

**ORIGINAL ARTICLE**

# Safety, pharmacokinetics and pharmacodynamics of BI 655064 in phase 1 clinical trials in healthy Chinese and Japanese subjects

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**Aims:** To evaluate the safety, pharmacokinetics and pharmacodynamics of BI 655064 in healthy Chinese and Japanese subjects after administration of single doses of 80-240 mg and multiple dosing of 240 mg once weekly over 4 weeks.

**Methods:** Two phase 1, double-blind, placebo-controlled studies were conducted (single-rising doses of BI 655064 in Chinese/Japanese male subjects [ $n = 12$  per BI 655064 dose group] or repeated 240 mg BI 655064 in Chinese male subjects [ $n = 9$ ]). Plasma samples were collected to investigate BI 655064 pharmacokinetics, pharmacodynamics (CD40 receptor occupancy [RO]) and immunogenicity, along with the safety and tolerability of BI 655064.

**Results:** BI 655064 showed good overall tolerability following single-dose administration of 80-240 mg and repeated administration of 240 mg BI 655064 over 4 weeks. More Chinese subjects reported adverse events compared with Japanese subjects following single-dose administration (59.4% vs 3.1%). BI 655064 exhibited nonlinear, saturable kinetics, with higher doses resulting in slower apparent clearance ( $0.514$ - $0.713$  mL min<sup>-1</sup>), and disproportionately higher total exposure ( $AUC_{0-inf}$ ;  $5610$ - $7780$  µg·h mL<sup>-1</sup>) and maximum plasma concentration ( $15$   $700$ - $21$   $300$  ng mL<sup>-1</sup>) with 240 mg BI 655064. Ninety percent inhibition of CD40 RO was achieved with doses  $\geq 120$  mg, and a direct relationship between BI 655064 plasma concentration and inhibition of CD40 RO was observed. Most subjects had a positive treatment-emergent antidrug antibody response.

**Conclusions:** BI 655064 pharmacokinetic and safety profiles in East Asian male subjects were consistent with those observed in a Western population. No adjustments in the BI 655064 dosing recommendations are warranted for future clinical trials.

**KEYWORDS**

anti-CD40, antibody, East Asian, healthy, lupus, monoclonal, pharmacokinetics

The authors confirm that the Principal Investigator for both studies reported in this paper is Prof. In-Jin Jang and that he had direct clinical responsibility for subjects who participated in these studies.

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## 1 | INTRODUCTION

The interaction of the cell surface receptor **CD40** and its ligand **CD40L** (CD154) plays an important role in the regulation of humoral and cellular immunity, and in the pathology of autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and lupus nephritis (LN).<sup>1-3</sup> SLE is a systemic autoimmune disease characterised by loss of B-cell tolerance to various autoantigens, particularly nucleic acids and their binding proteins. These autoantibodies form immune complexes that deposit in various tissues of the body and drive recruitment of inflammatory cells and mediators to the kidneys, leading to LN.<sup>4</sup> Renal involvement in SLE varies with ethnicity, with East Asian patients with SLE exhibiting high rates of renal involvement (50-60%) compared with Caucasians (30-38%), and the highest rates of LN observed in Thailand and Sri Lanka (70-100%).<sup>5</sup>

BI 655064 is a humanised, nondepleting, antagonistic therapeutic antibody that selectively binds human CD40 and blocks the CD40-CD40L interaction. Anti-CD40L antibodies lacking a functional fragment crystallisable (Fc) region are not associated with thromboembolic events.<sup>6-9</sup> Two mutations (Leu234Ala and Leu235Ala) were introduced into the Fc region of BI 655064 to prevent Fc-mediated complement-mediated cellular cytotoxicity and platelet activation.<sup>10,11</sup> In patients with active RA, BI 655064 has been associated with reductions in inflammatory and bone resorption markers (interleukin-6, matrix metalloproteinase-3 and receptor activator of nuclear factor- $\kappa$ B ligand), concentrations of autoantibodies (immunoglobulin [Ig]G, IgM and IgA rheumatoid factors) and CD95+ activated B-cell subsets.<sup>3</sup> The efficacy and safety of BI 655064 in patients with LN is currently being assessed in ongoing induction and maintenance studies.

BI 655064 has been administered as single-rising doses (SRDs)<sup>12</sup> and multiple-rising doses (MRDs)<sup>11</sup> to healthy Western volunteers. In the SRD study, BI 655064 was administered as intravenous (i.v.) doses between 0.2 and 120 mg and subcutaneous (s.c.) doses between 40 and 120 mg. BI 655064 exposure increased supraproportionally to dose, with a terminal half-life between 4 hours and 4 days i.v. and approximately 5 days s.c. Dose-related increases in the inhibition of CD40 receptor occupancy (RO) and **CD54** upregulation after both i.v. and s.c. BI 655064 dosing were observed, and increasing single i.v. and s.c. doses up to 120 mg BI 655064; doses  $\geq$ 20 mg i.v. and 120 mg s.c. showed >90% CD40 RO and inhibition of CD54 upregulation, which lasted for 7 days in the 120 mg i.v. and s.c. groups. All doses of BI 655064 were well tolerated.<sup>12</sup>

In the MRD study, BI 655064 plasma concentrations increased supraproportionally to dose, most probably due to target-mediated clearance for doses between 80 and 120 mg, but was near proportional for doses >120 mg. The terminal half-life ranged from 6 to 8 days. Following 4 weeks of dosing, >90% CD40 RO and inhibition of CD54 upregulation were observed at all dose levels, lasting for 17 days after the last dose. Ascending multiple s.c. doses of 80-240 mg BI 655064 were generally well tolerated, and no relevant signs of acute immune reaction were observed.<sup>11</sup>

Here, we present the results from two studies conducted to characterise the safety, pharmacokinetics (PK) and pharmacodynamics (PD)

### What is already known about this subject

- BI 655064 is a humanised, nondepleting antagonistic therapeutic antibody directed against human CD40.
- Single- and multiple-rising dose studies have been conducted in healthy Western volunteers.
- Dose-related increases in the inhibition of CD40 receptor occupancy and CD54 upregulation have been observed with BI 655064 administration.

