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Clinical and Biomarker Responses to BI 655064, an Antagonistic Anti-CD40 Antibody, in Patients With Active Lupus Nephritis: A Randomized, Double-Blind, Placebo-Controlled, Phase II Trial

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Objective. To characterize its dose-response relationship, BI 655064 (an anti-CD40 monoclonal antibody) was tested as an add-on to mycophenolate and glucocorticoids in patients with active lupus nephritis (LN).

Methods. A total of 121 patients were randomized (2:1:1:2) to receive placebo or BI 655064 120, 180, or 240 mg and received a weekly loading dose for 3 weeks followed by dosing every 2 weeks for the 120 and 180 mg groups, and 120 mg weekly for the 240 mg group. The primary endpoint was complete renal response (CRR) at week 52. Secondary endpoints included CRR at week 26.

Results. A dose-response relationship with CRR at week 52 was not shown (BI 655064 120 mg, 38.3%; 180 mg, 45.0%; 240 mg, 44.6%; placebo, 48.3%). At week 26, 28.6% (120 mg), 50.0% (180 mg), 35.0% (240 mg), and 37.5% (placebo) achieved CRR. The unexpected high placebo response prompted a post hoc analysis evaluating confirmed CRR (cCRR, at weeks 46 and 52). cCRR was achieved in 22.5% (120 mg), 44.3% (180 mg), 38.2% (240 mg), and 29.1% (placebo) of patients. Most patients reported ≥1 adverse event (BI 655064, 85.7–95.0%; placebo, 97.5%), most frequently infections and infestations (BI 655064 61.9–75.0%; placebo 60%). Compared with other groups, higher rates of serious (20% vs. 7.5–10%) and severe infections (10% vs. 4.8–5.0%) were reported with 240 mg BI 655064.

Conclusion. The trial failed to demonstrate a dose-response relationship for the primary CRR endpoint. Post hoc analyses suggest a potential benefit of BI 655064 180 mg in patients with active LN.

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INTRODUCTION

Lupus nephritis (LN) is the most common serious complication of systemic lupus erythematosus (SLE). Patients with class III–V LN are at high risk of irreversible kidney damage, end-stage renal disease, dialysis, and death (1,2). The recommended standard of care (SoC) for patients with LN is cyclophosphamide or mycophenolate mofetil (MMF) in combination with glucocorticoids (2,3); however, only 23–36% of patients achieve complete renal responses (CRRs) (4). Additionally, these regimens are associated with relapse, infection risks, and toxicities (3–6). Belimumab (7) and voclosporin (8) as add-on treatments to SoC showed improved responses leading to their approvals for the treatment of LN; however, more treatment options that are effective are needed.

CD40 is a transmembrane cell surface costimulatory receptor and a member of the tumor necrosis factor receptor superfamily (2). The interaction of CD40 with its ligand, CD40L (CD154), plays a critical role in immune regulation (9,10). CD40L expression is elevated on certain immune cells in patients with SLE, including B cells, T cells, monocytes, and dendritic cells (2). The CD40–CD40L pathway plays an essential role in the pathogenesis of SLE by mediating the generation and disposition of autoantibodies in the kidneys, leading to kidney injury (2,11).

Targeting the CD40–CD40L pathway is a promising approach for the treatment of LN (12). BG9588, a humanized anti-CD40L antibody, improved serologic markers in patients with proliferative LN; however, the trial was discontinued because of the incidence of thromboembolic events (13) that were possibly related to the Fc region of BG9588. BI 655064 is a second-generation humanized anti-CD40 antibody in which the Fc regions include two mutations that prevent Fc-mediated antibody-dependent or complement-mediated cellular cytotoxicity and platelet activation (14). The safety and tolerability of BI 655064 has been established in healthy volunteers and in a phase IIa trial in patients with rheumatoid arthritis, in which BI 655064 did not cause any thromboembolic events and reduced activated B cells, autoantibody production, and inflammatory markers (15,16). We report the safety, efficacy, and pharmacodynamic effects of BI 655064 in an exploratory, proof-of-concept dose-ranging trial in patients with active LN.

METHODS

Study design. This multicenter, randomized, placebo-controlled, double-blind, parallel-group, phase II trial in patients with active LN (ClinicalTrials.gov identifier NCT02770170) was conducted at 74 sites across 20 countries between August 2016 and August 2020. Patients were randomized 2:1:1:2 to receive placebo or 120, 180, or 240 mg BI 655064 (Supplementary Appendix S1, http://onlinelibrary.wiley.com/doi/10.1002/art.42557). All treatments were given in combination with SoC (MMF and glucocorticoids). Patients received a loading dose of two subcutaneous injections of BI 655064 or placebo per week on the same day for 3 weeks, followed by dosing every 2 weeks for the 120 and 180 mg groups, and 120 mg weekly for the 240 mg group, for up to 52 weeks. Randomization was stratified by race (Asian vs. non-Asian) and proteinuria at screening (urine protein/urine creatinine ratio [UP/UC] <3 vs. ≥3). Race was self-reported by patients. The complete study design is described in Supplementary Appendix S1, which can be found at http://onlinelibrary.wiley.com/doi/10.1002/art.42557.

Patients. Patients aged 18–70 years were eligible if diagnosed as having SLE by American College of Rheumatology (ACR) criteria (17), with ≥4 ACR criteria documented, including a positive finding for anti–double-stranded (ds) DNA antibody or positive antinuclear antibody at screening. Renal eligibility required a biopsy within the previous 3 months (6 months in the US; only one US patient with a >3-month biopsy window was randomized) with active LN class III/IV, with or without class V (2003 International Society of Nephrology/Renal Pathology Society classification) (18–20), and proteinuria ≥1.0 g/day (UP/UC ≥1) at screening. Exclusion criteria are described in Supplementary Appendix S1, which can be found at http://onlinelibrary.wiley.com/doi/10.1002/art.42557.

Written informed consent was obtained from all patients. The study was conducted and reported in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and other applicable regulatory requirements, which were reviewed and approved by the Independent Ethics Committees and/or Institutional Review Boards of participating sites.

