4) response by normalization of anti-dsDNA.

Methods: Data were assessed from the phase 2 trial JAHH (NCT02708095). The median change from BL in anti-dsDNA, IgG, C3, and C4 was evaluated over time among the following populations at BL: anti-dsDNA positive (≥ 30 IU/mL), low C3 (< 90 mg/dL), low C4 (< 10 mg/dL), and all patients for IgG. Statistical tests were conducted for BARI 2-mg and 4-mg compared with placebo (PBO). Among patients who were anti-dsDNA positive at BL, SRI-4 responder rate was compared for those who stayed positive or achieved normal levels by Week (Wk) 24.

Results: Among patients who were anti-dsDNA positive at BL, significant decreases of anti-dsDNA antibodies were observed for BARI 2-mg and 4-mg compared to PBO beginning at Wks 2 and 4, respectively, and continuing over Wk 24 (Figure 1 and Table 1). Moreover, reductions of IgG levels were found for BARI-treated patients including significant decreases for BARI 4-mg compared to PBO at Wks 12 and 24 (Table 1). Among patients who had low levels of C3 and C4 at BL, no significant differences in median change from BL were observed over time with BARI compared to PBO. For patients who were anti-dsDNA positive at BL, no relationship in SRI-4 responder rate was observed for those who stayed positive or achieved normal levels by Wk 24, possibly due to the limited sample size.

Conclusion: BARI treatment resulted in a rapid and sustained significant decrease in anti-dsDNA antibodies compared to PBO among anti-dsDNA positive SLE patients at BL, as well as a significant decrease in IgG levels in the 4-mg group at Wks 12 and 24. These data suggest that BARI may have an effect on B cell activity in SLE.

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Table 1.

	PBO			BARI 2-mg			BARI 4-mg		
Week	4	12	24	4	12	24	4	12	24
Anti-dsDNA (IU/mL) ^a	0.2 (-17.2, 2.6)	3.0 (-14.8, -14.9)	-15.4** (-31.4, -42.0)	-18.1* (-42.0, -55.1)	-29.6** (-55.1, -42.7)	-17.9** (-42.7, -50.9)	-23.3*** (-50.9, -71.9)	-15.1** (-28.3, 1.9)	-4.6 (-17.9, -4.6)
IgG (g/L) ^b	-0.31 (-1.1, 0.4)	0.09 (-1.1, 0.7)	-0.04 (-0.9, -1.3)	-0.60 (-1.3, 0.6)	-0.30 (-1.3, 0.6)	-0.51 (-1.7, 0.6)	-0.56 (-1.2, 0.2)	-0.65** (-1.3, 0.2)	-0.60** (-1.7, 0.2)

Data are median change from baseline (25th, 75th percentiles). ^aData were assessed for patients that were anti-dsDNA positive (≥ 30 IU/mL) at baseline (PBO N=51, BARI 2-mg N=56, BARI 4-mg N=53). ^bData were assessed for all patients (PBO N=105, BARI 2-mg N=105, BARI 4-mg N=104). * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ for BARI vs. PBO.

Figure. Median change from baseline in anti-dsDNA (IU/mL)^a

Number of patients									
Placebo	51	50	49	47	47	43	40	40	
Baricitinib 2-mg	56	55	53	51	48	46	42	43	
Baricitinib 4-mg	53	53	52	48	46	45	43	40	

^aData were assessed for patients that were anti-dsDNA positive (≥ 30 IU/mL) at baseline. dsDNA=double-stranded deoxyribonucleic acid.

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ for baricitinib compared with placebo

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POS0687

A RANDOMISED DOSE RANGING, PLACEBO-CONTROLLED, PHASE II STUDY ASSESSING THE EFFICACY AND SAFETY OF BI 655064, AN ANTAGONISTIC ANTI-CD40 ANTIBODY, IN PATIENTS WITH LUPUS NEPHRITIS