### What this study adds

- BI 655064 pharmacokinetic and safety profiles in East Asian male subjects (Chinese or Japanese ancestry) were consistent with those observed in a Western population.
- No adjustments to BI 655064 dosing would be warranted for future clinical trials.
- A high incidence of antidrug antibodies was observed in this East Asian population.

of BI 655064 in healthy Chinese and Japanese subjects after administration of SRD (80-240 mg) and multiple dosing of 240 mg BI 655064 once weekly (q1w) over 4 weeks.

## 2 | METHODS

### 2.1 | Subjects

Eligible subjects were healthy East Asian male subjects of Chinese ethnicity (ethnic Chinese, born in China or ethnic Chinese born outside of China and a descendent of four ethnic Chinese grandparents who were all born in China) or Japanese ethnicity (born in Japan, lived outside of Japan for <10 years and parents and grandparents who were all born in Japan), aged between 20 and 45 years, with a body mass index (BMI)  $\geq$ 18.5 and  $\leq$ 25 kg m<sup>-2</sup>.

### 2.2 | Study designs

Study 1 was a randomised, double-blind, placebo-controlled within-dose group, SRD study in healthy Chinese and Japanese male subjects (ClinicalTrials.gov identifier: NCT01917916). Subjects were randomised in a 3:1 ratio (BI 655064:placebo) to four sequential dose groups, 16 subjects (8 Chinese, 8 Japanese) per 80, 120, 180 and 240 mg BI 655064 dose group. Within each dose group, 12 subjects (6 Chinese, 6 Japanese) received BI 655064 and 4 subjects (2 Chinese, 2 Japanese) received placebo. Safety data were reviewed after each

dose escalation. The doses of 80-240 mg BI 655064 used in study 1 were selected based on the PK/PD modelling from Caucasian healthy volunteers,<sup>11,12</sup> demonstrating >90% inhibition of CD40 RO with weekly 80 mg BI 655064 dosing.

Study 2 was a randomised, double-blind, placebo-controlled, multiple-dose study in Chinese healthy male subjects (ClinicalTrials.gov identifier: NCT02331277). Subjects were randomised in a 3:1 ratio to receive 240 mg BI 655064 (9 subjects) or placebo (3 subjects) q1w over 4 weeks. The 240 mg dose was selected based on safety, and PK and PD data from previous clinical studies in healthy volunteers.<sup>11,12</sup> BI 655064 was administered as s.c. injections in both studies.

The objectives of these studies were to investigate the safety, tolerability, PK and PD of BI 655064 in healthy Chinese and Japanese male subjects following s.c. injection of SRDs of 80-240 mg and in healthy Chinese male subjects following multiple-doses of BI 655064 (q1w s.c. injections of 240 mg BI 655064 over 4 weeks).

These studies were conducted at the Seoul National University Hospital Clinical Trial Centre, Seoul, Korea, for subjects of Chinese ethnicity and at the Medical Co. LTA Sumida Hospital, Tokyo, Japan, for subjects of Japanese ethnicity. All subjects submitted written informed consent. Studies were conducted in accordance with the Seoul National University Hospital Institutional Review Board (Chinese ethnicity), Kyushu Clinical Pharmacology Research Institutional Review Board (Japanese ethnicity), Good Clinical Practice and the Declaration of Helsinki and its amendments.

### 2.3 | Safety assessments

Safety was assessed by monitoring treatment-emergent adverse events (AEs; using MedDRA terms), physical examinations, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory tests (haematology, coagulation including bleeding time, clinical chemistry and urinalysis).

Tolerability was judged by the investigator according to the presence or absence of "swelling", "induration", "heat", "redness", "pain" or "other findings".

### 2.4 | Pharmacokinetic assessments

Blood samples for PK analysis (2 mL) were collected from a forearm vein using an indwelling catheter into tripotassium ethylenediaminetetraacetic acid (K3 EDTA) anticoagulant tubes. For study 1, blood samples were collected pre dose and at regular intervals up to 1656 hours post dose. For study 2, blood samples were collected prior to the first dose, at regular intervals up to 144 hours post first dose, prior to the second, third and fourth doses (at 168, 336 and 504 hours post the first dose, respectively) and at regular intervals up to 3192 hours post the first dose.

Blood samples were immediately placed on ice after collection and centrifuged (2000-4000 × *g*) at 4-8 °C for 10 minutes within

30 minutes of sample collection. Plasma was transferred into two polypropylene sample vials (approximately 0.4 mL each) and stored at ≤−20 °C until shipment to the analytical laboratory.

Plasma concentrations of BI 655064 were assessed at all visits using a validated sandwich enzyme-linked immunosorbent assay (ELISA; Covance Laboratories Inc., Chantilly, VA, USA) with a lower limit of quantification of 30 ng mL<sup>−1</sup>. The ELISA was developed and validated for the quantification of BI 655064 in human plasma. The method met all prospective criteria for system suitability, accuracy, precision, limits of quantitation, selectivity, dilutional linearity and analyte stability. Accuracy and precision were tested in six analytical runs, and all levels had a total error (absolute % relative error plus % coefficient of variation [CV] of less than 30%). The intra- and interassay accuracy and precision acceptance criteria of ±20% and ±25% at lower limit of quantitation and upper limit of quantitation were met for this method. The quantitative range was from 30 to 800 ng mL<sup>−1</sup>. Dilution linearity was established to 1/50 000. Selectivity, based on recovery of BI 655064 in human plasma, was acceptable in normal, haemolysed and lipaemic samples. Stability evaluations indicated that BI 655064-spiked in human plasma was stable after six freeze-thaw cycles for approximately 24 hours at ambient room temperature, 72 hours at 2-8 °C, up to 12 months at −15 to −30 °C and 20 months at −60 to −80 °C, and BI 655064 was stable in whole blood for up to 4 hours. Complete assay details are provided by Schwabe et al.<sup>11</sup>