Assessments. *Primary and secondary endpoints.* The primary endpoint was the proportion of patients with CRR at week 52. CRR was defined as proteinuria <0.5 g/day (average of two 24-hour collections) at week 52, and either an estimated glomerular filtration rate (eGFR; calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula) ≥90 mL/min/1.73 m^2 or a <20% decrease from baseline if eGFR was <90 mL/min/1.73 m^2 at week 52. Secondary endpoints included the proportion of patients with CRR at week 26 and with partial renal response (PRR; ≥50% reduction in proteinuria from baseline and eGFR ≥90 mL/min/1.73 m^2 or a <20% decrease from baseline if eGFR was <90 mL/min/1.73 m^2) at weeks 26 and 52.

Additional endpoints. Additional endpoints, including time to CRR and change from baseline in Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)–Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Patient-Reported Outcome tool (LupusPRO), and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F), are described in Supplementary Appendix S1 (http://onlinelibrary.wiley.com/doi/10.1002/art.42557), as are pharmacokinetic, immunogenicity, and exploratory biomarker analyses.

Safety. The safety of BI 655064 was assessed descriptively by evaluating adverse events (AEs) and tolerability. AE intensity was graded according to Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (21).

Statistical methods. To establish proof of concept and characterize the dose-response relationship, the primary analysis used methodology employing both multiple comparison procedures and modeling techniques (MCPMod) (22,23). The trial was powered to reject the null hypothesis of a flat dose-response curve under the assumption that a placebo response rate of approximately 25% would be observed with a treatment benefit of approximately 20%. With the planned sample size of 120 patients (40:20:20:40), the success probability was approximately 82% for this base case (CRR treatment rate of 45% vs. placebo rate of 25% at week 52). Because of the the exploratory nature of the trial, a one-sided alpha level of 20% was used. The MCPMod procedure allowed for the simultaneous evaluation of different potential dose-response patterns (four patterns were pre-specified) while maintaining the overall Type I error at 20%.

CRR at week 52 (derived using proteinuria from 24-hour urine collections, using UP/UC from 24-hour urine collections and UP/UC from spot urines) was analyzed using a logistic regression model, with factors including treatment, and the covariates race (Asian vs. non-Asian) and proteinuria at screening (UP/UC <3 vs. ≥3). From this model, placebo-adjusted treatment estimates for each active dose group, and their corresponding variance-covariance matrix were estimated and used in the analysis.

Pairwise comparisons of the modeled and observed proportions of patients with CRR at each dose level versus placebo were performed; *P* values and confidence intervals should be interpreted as nominal p-values as the trial was not powered for the pairwise comparisons. Other endpoint analyses are described in Supplementary Appendix S1, which can be found at http://onlinelibrary.wiley.com/doi/10.1002/art.42557.

Spot urine could be used if a patient did not have two 24-hour urine collections, and a screening eGFR value could be used if baseline eGFR was not available. Descriptive statistical methods were used to analyze further endpoints. Analyses were performed on an intent-to-treat set, which included all treated patients. The definition/derivation of CRR for patients who prematurely discontinued trial medication is described in Supplementary Appendix S1, which can be found at http://onlinelibrary.wiley.com/doi/10.1002/art.42557.

RESULTS

Patient disposition and baseline characteristics. In total, 121 patients were randomized and received ≥1 dose of trial medication (BI 655064 120 mg n = 21; 180 mg n = 20; 240 mg n = 40; placebo n = 40). Discontinuations occurred in 33.3%, 15.0%, and 12.5% of patients in the 120, 180, and 240 mg groups, respectively, and in 17.5% patients receiving placebo (Supplemental Figure S1, http://onlinelibrary.wiley.com/doi/10.1002/art.42557). Patient age ranged from 24–47 years; most were female (76.2–95.0%) and had been diagnosed as having LN for ≥6 months (52.5–71.4%) (Table 1); 28.6%, 30.0%, 42.5%, and 47.5% receiving 120, 180, and 240 mg and placebo, respectively, had been diagnosed with LN for <6 months (Table 1). According to local pathologist assessment, most patients in each group had class IV LN, with the distribution of class III and IV comparable across all groups. By central evaluation assessment, the mean activity index was comparable across all treatment groups, whereas the mean chronicity index (CI) at baseline in the placebo group (1.5) was lower than the 120 and 180 mg treatment groups (3.0 and 2.6, respectively) and comparable to the 240 mg group (1.8) (Table 1). More patients in the placebo group (82.5%) had on-treatment use of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) than those receiving BI 655064 (61.9–77.5%) (Supplemental Table S1, http://onlinelibrary.wiley.com/doi/10.1002/art.42557).

Efficacy. A dose-response relationship with CRR at week 52 was not shown. None of the prespecified dose-response models tested using MCPMod were statistically significant; therefore, the null hypothesis of a flat dose-response curve was not rejected. The adjusted proportion of patients who achieved CRR at week 52 was 38.3%, 45.0%, and 44.6% in the 120, 180, and 240 mg groups, respectively, and 48.3% for placebo (Figure 1A). For the secondary endpoint, the proportion of patients who achieved CRR at week 26 was 28.6%, 50.0%, and 35.0% in the 120, 180, and 240 mg groups, respectively, and 37.5% for placebo (Figure 1B). The proportion of patients achieving CRR at week 52 based on UP/UC from spot urine (Figure 1C) was 23.8%, 50.0%, and 47.5% in the 120, 180, and 240 mg groups, respectively, and 42.5% for placebo.

Additional endpoints. Patients in the 180 mg group achieved CRR slightly earlier than patients in the other groups (Table 2) and had the greatest median change from baseline over time for UP/UC based on spot urine (Figure 2). After 26 and 52 weeks, patients in the 240 mg group had the greatest increase in eGFR (mean change from baseline of 12.3 and 12.8 mL/min/1.73 m^2, respectively) (Table 2). Patients in the 180 mg group received the lowest mean glucocorticoid dose per day (mean daily glucocorticoid dose 8.75 mg in those receiving 120 mg BI 655064, 6.87 mg in those receiving 180 mg BI 655064, 7.88 mg in those receiving 240 mg BI 655064, and 8.26 mg in those receiving placebo).