D. Jayne¹, J. Steffen², J. Romero-Diaz³, H. Amano⁴, K. Noppakun⁵, H. M. Gomez⁶, R. Recto⁷, V. Belsack⁸, N. Fagan⁹, S. Padula¹⁰, I. Revollo¹¹, J. Wu¹², S. Visvanathan¹³, R. Furie¹⁴. ¹University of Cambridge, Department of Medicine, Cambridge, United Kingdom; ²Boehringer Ingelheim International GmbH, TA Inflammation Medicine, Biberach, Germany; ³Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubiran", Immunology and Rheumatology, Mexico City, Mexico; ⁴Juntendo University Hospital, Department of Medicine, Japan, Japan; ⁵Chiang Mai University, Thailand, Department of Internal Medicine, Chiang Mai, Thailand; ⁶Angeles University Foundation Medical Center, Rheumatology, Angeles City, Philippines; ⁷Mary Mediatrix Medical Center, Internal Medicine, Lipa City, Philippines; ⁸SCS Boehringer Ingelheim, Clinical Operations, Brussels, Belgium; ⁹Boehringer Ingelheim Pharmaceuticals Inc., Biostatistics & Data Science, Ridgefield, United States of America; ¹⁰Boehringer Ingelheim International GmbH, Ingelheim, TA Inflammation Medicine, Ingelheim, Germany; ¹¹Boehringer Ingelheim International GmbH, Pharmacovigilance Corporate, Ingelheim, Germany; ¹²Boehringer Ingelheim Pharmaceuticals Inc., Translational Medicine and Clinical Pharmacology, Ridgefield, United States of America; ¹³Boehringer Ingelheim Pharmaceuticals Inc., Translational Medicine and Clinical Pharmacology, Ridgefield, United States of America; ¹⁴Northwell Health and Zucker School of Medicine at Hofstra/Northwell, Department of Rheumatology, Great Neck, United States of America

Background: In patients with SLE, activation of the CD40-CD40L pathway results in stimulation and proliferation of B cells and other inflammatory cell types. The subsequent generation of autoantibodies and their deposition in the kidney, as well as activation of myeloid and resident kidney cells, result in local inflammation and eventually, kidney injury. Thus, CD40 is an appealing therapeutic target in lupus nephritis (LN). BI 655064 is a humanised anti-CD40 monoclonal antibody that blocks the CD40 pathway in a nanomolar range and downregulates activated B cells.

Objectives: To assess the efficacy and safety over 52 weeks of three doses of subcutaneous BI 655064 compared with placebo, as add-on to mycophenolate and steroids, in patients with active proliferative LN (ClinicalTrials.gov number: NCT02770170).

Methods: Overall, 121 patients with LN were randomised, double blind, in a 2:1:1:2 ratio to placebo or BI 655064 120 mg, 180 mg or 240 mg, and received a weekly loading dose for the first 3 weeks, followed by dosing every 2 weeks for the 120 and 180 mg doses, and weekly (120 mg) for the 240 mg group. Key inclusion criteria included an active ISN/RPS class III or IV ($\pm$ V) renal biopsy within 3 months prior to screening and a screening protein/creatinine ratio of ≥ 1 mg/mg. Randomisation was stratified based on race (Asian vs non-Asian) and screening protein/creatinine (UP/UC) ratio (< 3 vs ≥ 3). The primary efficacy endpoint was complete renal response (CRR), defined as 24 h proteinuria < 0.5 g/day and stable eGFR at Week 52.

Results: The placebo response in this trial was higher than expected (48.3%; Table 1); none of the

BI 655064 doses increased rates of CRR at Week 52 compared with placebo. However, CRR at Week 52 based on creatinine-adjusted proteinuria, assessed using spot urine, showed a better response in the 180 mg group (50%) vs placebo (42.5%), and the 180 mg dose showed a greater change from baseline over

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.

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POS0688

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

Y. L. Chia¹, R. Tummala², T. Mai³, T. Rouse⁴, W. White², E. F. Morand⁵, R. Furie⁶.
¹AstraZeneca, BioPharmaceuticals R&D, South San Francisco, United States of America; ²AstraZeneca, BioPharmaceuticals R&D, Gaithersburg, United States of America; ³Genentech, Clinical Pharmacology and Modeling & Simulation, South San Francisco, United States of America; ⁴AstraZeneca, BioPharmaceuticals R&D, Gothenburg, Sweden; ⁵Monash University, Centre for Inflammatory Disease Monash Health, Melbourne, Australia; ⁶Zucker School of Medicine at Hofstra/Northwell, Division of Rheumatology, Great Neck, United States of America

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

A) TULIP-1

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.