Plasma BI 655064 concentration-time data were analysed by a noncompartmental approach using Phoenix® WinNonlin® software (version 6.3, Certara L.P., Princeton, NJ 08540, USA). Parameters included maximum plasma concentration ( $C_{max}$ ), minimum plasma concentration ( $C_{min}$ ), time to achieve  $C_{max}$  ( $t_{max}$ ) and terminal half-life ( $t_{1/2}$ ) using the standard WinNonlin procedure. Area under the concentration-time curve over time zero to the last quantifiable plasma concentration ( $AUC_{0-t_z}$ ) and AUC over the uniform dosing interval  $\tau$  ( $AUC_{\tau}$ ) were calculated using the WinNonlin linear up/log down algorithm. In study 1, the apparent clearance ( $CL/F$ ) was calculated as dose/ $AUC_{0-inf}$ , where  $F$  is the systemic availability and  $AUC_{0-inf}$  is the AUC over the dose interval from time 0 extrapolated to infinity. In study 1, the apparent volume of distribution ( $V_z/F$ ) was determined as  $(CL/F)/$ terminal elimination constant ( $\lambda_z$ ). In study 2, the accumulation ratios ( $R_{A,Cmax}$  based on  $C_{max}$ ,  $R_{A,AUC}$  based on  $AUC_{\tau}$ ) were calculated as the ratio of the value after the fourth dose to the value after the first dose.

### 2.5 | Pharmacodynamic assessments

Blood samples for the determination of CD40 RO (2.7 mL) were collected from a forearm vein in a heparin anticoagulant tube. Afterwards, 1 mL of whole blood was transferred into a TransFix stabilisation tube and sent on ice to Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany for further analysis. Blood samples were collected pre dose and at regular intervals up to 1320 hours post dose for study 1 and prior to the first dose, at 72 hours post the

first dose, prior to the second and fourth doses, and at regular intervals up to 3192 hours post the first dose for study 2.

CD40 RO was analysed using a validated fluorescence activated cell sorting assay, as described by Albach et al.<sup>12</sup> CD40 RO was calculated using the ratio of observed fluorescence values from samples incubated with and without fluorescein isothiocyanate-labelled BI 655064. Inhibition of CD40 RO was expressed as a percentage and was calculated by putting the CD40 RO values from post-dose measurements in relation to the respective predose baseline value for each individual subject.

## 2.6 | Immunogenicity assessments

Blood samples for measurement of antibodies against BI 655064 (antidrug antibodies [ADAs], 2 mL) were collected from a forearm vein in a K3-EDTA anticoagulant tube. Blood samples were collected pre dose and at 264, 984 and 1656 hours post dose for study 1, and prior to the first and fourth doses, and at 912, 1848, 2520, 3192 and 5880 hours post the first dose (follow-up visit) for study 2.

Blood samples were immediately placed on ice after collection and centrifuged (2000–4000 × *g*) at 4–8 °C for 10 minutes within 30 minutes of sample collection. Plasma was transferred into two cryotubes (approximately 0.4 mL each) and stored at ≤−20 °C until shipment to the analytical laboratory.

Antidrug antibodies (ADAs) to BI 655064 were analysed in plasma samples using a validated bridging assay (Covance Laboratories Inc., Chantilly, VA, USA). An electrochemiluminescence (ECL) assay using biotin- and ruthenium-labelled BI 655064 was validated with normal human plasma for the detection of anti-BI 655064 antibodies. For the confirmatory tier, the confirmatory cut point in healthy plasma was determined to be 35.7% inhibition in the presence of exogenously added BI 655064. The precision of the method was determined by the positive control to have CV <10%. BI 655064 drug

tolerance for the anti-BI 655064 at a positive control antibody level of 250 ng mL<sup>−1</sup> was 50 µg mL<sup>−1</sup>.

A sample was considered ADA positive if its response in the screening assay was greater than or equal to a plate-specific cut point and if it was confirmed positive in a specificity test (response blocked by the addition of BI 655064); confirmed ADA-positive samples were further characterised in a titre assay. Titres were determined by analysing serial two-fold sample dilutions. The reported titre was the highest-fold dilution that produced a mean electrochemiluminescent value greater than or equal to the confirmatory cut point. Complete assay details are provided by Schwabe et al.<sup>11</sup>

## 2.7 | Statistical analysis

Study results were analysed using descriptive statistics for safety, PK and PD. No formal calculation of sample size was performed. The safety population included all subjects who had received BI 655064. The PK and PD populations included all subjects who had received BI 655064 and provided valuable data for PK and PD analysis without relevant important protocol violations. A power model was used to explore the dose proportionality of  $C_{max}$ ,  $AUC_{0-tz}$  and  $AUC_{0-inf}$  in study 1. The model was defined as  $\exp(Y_{ij}) = \alpha * \exp(X_i) \beta + \epsilon'_{ij}$ . After logarithmic transformations, the model was converted to the linear form  $Y_{ij} = \alpha + \beta * X_i + \epsilon_{ij}$ . Dose proportionality was assumed if the slope of the regression line ( $\beta$ ) was equal to 1.

## 2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

**TABLE 1** Demographics and baseline characteristics

	Study 1							
	BI 655064							
	80 mg		120 mg		180 mg		240 mg	
	CHI (n = 6)	JPN (n = 6)	CHI (n = 6)	JPN (n = 6)	CHI (n = 6)	JPN (n = 6)	CHI (n = 6)	JPN (n = 6)
Mean age, years (SD)	26.0 (3.0)	29.0 (9.3)	25.5 (2.7)	23.7 (2.3)	25.2 (5.8)	28.2 (6.4)	23.2 (0.8)	36.2 (10.3)
Mean weight, kg (SD)	71.2 (3.9)	65.7 (6.0)	74.3 (7.3)	67.2 (9.4)	66.3 (4.6)	59.8 (7.5)	67.0 (6.9)	67.5 (5.2)
Mean BMI, kg m <sup>−2</sup> (SD)	23.6 (0.9)	21.4 (1.8)	23.5 (1.4)	22.3 (1.7)	22.7 (0.7)	20.9 (2.7)	22.5 (2.1)	22.0 (1.6)
Smoking history, n (%)								
Never smoked	3.0 (50.0)	4.0 (66.7)	2.0 (33.3)	6.0 (100.0)	1.0 (16.7)	5.0 (83.3)	3.0 (50.0)	4.0 (66.7)
Ex-smoker	0	2.0 (33.3)	0	0	2.0 (33.3)	1.0 (16.7)	1.0 (16.7)	2.0 (33.3)
Current smoker <sup>a</sup>	3.0 (50.0)	0	4.0 (66.7)	0	3.0 (50.0)	0	2.0 (33.3)	0
Alcohol history, n (%)								
Non-drinker	2.0 (33.3)	2.0 (33.3)	3.0 (50.0)	3.0 (50.0)	2.0 (33.3)	3.0 (50.0)	5.0 (83.3)	3.0 (50.0)
Drinker <sup>b</sup>	4.0 (66.7)	4.0 (66.7)	3.0 (50.0)	3.0 (50.0)	4.0 (66.7)	3.0 (50.0)	1.0 (16.7)	3.0 (50.0)

Abbreviations: BMI, body mass index; CHI, Chinese subject; JPN, Japanese subject; SD, standard deviation.