Changes in SELENA–SLEDAI mean scores are shown in Table 2. Numerically more patients in the 180 and 240 mg groups had 4-, 5-, and 6-point changes from baseline in total SELENA-SLEDAI score than in the placebo group (55.0–77.5% at week

Table 1. Baseline demographics, clinical characteristics, and medication use*

Characteristic	Placebo (n = 40)	BI 655064 120 mg (n = 21)	BI 655064 180 mg (n = 20)	BI 655064 240 mg (n = 40)
Age, years, mean ± SD	33.9 ± 9.8	35.9 ± 11.4	34.5 ± 9.9	34.3 ± 10.3
Female, n (%)	38 (95.0)	16 (76.2)	18 (90.0)	36 (90.0)
Race, n (%)				
Asian	17 (42.5)	9 (42.9)	9 (45.0)	17 (42.5)
Black/African American	1 (2.5)	1 (4.8)	0	2 (5.0)
White	22 (55.0)	9 (42.9)	11 (55.0)	21 (52.5)
Multiple	0	1 (4.8)	0	0
Missing, but known to be non-Asian	0	1 (4.8)	0	0
Time since diagnosis with LN, n (%)				
<6 months	19 (47.5)	6 (28.6)	6 (30.0)	17 (42.5)
≥6 months	21 (52.5)	15 (71.4)	14 (70.0)	23 (57.5)
LN classification, n (%)†				
III	14 (35.0)	7 (33.3)	6 (30.0)	13 (32.5)
IV	26 (65.0)	14 (66.7)	14 (70.0)	27 (67.5)
Concomitant V	15 (37.5)	11 (52.4)	9 (45.0)	22 (55.0)
Activity index from renal biopsy, mean ± SD‡	6.9 ± 3.6§	5.6 ± 3.5¶	7.6 ± 4.0#	7.1 ± 4.2**
Chronicity index from renal biopsy, mean ± SD‡	1.5 ± 1.7§	3.0 ± 3.3¶	2.6 ± 2.4#	1.8 ± 2.3**
SLEDAI total score, mean ± SD	10.8 ± 5.8	11.5 ± 5.7	10.1 ± 6.3	11.6 ± 5.5
Nonrenal	4.0 ± 3.3	4.1 ± 3.2	3.1 ± 3.6	4.4 ± 3.4
Renal	6.8 ± 4.2	7.4 ± 4.1	7.0 ± 3.6	7.2 ± 3.9
FACIT-F total score, mean ± SD	36.0 ± 9.8	31.8 ± 12.2	37.0 ± 12.1	32.4 ± 11.0
Anti-dsDNA >ULN at baseline, n (%)				
Yes	22 (55.0)	11 (52.4)	6 (30.0)	27 (67.5)
No	18 (45.0)	10 (47.6)	13 (65.0)	13 (32.5)
Missing	0	0	1 (5.0)	0
C3 <LLN at baseline, n (%)	26 (65.0)	14 (66.7)	10 (50.0)	28 (70.0)
C4 <LLN at baseline, n (%)	12 (30.0)	3 (14.3)	7 (35.0)	13 (32.5)
eGFR at baseline, mL/min/1.73 m^2, mean ± SD	88.8 ± 29.9	85.9 ± 34.3	99.9 ± 21.1	91.1 ± 32.7
UP/UC at baseline from spot urine, mean ± SD	2.9 ± 2.4	4.4 ± 3.8	4.0 ± 3.2	2.9 ± 2.0
UP/UC <3 at screening from spot urine, n (%)	24 (60.0)	10 (47.6)	10 (50.0)	21 (52.5)
UP/UC ≥3 at screening from spot urine, n (%)	16 (40.0)	11 (52.4)	10 (50.0)	19 (47.5)

* dsDNA = double-stranded DNA; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; LLN = lower limit of normal; LN = lupus nephritis; SD = standard deviation; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; ULN = upper limit of normal; UP/UC = urine protein/urine creatinine ratio.
† Based on local renal pathologist's assessment.
‡ Based on central assessment.
§ n = 33.
¶ n = 19.
# n = 18.
** n = 33.

26 and 62.5–80.0% at week 52 for the 180 and 240 mg groups; 52.5–62.5% at weeks 26 and 52 for placebo) (Table 2). A post hoc analysis of nonrenal SLEDAI is reported in Supplementary Appendix S1, which can be found at http://onlinelibrary.wiley.com/doi/10.1002/art.42557.

At weeks 12, 26, and 52, there was a numerical increase in the mean LupusPRO health-related quality of life (HRQoL) score with BI 655064 compared with placebo. For the mean total LupusPRO HRQoL score, a marked increase was observed in the 120 and 180 mg groups at weeks 26 and 52; observed increases were lower in the 240 mg and placebo groups (Table 3). Based on the FACIT-F scores, patients in all BI 655064 groups performed better than those receiving placebo after 52 weeks; the 240 mg group had the largest change (Table 3). Post hoc analyses of FACIT-F and LupusPRO are reported in Supplementary Appendix S1, which can be found at http://onlinelibrary.wiley.com/doi/10.1002/art.42557.

Post hoc analyses. The unexpectedly high placebo responses for the primary endpoint prompted a post hoc analysis, which required confirmation of CRR (cCRR; CRR at both