<sup>a</sup>Did not smoke more than 10 cigarettes, 3 cigars or 3 pipes per day.

<sup>b</sup>At a level that did not interfere with study participation.

**TABLE 1** Continued

	Study 1				Study 2		
	Placebo		Total		BI 655064 240 mg (n = 9)	Placebo (n = 3)	Total (N = 12)
	CHI (n = 8)	JPN (n = 8)	CHI (N = 32)	JPN (N = 32)			
Mean age, years (SD)	25.9 (4.1)	26.3 (7.1)	25.2 (3.6)	28.5 (8.2)	25.1 (3.4)	29.0 (4.4)	26.1 (3.9)
Mean weight, kg (SD)	68.5 (9.5)	60.6 (5.9)	69.4 (7.1)	63.9 (7.2)	63.7 (10.1)	68 (4.6)	64.8 (9.0)
Mean BMI, kg m <sup>-2</sup> (SD)	22.8 (2.2)	20.3 (1.0)	23.0 (1.6)	21.3 (1.8)	22.1 (2.5)	21.8 (1.3)	22.0 (2.2)
Smoking history, n (%)							
Never smoked	2.0 (25.0)	7.0 (87.5)	11.0 (34.4)	26.0 (81.3)	5.0 (55.6)	0	5.0 (41.7)
Ex-smoker	1.0 (12.5)	1.0 (12.5)	4.0 (12.5)	6.0 (18.8)	2.0 (22.2)	1.0 (33.3)	3.0 (25.0)
Current smoker <sup>a</sup>	5.0 (62.5)	0	17.0 (53.1)	0	2.0 (22.2)	2.0 (66.7)	4.0 (33.3)
Alcohol history, n (%)							
Non-drinker	1.0 (12.5)	5.0 (62.5)	13.0 (40.6)	16.0 (50.0)	4.0 (44.4)	3.0 (100.0)	7.0 (58.3)
Drinker <sup>b</sup>	7.0 (87.5)	3.0 (37.5)	19.0 (59.4)	16.0 (50.0)	5.0 (55.6)	0	5.0 (41.7)

Abbreviations: BMI, body mass index; CHI, Chinese subject; JPN, Japanese subject; SD, standard deviation.

<sup>a</sup>Did not smoke more than 10 cigarettes, 3 cigars or 3 pipes per day.

<sup>b</sup>At a level that did not interfere with study participation.

### 3 | RESULTS

#### 3.1 | Subjects

The demographic and baseline characteristics for studies 1 and 2 are summarised in Table 1. Study 1 enrolled 64 healthy male subjects (32 Chinese and 32 Japanese) and all subjects completed the study. Japanese subjects were slightly older than the Chinese subjects (mean age 28.5 years vs 25.2 years). Furthermore, Japanese subjects had a lower body weight and BMI compared with the Chinese subjects (overall mean body weight 63.9 kg vs 69.4 kg and overall mean BMI 21.3 kg m<sup>-2</sup> vs 23.0 kg m<sup>-2</sup>, respectively). None of the Japanese subjects were smokers, whereas 17 of the 32 Chinese subjects were smokers.

There were no relevant differences in demographic characteristics between the different dose groups for Chinese and Japanese subjects, except that the Japanese subjects in the 240 mg dose group in study 1 were slightly older than the Chinese subjects (mean age 36.2 vs 23.2 years; Table 1).

Study 2 enrolled 12 healthy Chinese subjects: 1 subject withdrew consent after receiving all four doses of placebo and 11 subjects completed the study.

There were no relevant differences in demographic characteristics between the treatment groups in study 2, except that the placebo group only contained subjects who were current or ex-smokers and none of the subjects in the placebo group drank alcohol (Table 1).

#### 3.2 | Safety

SRD of BI 655064 up to 240 mg were well tolerated by Chinese and Japanese subjects, and multiple dosing of 240 mg BI 655064 q1w over 4 weeks was well tolerated by Chinese subjects. There were no

serious AEs or AEs leading to discontinuation reported in either of these two studies, and all AEs were mild or moderate in severity and resolved by the end of study (Table 2). In study 1, only subjects of Chinese ethnicity experienced treatment-related AEs, and more treatment-related AEs were observed following single-dose administration of BI 655064 than placebo. The most frequently reported AE considered to be drug-related was diarrhoea, which was reported by 2 of the 24 Chinese subjects (8.3%) in the pooled BI 655064 dose group compared with none of the 8 Chinese subjects (0%) who received placebo in study 1. In study 2, the only AEs that were considered to be drug-related and reported for more than one subject were chest pain, headache, arthralgia, pain in extremity and acne; of these, headache was the only event that was reported for a higher incidence rate in the BI 655064 group than in the placebo group (2 subjects [22.2%] on BI 655064 vs 0 subjects on placebo).

No clinically relevant findings with respect to clinical laboratory tests (including bleeding times), vital signs, ECG, physical examinations or local tolerability were observed, except for one subject enrolled in the BI 655064 240 mg treatment group of study 2 who experienced pain after the third injection and "other findings" (not specified further) after the fourth injection.

#### 3.3 | Pharmacokinetics

Following SRD administration in study 1, BI 655064 plasma concentrations increased with rising doses. The BI 655064 plasma concentration-time curves reached a peak at 96-144 hours post dose, followed by at least a biphasic decline (Figure 1). The terminal elimination half-life ( $t_{1/2}$ ) was generally long ranging, from 97.4 to 225 hours. Mean  $CL/F$  values were small (range 0.467-4.04 mL min<sup>-1</sup>) and tended to decrease with increasing dose. Mean  $V_z/F$  values also decreased with increasing dose (range 8.28-40.3 L). Coefficients of

**TABLE 2** Summary of AEs and frequency of treatment-related AEs

n (%)	Study 1					Study 2		
	BI 655064					BI 655064		
	80 mg (n = 12)	120 mg (n = 12)	180 mg (n = 12)	240 mg (n = 12)	Placebo (n = 16)	Total BI 655064 (N = 48)	240 mg (n = 9)	Placebo (n = 3)
Any AEs	3 (25.0)	3 (25.0)	5 (41.7)	4 (33.3)	5 (31.3) <sup>a</sup>	15 (31.3)	6 (66.7)	3 (100.0)
Any serious AEs <sup>b</sup>	0	0	0	0	0	0	0	0
Any severe AEs <sup>c</sup>	0	0	0	0	0	0	0	0
Infections	2 (16.7)	0	1 (8.3)	1 (8.3)	2 (12.5)	4 (8.3)	2 (22.2)	1 (33.3)
Upper respiratory tract	2 (16.7)	0	1 (8.3)	1 (8.3)	2 (12.4)	4 (8.3)	2 (22.2)	1 (33.3)
AEs leading to discontinuation	0	0	0	0	0	0	0	0
Any treatment-related AE <sup>d</sup>	2 (16.7)	1 (8.3)	4 (33.3)	2 (16.7)	1 (6.3)	9 (18.8)	5 (55.6)	2 (66.7)
Most common treatment-related AEs <sup>e</sup>								
Diarrhoea	1 (8.3)	0	0	1 (8.3)	0	2 (4.2)	0	0
Chest pain	0	0	0	0	0	0	2 (22.2)	1 (33.3)
Headache	0	0	0	0	0	0	2 (22.2)	0

Abbreviation: AE, adverse event.

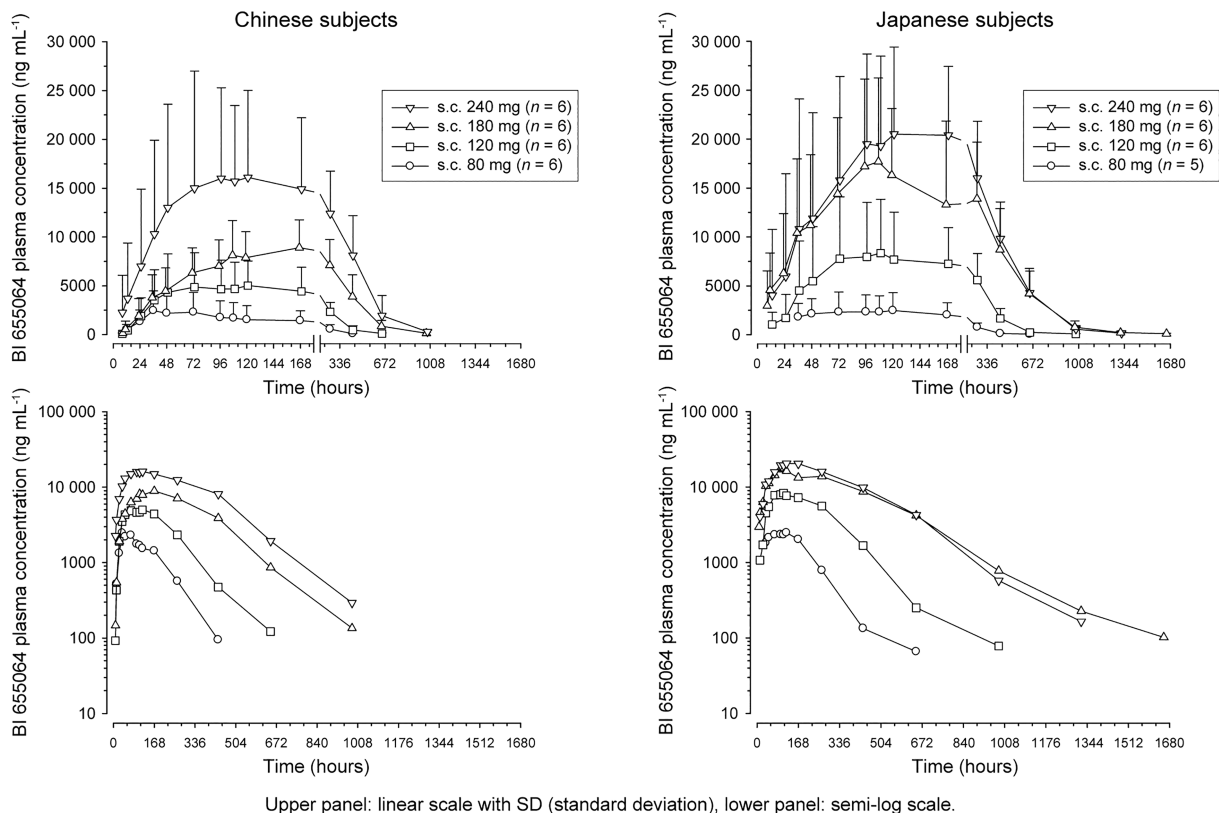
<sup>a</sup>Included one subject of Japanese ethnicity (all other subjects with AEs were of Chinese ethnicity).

<sup>b</sup>Defined as an AE that resulted in death, was immediately life-threatening, resulted in persistent or significant disability or incapacity, required or prolonged subject hospitalisation, was a congenital anomaly or birth defect, cancer or deemed serious for any other reason.

<sup>c</sup>Defined as an AE that was incapacitating or caused an inability to work or perform usual activities.

<sup>d</sup>Defined by the investigator.

<sup>e</sup>AEs occurring in two or more subjects receiving BI 655064 are reported.



Upper panel: linear scale with SD (standard deviation), lower panel: semi-log scale.