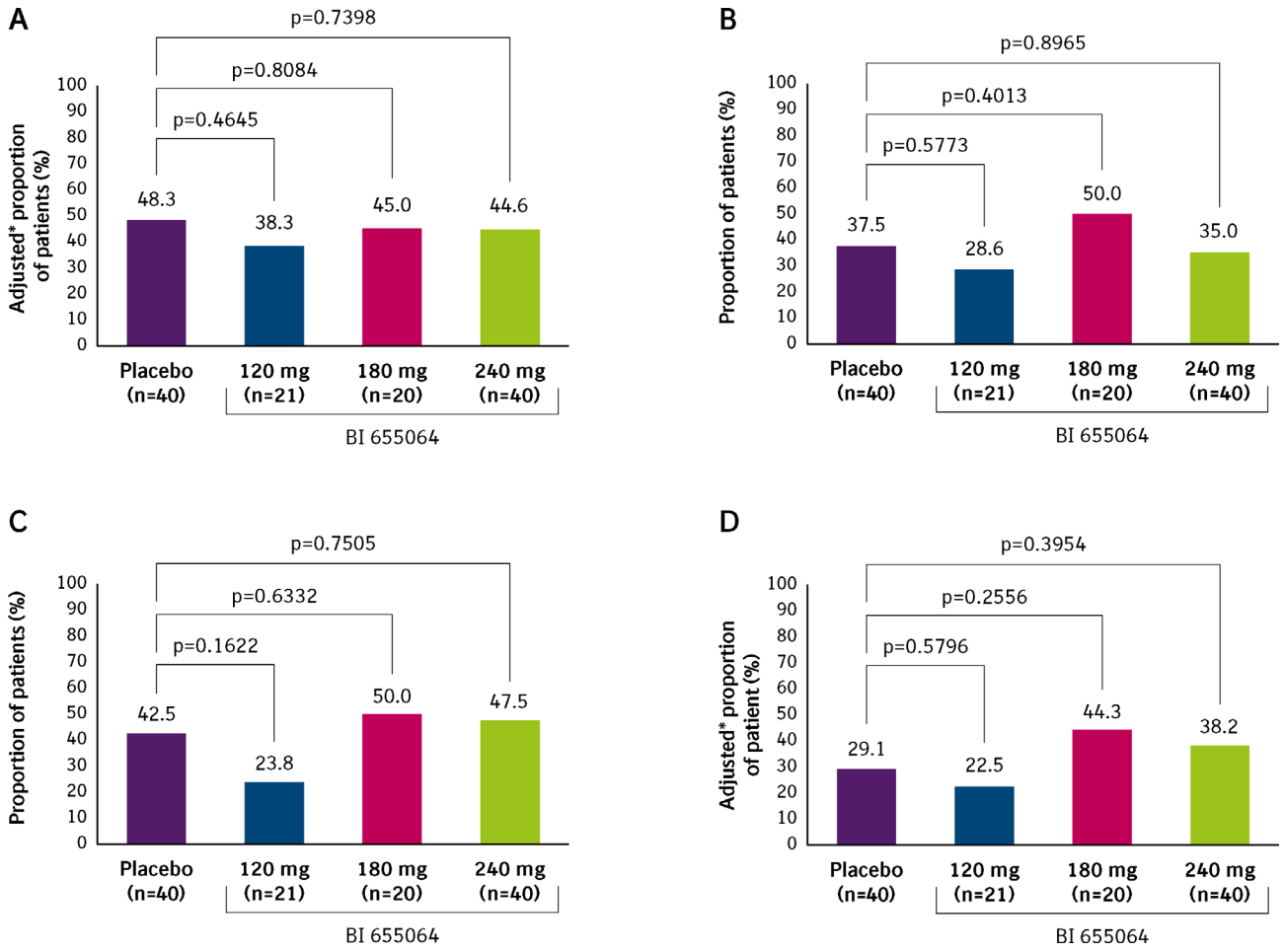

Figure 1. Efficacy of BI 655064. (**A**) Adjusted proportion of patients achieving CRR at week 52 (primary endpoint, based on proteinuria from 24-hour collections). (**B**) Proportion of patients achieving CRR based on proteinuria from 24-hour collections at week 26. (**C**) Proportion of patients achieving CRR (UP/UC from spot urine) at week 52. (**D**) Adjusted proportion of patients achieving cCRR (CRR at both weeks 46 and 52, using UP/UC from spot urine for measurement of proteinuria) based on post hoc analyses. Nominal *P* values are shown. *Factors in the model included treatment and the covariates race (Asian or non-Asian) and proteinuria at screening (UP/UC <3 or ≥3). cCRR = confirmed complete renal response; CRR = complete renal response; UP/UC = urine protein/urine creatinine ratio.

week 46 [penultimate visit during treatment] and week 52), using UP/UC from spot urine for measurement of proteinuria. In this post hoc analysis cCRR was achieved by 22.5%, 44.3%, and 38.2% of patients receiving 120, 180, and 240 mg, respectively, and 29.1% of those receiving placebo (Figure 1D). The post hoc MCPMod analysis of cCRR showed two dose-response curves (the sigEmax and exponential models) to be significant at the prespecified alpha level (<0.20). A sensitivity analysis demonstrated that for patients with UP/UC <3 the highest proportion of patients achieving cCRR were in the 180 mg group, and, for patients with UP/UC ≥3, they were in the 240 mg group (Table 2). For Asian and non-Asian patients, the highest proportion of patients achieving cCRR were in the 180 mg group (Table 2). Likewise, the highest proportion of patients achieving cCRR at weeks 21 and 26 received 180 mg.

An additional post hoc analysis of cCRR stratified by CI demonstrated that patients with a CI <1 (the median score) tended to have a higher probability of achieving cCRR than those with a CI ≥1. cCRR occurred more frequently in patients with CI <1 versus ≥1 in the 120 and 180 mg and placebo groups (120 mg: 50.0% vs. 23.5%; 180 mg: 50.0% vs. 42.9%; placebo: 53.8% vs. 25.0%). The opposite was seen in the 240 mg group, with 28.6% versus 48.0% of patients with CI <1 versus ≥1 achieving cCRR.

Pharmacokinetics and immunogenicity. Geometric mean steady-state trough plasma concentrations of BI 655064 over weeks 8 and 52 were 7.95, 16.7, and 32.7 µg/mL for the 120, 180, and 240 mg doses, respectively, demonstrating a more than dose-proportional increase (in line with the nonlinear pharmacokinetics observed in healthy volunteers (15)). However, several patients receiving BI 655064 had low/undetectable exposure over several months during the second half of treatment, despite reporting regular administration of their injections.