**FIGURE 1** Mean (±SD) BI 655064 plasma concentration-time profile following single-dose administration to Chinese and Japanese subjects in study 1. s.c., subcutaneous; SD, standard deviation

**TABLE 3** Summary of selected BI 655064 pharmacokinetic parameters following single-dose administration to Chinese and Japanese subjects in study 1

Parameter (unit)	BI 655064											
	80 mg			120 mg			180 mg			240 mg		
	CHI (n = 6)	JPN (n = 5)	CHI (n = 6)	JPN (n = 6)	CHI (n = 6)	JPN (n = 6)	CHI (n = 6)	JPN (n = 6)	CHI (n = 6)	JPN (n = 6)	CHI (n = 6)	JPN (n = 6)
$C_{max}$ (ng mL <sup>-1</sup> )	888 (501)	1,550 (315)	5,160 (51.6)	7,210 (92.8)	8,650 (41.1)	16,300 (73.6)	15,700 (54.2)	21,300 (53.4)				
$C_{max,norm}$ (ng mL <sup>-1</sup> mg <sup>-1</sup> )	11.1 (501)	19.4 (315)	43.0 (51.6)	60.0 (92.8)	48.1 (41.1)	90.8 (73.6)	65.4 (54.2)	88.8 (53.4)				
AUC <sub>0-tz</sub> (µg·h mL <sup>-1</sup> )	126 (1740)	365 (165)	1,110 (47.2)	2010 (79.8)	2,900 (60.4)	6,380 (84.6)	5,680 (52.4)	7,750 (57.2)				
AUC <sub>0-tz,norm</sub> (µg·h mL <sup>-1</sup> mg <sup>-1</sup> )	1.58 (1740)	4.56 (165)	9.23 (47.2)	16.7 (79.8)	16.1 (60.4)	35.4 (84.6)	23.7 (52.4)	32.3 (57.2)				
AUC <sub>0-inf</sub> (µg·h mL <sup>-1</sup> )	330 (111) <sup>a</sup>	464 (74.1)	1,120 (46.6)	2020 (78.8)	2,910 (60.1)	6,430 (83.3)	5,610 (59.0) <sup>a</sup>	7,780 (57.1)				
AUC <sub>0-inf,norm</sub> (µg·h mL <sup>-1</sup> mg <sup>-1</sup> )	4.12 (111) <sup>a</sup>	5.80 (74.1)	9.34 (46.6)	16.9 (78.8)	16.2 (60.1)	35.7 (83.3)	23.4 (59.0) <sup>a</sup>	32.4 (57.1)				
$t_{1/2}$ (h)	102 (54.2) <sup>a</sup>	162 (157)	97.4 (42.2)	178 (45.0)	168 (55.4)	225 (62.8)	140 (54.6) <sup>a</sup>	186 (42.1)				
CL/F (mL min <sup>-1</sup> )	4.04 (111) <sup>a</sup>	2.87 (74.1)	1.78 (46.6)	0.989 (78.8)	1.03 (60.1)	0.467 (83.3)	0.713 (59.0) <sup>a</sup>	0.514 (57.1)				
V <sub>z</sub> /F (L)	35.9 (233) <sup>a</sup>	40.3 (433)	15.0 (59.2)	15.2 (104)	15.0 (73.5)	9.11 (187)	8.66 (112) <sup>a</sup>	8.28 (76.9)				
$t_{max}$ (h)	96.0 (48.0-168)	120 (72.0-168)	102 (48.0-120)	138 (72.0-264)	144 (108-172)	102 (72.0-120)	108 (72.0-168)	144 (36.0-168)				

Note. Data shown as geometric means (geometric coefficient of variation %), except for  $t_{max}$ , which is presented as median (range).

Abbreviations: AUC<sub>0-inf</sub>, area under the concentration-time curve from time zero extrapolated to infinity; AUC<sub>0-inf,norm</sub>, dose normalised AUC<sub>0-inf</sub>; AUC<sub>0-tz</sub>, area under the concentration-time curve over time zero to the last quantifiable plasma concentration; AUC<sub>0-tz,norm</sub>, dose normalised AUC<sub>0-tz</sub>; CL/F, apparent clearance; CHI, Chinese subjects; C<sub>max</sub>, maximum plasma concentration; C<sub>max,norm</sub>, dose normalised C<sub>max</sub>;  $t_{1/2}$ ; terminal half-life; JPN, Japanese subjects;  $t_{max}$ , time to achieve C<sub>max</sub>; V<sub>z</sub>/F, apparent volume of distribution.

<sup>a</sup>n = 5.

variation for  $C_{max}$  and AUC parameters for the 120-240 mg dose groups were typically within the range of 40-90%, suggesting moderate to high variability, and up to 1740% for the 80 mg dose group, suggesting very high variability (driven by one subject with very low AUC). Exposures ( $C_{max}$  and AUCs) in Japanese subjects were generally higher than exposures in Chinese subjects in all dose groups; however, the exposure ratios (Japanese/Chinese) were smaller in the highest (240 mg) dose group ( $C_{max}$  1.36,  $AUC_{0-inf}$  1.39). The  $t_{1/2}$  values in Japanese subjects were slightly longer than that in the Chinese subjects, while the  $t_{max}$  values showed no apparent difference (Table 3).

Dose proportionality in Chinese and Japanese subjects was analysed over the entire dose range (80-240 mg). BI 655064 showed a more than dose proportional increase in AUCs (slope  $\beta = 2.6-3.4$ ) and  $C_{max}$  (slope  $\beta = 2.3-2.5$ ) over the entire dose range (80-240 mg). Visual inspection using dose-normalised exposure also supported the supraproportional increase in BI 655064 exposure (data not shown).