Table 2. Additional efficacy endpoints and post hoc sensitivity analysis*

Endpoint	Placebo (n = 40)	BI 655064 120 mg (n = 21)	BI 655064 180 mg (n = 20)	BI 655064 240 mg (n = 40)
PRR (UP 24 h) at week 26, n (%)	25 (62.5)	9 (42.9)	15 (75.0)	25 (62.5)
PRR (UP 24 h) at week 52, n (%)	24 (60.0)	7 (33.3)	13 (65.0)	22 (55.0)
CRR or PRR at week 26, n (%)	26 (65.0)	11 (52.4)	16 (80.0)	25 (62.5)
CRR or PRR at week 52, n (%)	25 (62.5)	10 (47.6)	14 (70.0)	25 (62.5)
Additional endpoints				
Time to CRR, weeks (UP 24 h), mean ± SD	20.4 ± 16.2	26.8 ± 22.3	17.3 ± 14.2	21.7 ± 15.9
Time to CRR, weeks (UP/UC 24 h), mean ± SD	19.7 ± 16.2	25.1 ± 21.0	15.9 ± 14.4	21.9 ± 16.0
Average daily glucocorticoid dose, mg, mean ± SD	8.26 ± 4.84	8.75 ± 2.69	6.87 ± 2.37	7.88 ± 2.56
Change from baseline in eGFR, mL/min/1.73 m^2, mean ± SD				
Week 26	2.9 ± 20.6	2.0 ± 19.9	−1.4 ± 14.2	12.3 ± 22.0
Week 52	6.2 ± 21.5	9.0 ± 22.5	−0.5 ± 17.2	12.8 ± 19.2
Change from baseline in SELENA-SLEDAI at week 26, mean ± SD				
Total score	−5.86 ± 5.67	−6.12 ± 6.11	−7.16 ± 6.74	−7.11 ± 4.98
Nonrenal score	−1.51 ± 2.81	−2.59 ± 2.45	−1.89 ± 3.09	−2.47 ± 3.27
Renal score	−4.34 ± 4.48	−3.53 ± 5.27	−5.26 ± 4.82	−4.63 ± 3.66
Clinical score	−5.17 ± 5.36	−4.59 ± 5.68	−6.11 ± 6.20	−5.95 ± 4.59
SELENA-SLEDAI total score 4-point change at week 26, n (%)	25 (62.5)	11 (52.4)	15 (75.0)	31 (77.5)
SELENA-SLEDAI total score 5-point change at week 26, n (%)	21 (52.5)	8 (38.1)	11 (55.0)	24 (60.0)
SELENA-SLEDAI total score 6-point change at week 26, n (%)	21 (52.5)	8 (38.1)	11 (55.0)	24 (60.0)
Change from baseline in SELENA-SLEDAI at week 52, mean ± SD				
Total score	−6.52 ± 7.50	−6.08 ± 5.87	−9.65 ± 6.45	−8.17 ± 5.44
Nonrenal score	−1.42 ± 4.15	−3.00 ± 1.83	−2.82 ± 3.75	−3.14 ± 3.52
Renal score	−5.09 ± 4.82	−3.71 ± 5.76	−6.82 ± 3.94	−5.03 ± 4.59
Clinical score	−5.67 ± 7.23	−3.92 ± 5.75	−7.88 ± 5.98	−6.51 ± 5.29
SELENA-SLEDAI total score 4-point change at week 52, n (%)	25 (62.5)	10 (47.6)	16 (80.0)	29 (72.5)
SELENA-SLEDAI total score 5-point change at week 52, n (%)	21 (52.5)	7 (33.3)	14 (70.0)	25 (62.5)
SELENA-SLEDAI total score 6-point change at week 52, n (%)	21 (52.5)	6 (28.6)	14 (70.0)	25 (62.5)
Post hoc sensitivity analysis				
cCRR (UP/UC <3), n/N (%)†	10/24 (41.7)	4/10 (40.0)	7/10 (70.0)	8/21 (38.1)
cCRR (UP/UC ≥3), n/N (%)†	3/16 (18.8)	1/11 (9.1)	2/10 (20.0)	8/19 (42.1)
cCRR (Asian), n/N (%)†	5/17 (29.4)	1/9 (11.1)	4/9 (44.4)	6/17 (35.3)
cCRR (non-Asian), n/N (%)†	8/23 (34.8)	4/12 (33.3)	5/11 (45.5)	10/23 (43.5)
CRR at weeks 21 and 26, n/N (%)†	14/40 (35.0)	3/21 (14.3)	9/20 (45.0)	9/40 (22.5)

* CRR = complete renal response; cCCR = confirmed complete renal response; eGFR = estimated glomerular filtration rate; PRR, = partial renal response; SD, = standard deviation; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; UP = urine protein; UP/UC = urine protein/urine creatinine ratio.
† CRR at both Week 46 and Week 52, using UP/UC from spot urine for measurement of proteinuria.

Across all groups, 9/121 patients (7.4%) had a positive anti-drug antibody (ADA) response (placebo: n = 3, 120 mg: n = 2, 180 mg: n = 3, 240 mg: n = 1). Six patients had a treatment-induced positive ADA response (120 mg: n = 2, 180 mg: n = 2, 240 mg: n = 1, placebo: n = 1): one patient receiving 120 mg had a titer value of 243.2; the remaining patients had low titer values of 30.4 or 60.8. Similar BI 655064 plasma concentrations were seen between ADA-positive and ADA-negative patients for all BI 655064 groups.

Biomarkers. At week 52, a decrease in anti-dsDNA levels was observed in all groups, including placebo. However, enrolled patients were not required to be anti-dsDNA positive to participate in the study. The median change from baseline in anti-dsDNA in patients with positive anti-dsDNA at baseline (Supplementary Figure S2, http://onlinelibrary.wiley.com/doi/10.1002/art.42557) was largest in the 180 mg group (change from baseline of −199.85 at week 52 [n = 6] versus −79.90 for placebo [n = 17]). Median increase in C3 complement levels in patients with baseline levels below the lower limit of normal did not show a separation between dose groups; however, the 180 mg group showed the greatest improvement in C4 complement levels versus other treatment groups and placebo (median change from baseline for the 180 mg group at Week 52 was 0.08 vs. 0.05 for placebo [n = 7 and n = 10, respectively]) (Supplementary Figures S3A and S3B, http://onlinelibrary.wiley.com/doi/10.1002/art.42557).