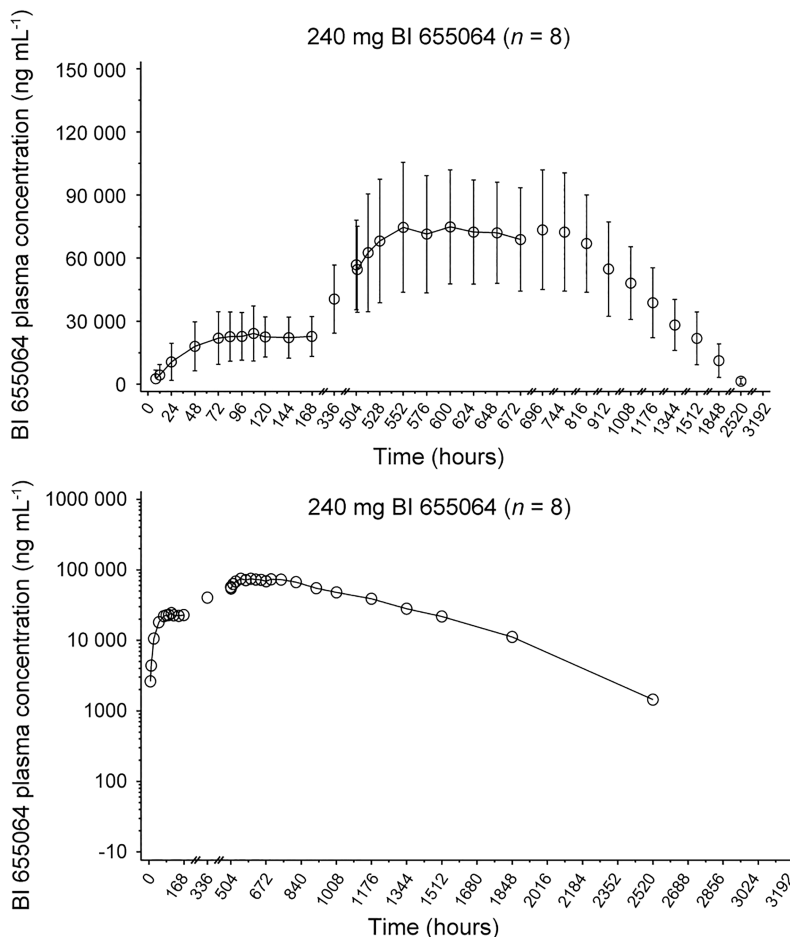
When dose proportionality was evaluated over the dose range of 120-240 mg, slope  $\beta$  estimates remained  $>1.5$ , but the 95% confidence intervals included unity for  $C_{max}$  (Chinese and Japanese subjects) and AUCs (Japanese subjects).

In study 2, one subject who received a single dose of 240 mg BI 655064 in study 1 (approximately 1.5 years prior to enrolling into study 2) developed ADAs. The titre value was significantly boosted from 16 (baseline) up to 65 536 (just before the fourth dose of 240 mg BI 655064 q1w). Preliminary investigations suggest that this subject's ADAs interfered with the bioanalytical measurement of BI 655064 in the plasma, therefore data from this subject were excluded from the PK analyses presented here.

After doses of 240 mg BI 655064 q1w over 4 weeks in study 2, the plasma concentration-time curve reached a peak by 84.2 hours after the last dose followed by at least a biphasic decline with a  $t_{1/2}$  of 247 hours. Plasma concentrations did not reach steady state after the fourth dose (Figure 2). The accumulation ratios based on  $C_{max}$  and  $AUC_{\tau}$  after the fourth dose were 3.24 and 4.19, respectively (Table 4).

### 3.4 | Immunogenicity

In study 1, positive ADA responses were detected in most subjects (45/48 subjects) after a single dose of BI 655064, with response onset times in the terminal elimination phase of BI 655064 (day 42 or day 70 post dose) in most cases (Table 5).



**FIGURE 2** Mean ( $\pm$ SD) BI 655064 plasma concentration-time profile following multiple-dose administration to Chinese subjects in study 2. SD, standard deviation

Upper panel: linear scale with SD (standard deviation), lower panel: semi-log scale.



**TABLE 4** Summary of selected BI 655064 pharmacokinetic parameters following multiple-dose administration to Chinese subjects in study 2

Dose	Parameter (unit)	BI 655064 240 mg q1w (n = 8)
First dose	$C_{max,1}$ ( $\mu\text{g mL}^{-1}$ )	22.9 (72.3)
	$AUC_{r,1}$ ( $\mu\text{g}\cdot\text{h mL}^{-1}$ ) <sup>a</sup>	2,610 (79.0)
	$t_{max,1}$ (h)	132 (72.0-168)
Fourth dose	$C_{max,4}$ ( $\mu\text{g mL}^{-1}$ )	74.1 (50.4)
	$C_{min,4}$ ( $\mu\text{g mL}^{-1}$ )	49.0 (53.7)
	$AUC_{r,4}$ ( $\mu\text{g}\cdot\text{h mL}^{-1}$ ) <sup>a</sup>	10,900 (49.9)
	$t_{1/2,4}$ (h)	247 (39.8)
	$t_{max,4}$ (h)	84.2 (12.0-144)
	$R_{A,AUC,4}$	4.19 (32.9)
	$R_{A,Cmax,4}$	3.24 (24.8)

Note. Data shown as geometric means (geometric coefficient of variation %), except for  $t_{max}$ , which is presented as median (range). Abbreviations:  $AUC_{r,1}$ , area under the plasma concentration-time curve over a uniform dosing interval after the first dose;  $AUC_{r,4}$ , area under the plasma concentration-time curve over a uniform dosing interval after the fourth dose;  $C_{max,1}$ , maximum observed concentration after the first dose;  $C_{max,4}$ , maximum observed concentration after the fourth dose;  $C_{min,4}$ , minimum measured concentration of the analyte in plasma after the fourth dose; q1w, once weekly;  $R_{A,AUC,4}$ , is equal to  $AUC_r$  after the fourth dose divided by  $AUC_r$  after the first dose;  $R_{A,Cmax,4}$ , is equal to  $C_{max}$  after the fourth dose divided by  $C_{max}$  after the first dose;  $t_{1/2,4}$ , terminal elimination half-life after the fourth dose;  $t_{max}$ , time to maximum observed concentration;  $t_{max,4}$ , time to maximum observed concentration after the fourth dose.

<sup>a</sup> $AUC_r$  is synonymous with  $AUC_{0-168h}$ .