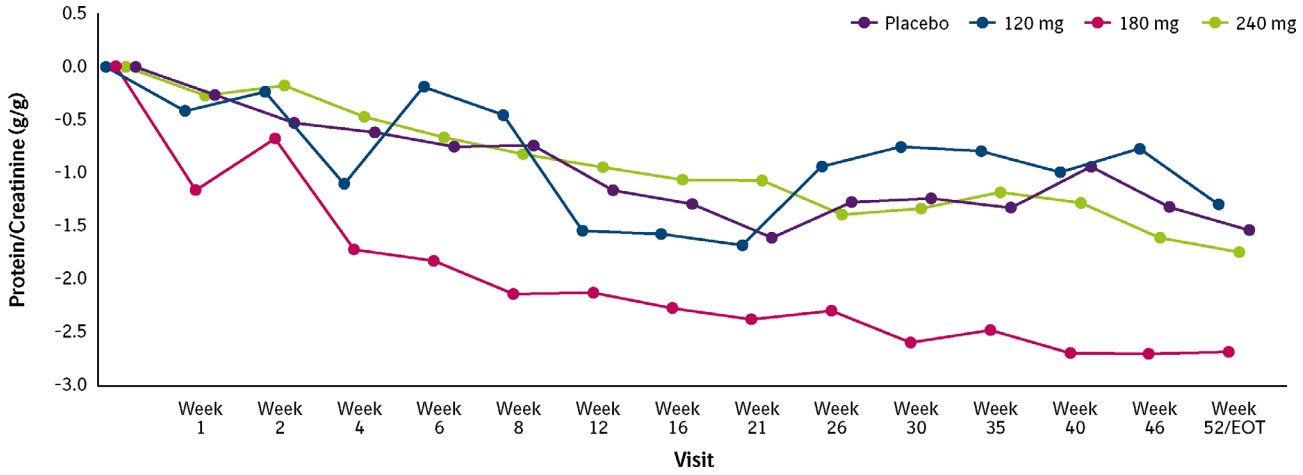

Figure 2. Median change from baseline in UP/UC over time. EOT = end of trial; UP/UC = urine protein/urine creatinine ratio. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42557/abstract.

Treatment with BI 655064 had no overall effect on the proportion of CD19+ naive B cells. However, large decreases were observed over 26 weeks in the activated double-negative (CD27–IgD–CD95+), double-positive (CD27+IgD+CD95+), post-switched (CD27+IgD–CD95+) and preswitched (CD27–IgD+CD95+) B-cell subsets in the 180 and 240 mg groups versus placebo (Supplementary Figure S4A, http://onlinelibrary.wiley.com/doi/10.1002/art.42557). Additionally, increases were observed in the 180 and 240 mg groups versus placebo in the CD3+CD4–CD8–CD154+ and CD3+CD8+CD4–CD154+ T cell subsets at week 12 and 26 (Supplementary Figure S4B, http://onlinelibrary.wiley.com/doi/10.1002/art.42557). Treatment with 180 and 240 mg resulted in a reduction in soluble CD40L levels over time versus placebo, with more consistent reduction in the 240 mg group.

Safety. Most patients experienced AEs (Table 4), with AEs being the main reason for treatment discontinuation in 12.4% of patients (Supplemental Figure S1, http://onlinelibrary.wiley.com/doi/10.1002/art.42557). Infections were common in all treatment groups; however, more patients in the 240 mg group experienced serious (Table 4) and severe infections than in other groups, including two patients with RCTC grades 3 and 4 septic shock (Supplemental Table S2, http://onlinelibrary.wiley.com/doi/10.1002/art.42557). Neutropenia, lymphopenia, and leucopenia were more common in the 240 mg group; however, there was no indication of an increase in infections among patients with neutropenia, with neutropenia resolving spontaneously, upon reduction of MMF, or with granulocyte colony–stimulating factor therapy. No thromboembolic events were observed in any group. More patients experienced AEs of maximum RCTC grade

Table 3. Patient-reported outcomes*

Outcome	Placebo (n = 40)	BI 655064 120 mg (n = 21)	BI 655064 180 mg (n = 20)	BI 655064 240 mg (n = 40)
Change from baseline in LupusPRO score at Week 12, mean ± SD†				
Total HRQoL	5.47 ± 9.48	6.74 ± 11.62	7.01 ± 12.87	10.05 ± 18.61
Non-HRQoL	−0.01 ± 12.46	6.61 ± 16.86	−1.26 ± 10.46	−2.11 ± 14.28
Change from baseline in LupusPRO score at Week 26, mean ± SD‡				
Total HRQoL	6.89 ± 8.55	13.58 ± 10.41	13.07 ± 12.14	10.82 ± 17.76
Non-HRQoL	−0.13 ± 14.81	2.83 ± 16.19	5.40 ± 14.37	0.49 ± 13.06
Change from baseline in LupusPRO score at Week 52, mean ± SD§				
Total HRQoL	8.54 ± 9.71	11.94 ± 10.47	13.39 ± 13.36	12.57 ± 17.54
Non-HRQoL	2.18 ± 13.41	1.26 ± 19.58	9.56 ± 12.18	0.95 ± 15.12
Change from baseline in FACIT-F, mean ± SD				
Week 26¶	3.19 ± 8.40	3.81 ± 9.21	5.53 ± 10.52	6.58 ± 11.67
Week 52#	2.84 ± 8.36	4.50 ± 7.01	3.59 ± 9.04	6.57 ± 11.14

* FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; HRQoL = health-related quality of life; LupusPRO = Lupus Patient-Reported Outcome tool; SD = standard deviation.
† n = 38, n = 19, n = 19, and n = 40, for placebo and 120, 180, and 240 mg BI 655064, respectively.
‡ n = 36, n = 16, n = 19, and n = 38, for placebo and 120, 180, and 240 mg BI 655064, respectively.
§ n = 33, n = 14, n = 17, and n = 35, for placebo and 120, 180, and 240 BI 655064, respectively.
¶ n = 36, n = 16, n = 19, and n = 38, for placebo and 120, 180, and 240 mg BI 655064, respectively.
# n = 32, n = 14, n = 17, and n = 35, for placebo and 120, 180, and 240 mg BI 655064, respectively.

Table 4. Common AEs in ≥10% of patients in any treatment group and summary of overall safety and serious AEs*

Adverse events	Placebo (n = 40)	BI 655064 120 mg (n = 21)	BI 655064 180 mg (n = 20)	BI 655064 240 mg (n = 40)
Any AE, n (%)	39 (97.5)	18 (85.7)	19 (95.0)	36 (90.0)
Common AEs, n (%)†				
Upper respiratory tract infection	8 (20.0)	5 (23.8)	7 (35.0)	7 (17.5)
Diarrhea	6 (15.0)	5 (23.8)	3 (15.0)	9 (22.5)
Alopecia	7 (17.5)	0	3 (15.0)	9 (22.5)
Headache	5 (12.5)	3 (14.3)	1 (5.0)	6 (15.0)
Nasopharyngitis	7 (17.5)	2 (9.5)	1 (5.0)	4 (10.0)
Urinary tract infection	6 (15.0)	2 (9.5)	2 (10.0)	4 (10.0)
Arthralgia	6 (15.0)	3 (14.3)	0	4 (10.0)
Neutropenia	1 (2.5)	1 (4.8)	3 (15.0)	7 (17.5)
Weight increased	2 (5.0)	2 (9.5)	2 (10.0)	5 (12.5)
Arthritis	5 (12.5)	0	1 (5.0)	4 (10.0)
Herpes zoster	3 (7.5)	1 (4.8)	1 (5.0)	5 (12.5)
Rash	2 (5.0)	2 (9.5)	0	6 (15.0)
Edema peripheral	2 (5.0)	3 (14.3)	1 (5.0)	3 (7.5)
Hypokalemia	5 (12.5)	0	1 (5.0)	2 (5.0)
Cushingoid	2 (5.0)	1 (4.8)	3 (15.0)	2 (5.0)
Cough	1 (2.5)	1 (4.8)	1 (5.0)	5 (12.5)
Dizziness	3 (7.5)	1 (4.8)	2 (10.0)	1 (2.5)
Erythema	3 (7.5)	0	0	4 (10.0)
Pyrexia	2 (5.0)	3 (14.3)	0	2 (5.0)
Anemia	1 (2.5)	3 (14.3)	0	3 (7.5)
Insomnia	1 (2.5)	1 (4.8)	2 (10.0)	3 (7.5)
Gastroenteritis	1 (2.5)	0	1 (5.0)	4 (10.0)
Leukopenia	1 (2.5)	1 (4.8)	0	4 (10.0)
Lymphopenia	1 (2.5)	0	0	5 (12.5)
Gastroenteritis viral	1 (2.5)	1 (4.8)	2 (10.0)	0
Hypotension	1 (2.5)	0	2 (10.0)	1 (2.5)
AEs leading to discontinuation of trial drug	3 (7.5)	4 (19.0)	3 (15.0)	5 (12.5)
Serious AEs‡	8 (20.0)	6 (28.6)	6 (30.0)	10 (25.0)
Infections and infestations	3 (7.5)	2 (9.5)	2 (10.0)	8 (20.0)
Other medically important serious event	2 (5.0)	0	0	7 (17.5)
Investigator-assessed opportunistic infections	5 (12.5)	4 (19.0)	2 (10.0)	10 (25.0)
RCTC Grade 3	9 (22.5)	3 (14.3)	2 (10.0)	12 (30.0)
RCTC Grade 4	1 (2.5)	1 (4.8)	2 (10.0)	6 (15.0)
Infections RCTC Grade 3 and 4	2 (5.0)	1 (4.8)	1 (5.0)	4 (10.0)
Death	0	0	0	1 (2.5)

* AE = adverse event; RCTC = Rheumatology Common Toxicity Criteria.
† Ordered according to the total number of AEs.
‡ Serious AEs leading to death were bacterial pneumonia, acute respiratory failure, and ventricular tachycardia.

3 or 4 in the 240 mg group compared with other groups (45.0% of patients vs. 19.0–25.0%).

Investigator-assessed opportunistic infections were most common in the 240 mg group and included serious AEs of RCTC grade 3 pulmonary tuberculosis (n = 1) and cryptococcal meningitis (n = 1), both of which required treatment discontinuation (Supplemental Table S3, http://onlinelibrary.wiley.com/doi/10.1002/art.42557). The only reported death was a 30-year-old woman from Thailand who received 240 mg for 10 months before developing acute pharyngitis and bronchitis, followed by severe pneumonia and pulmonary tuberculosis. Treatment was discontinued, but four weeks later the patient died of bacterial pneumonia, acute respiratory failure, and ventricular tachycardia, all of which were considered by the investigator to be unrelated to the study drug.

Evaluation of laboratory parameters revealed that neutropenia was more common in the 240 mg group (37.5%) than in the placebo group (15.0%) or the 120 mg (14.3%) and 180 mg (10.0%) groups.

DISCUSSION

In this exploratory, dose-ranging, proof-of-concept trial, the null hypothesis of a flat dose-response curve for the primary endpoint could not be rejected. At 52 weeks, the BI 655064 groups

had lower proportions of patients with CRR than the placebo group. A post hoc analysis showed numerically higher proportions of patients achieved cCRR at weeks 46 and 52 in the 180 and 240 mg groups versus placebo. MCPMod analysis using cCRR showed two dose-response curves (sigEmax and exponential models) to be significant at the prespecified alpha level (<0.20). The concept of confirmed demonstration of CRR, in which achievement of CRR is required at two consecutive visits, was successfully used in a phase II study of voclosporin (24) and a phase III study of belimumab (7). Durability of renal remission has also been found to predict renal outcome and survival (25). Numerical benefits of 180 mg BI 655064 versus placebo (n = 20 vs. n = 40) were also demonstrated based on a greater reduction in proteinuria from baseline, shorter time to response, lower average daily glucocorticoid dose, and improvement in SELENA–SLEDAI, LupusPro, and FACIT-F scores.

Although 24-hour urine collection has been considered as the gold-standard method for quantifying proteinuria, over- and undercollections are common in both routine clinical practice and clinical trials. An inadequate urine collection will underestimate the total proteinuria, resulting in higher rates of CRR; this may be a factor that contributed to the high placebo response in this trial. Although spot urine is a snapshot and does not account for variations in protein and creatinine excretion during a 24-hour period, it adjusts for body size by including creatinine excretion as the denominator in the calculation and thus is not affected by inadequate collections. Spot urine from two consecutive visits further support the validity of this endpoint because it provides information on a trend instead of an absolute value. The use of spot urine is therefore gaining advocates in clinical trial settings (26).

The biomarker analysis supported the efficacy results of BI 655064 in patients with LN, with larger decreases observed over 26 weeks in the activated double-negative, double-positive, post-switched, and preswitched B cell subsets in the 180 and 240 mg groups versus placebo. However, the increases in the proportions of select CD40L+ T cell subsets over 26 weeks in the 180 and 240 mg groups versus placebo may be related to a compensatory effect of the decrease in expression of activated pathogenic B cell subsets.

A potential reason for the loss of efficacy during the second half of treatment was the low/undetectable BI 655064 exposure detected in some patients, despite self-reports of continued injections. Also, low urine volumes were collected from several patients despite reported 24-hour collection times, possibly indicating incomplete collection. In addition, the high discontinuation rate among patients in the 120 mg group reduced the proportion of patients achieving CRR in the primary analysis. Notably, the placebo CRR at week 52 in our trial was higher than with previous trials (48.3% vs. 24–35%) (7,24), and there are several reasons why this may have occurred. Almost half of the placebo group were diagnosed as having LN for <6 months (47.5%) and had low UP/UC ratio at baseline (mean ± SD 2.9 ± 2.4). Because patients with induction treatment in the previous 6 months were excluded, all patients with diagnosis <6 months received their first induction treatment in the trial; these patients were more likely to improve with SoC than those with sustained proteinuria and may also have had better renal function, both of which provide a potential advantage in both components of the primary endpoint. Thus, potentially, almost half the patients receiving placebo were likely to respond to treatment, so it appears doubtful that outcomes were affected by allowing an MMF dose of 2–3 g during induction therapy (as per the guidelines when the trial was designed) because 3 g MMF was used in the phase III study of belimumab in which 35% of patients given placebo achieved the primary efficacy renal response at week 52 (7). Ethically, patients with active nephritis receiving placebo should not receive a less than standard dose of a treatment. In addition, pulsing of glucocorticoids may have increased the response to SoC and might mitigate the advantages of the rapid glucocorticoids taper. Usually in LN trials, steroid rescue with large doses of glucocorticoids occurs when there is no improvement with therapy or major extrarenal lupus feature; for minor changes, a glucocorticoids rescue dose of +5–10 mg is frequently used (information on higher glucocorticoid use in this trial is provided in Supplementary Appendix S1, http://onlinelibrary.wiley.com/doi/10.1002/art.42557).

A higher than expected placebo response may also be due to patients receiving placebo having more reversible disease and better control of protein levels compared with those receiving 120 and 180 mg, because more patients receiving placebo had lower CI (1.5 vs. 2.6–3.0) and higher use of ACE-Is/ARBs (82.5% vs. 61.9%–70.0%). A post hoc analysis of cCRR stratified by baseline CI <1 versus ≥1 demonstrated that patients with a CI <1 receiving placebo had the highest proportion of patients achieving cCRR (54%). In contrast, the highest proportions of patients with a CI ≥1 achieving cCRR were seen in the 180 mg (43%) and 240 mg (48%) groups. Therefore, assumptions about expected placebo response rates may need to be reconsidered in the future.

The trial protocol recommended that patients treated with ACE-Is/ARBs before screening continue treatment with the same dose during the trial; however, deviations from this recommendation occurred, which could have reduced proteinuria and thus favorably affected the response rate. In the BLISS-LN trial (7), patients who received ACE-Is/ARBs after week 24 were considered treatment failures. Applying this rule to our trial reduced the CRR of the placebo group by 12.5% but had minimal impact on CRR for the BI 655064 groups (Supplementary Table S4, http://onlinelibrary.wiley.com/doi/10.1002/art.42557).

Previous studies have shown that nephrotic syndrome at baseline could decrease the probability of achieving a renal response at one year (26). The BI 655064 groups had more patients with UP/UC ≥3 at screening compared with those receiving placebo (47.5–52.4% vs. 40.0%, respectively), which may

have caused more rapid urinary clearance of BI 665064. High baseline proteinuria was reported to be an independent predictor of renal nonresponse to add-on belimumab therapy (27).

The incidence of ADAs was relatively low (7.4%) and had no impact on drug exposure because BI 655064 plasma concentrations from ADA-positive patients were similar to those from ADA-negative patients. The safety findings support the tolerability of 180 mg BI 665064. Unlike patients treated with first-generation anti-CD40L antibodies (2,28,29), thromboembolic events were not observed in patients treated with BI 655064. AEs were the main reason for discontinuation, with the incidence highest in the 120 mg group. The 240 mg group had the highest proportion of patients with severe and serious infections, perhaps reflecting higher exposure with 240 mg (approximately twice that seen with 180 mg). The frequency of opportunistic infections needs to be evaluated further in larger trials. Neutropenia was also more frequent in the 240 mg group; however, there was no indication of an increase in serious infections in patients with neutropenia. There was one death in the trial caused by bacterial pneumonia, acute respiratory failure, and ventricular tachycardia, which was considered unrelated to treatment.

This study had several limitations. A high discontinuation rate reduced the proportion of patients achieving CRR in the primary analysis. There were also some imbalances in demographics and baseline characteristics between the groups (e.g., lower mean CI in the placebo vs. 120 and 180 mg groups). The small group size, protocol-allowed treatments overlaying a complicated disease, and higher use of on-treatment ACE-Is/ARBs in the placebo and 240 mg groups may also have increased imbalances between treatment groups. Finally, there was underrepresentation of the 180 mg group, which showed some evidence of efficacy.

In summary, although the trial did not meet its primary objectives, a post hoc analysis suggests that 180 mg BI 655064 may be beneficial in the treatment of patients with active LN. Results from the second year of treatment of responders from this trial are pending. The observed improvement in SELENA–SLEDAI scores and patient-reported outcomes may suggest that BI 655064 could be useful for the treatment of nonrenal SLE. The results of this trial warrant further evaluation.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Jayne had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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