Positive ADA responses were also detected after repeat dosing with 240 mg BI 655064 in study 2 (Table 6). By day 245, all nine subjects enrolled into the BI 655064 treatment group had a positive ADA response (median onset time 105 days post first dose). ADA responses were designated as treatment-induced or treatment-boosted based on recommendations from the 2014 White Paper on immunogenicity reporting by Shankar et al.<sup>13</sup> Seven of nine subjects (77.8%) exhibited a treatment-induced ADA-positive response and 2/9 subjects (22.2%) with preexisting ADAs exhibited a treatment-boosted ADA-positive response. One subject with a baseline titre of 1 was classified as boosted based on an increased titre later in the study. The ADA response from the subject who also participated in study 1 was significantly boosted from 16 to 65 536.

### 3.5 | Pharmacodynamics

In the placebo dose group in study 1, no inhibition of CD40 RO was observed, while RO was inhibited in all active dose groups. Single s.c. administration of BI 655064 at doses  $\geq 120$  mg resulted in 90% inhibition of CD40 RO in Chinese subjects, and 90% inhibition of CD40 RO was achieved with all BI 655064 doses in Japanese

**TABLE 5** Summary of positive ADA response following single-dose administration to Chinese and Japanese subjects in study 1

Timepoint	BI 655064		Placebo (n = 16)		240 mg (n = 12)		180 mg (n = 12)		120 mg (n = 12)	
	Number of subjects with positive ADA response	Titre, median (range)	Number of subjects with positive ADA response	Titre, median (range)	Number of subjects with positive ADA response	Titre, median (range)	Number of subjects with positive ADA response	Titre, median (range)	Number of subjects with positive ADA response	Titre, median (range)
Pre dose	0	NC	0	NC	0	NC	0	NC	0	NC
Day 12 (264 h post dose)	4	3 (2-40)	1	4 (NC)	1	1 (NC)	0	1 (NC)	1	4 (NC)
Day 42 (984 h post dose)	10	18 (4-800)	12	6 (1-400)	7	20 (4-160)	8	20 (4-160)	12	18 (4-400)
Day 70 (1656 h post dose)	11	40 (8-400)	12	28 (2-400)	11	20 (2-400)	11	20 (2-400)	11	80 (2-160)

Abbreviations: ADA, antidrug antibody; NC, not calculated.

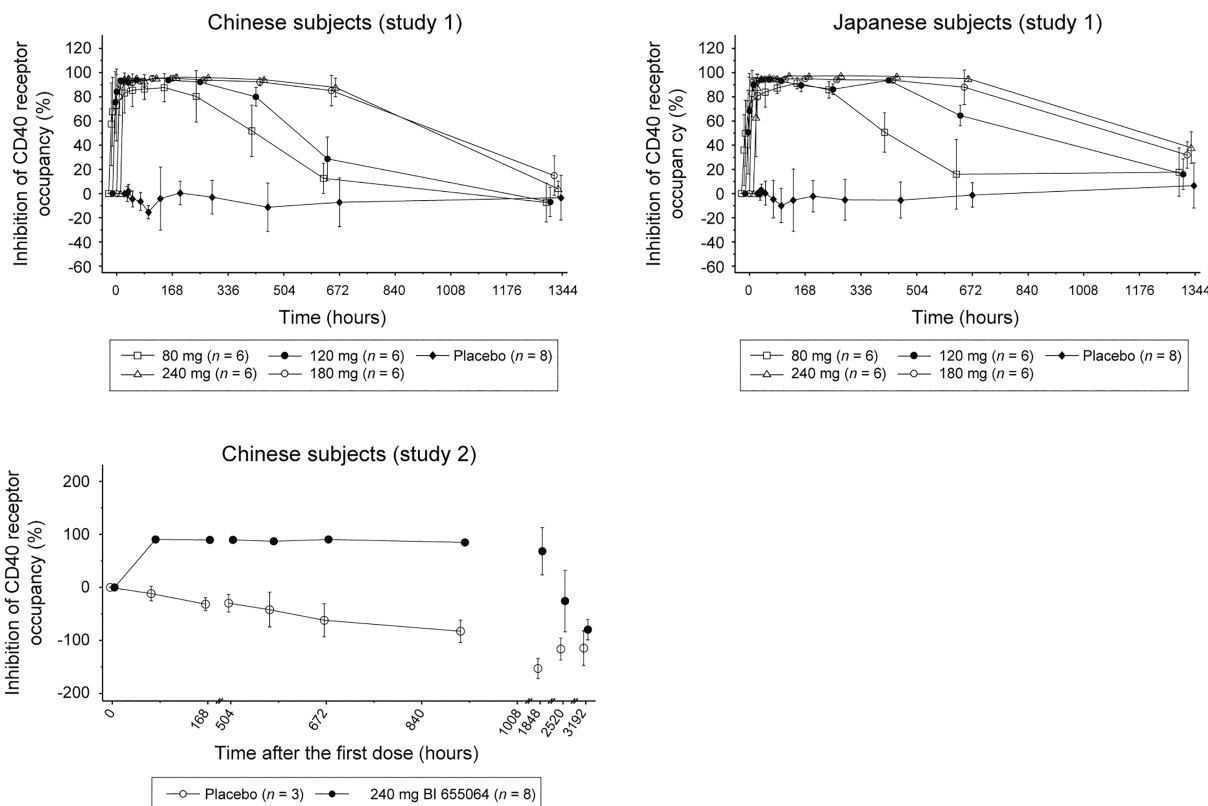
**TABLE 6** Summary of positive ADA response following multiple-dose administration to Chinese subjects in study 2

Timepoint	BI 655064 240 mg, q1w (n = 9)		Placebo (n = 3)	
	Number of subjects with positive ADA response	Titre, median (range)	Number of subjects with positive ADA response	Titre, median (range)
Pre dose	2	9 (1-16)	0	NC
Day 21 (503.5 h after first dose)	1	65,536 (NC)	0	NC
Day 38 (912 h after first dose)	1	32,768 (NC)	0	NC
Day 77 (1848 h after first dose)	2 <sup>a</sup>	8,193 (1-16,384)	0	NC
Day 105 (2520 h after first dose)	7	16 (1-16,384)	1	1 (NC)
Day 133 (3192 h after first dose)	8	24 (4-8,192)	1	1 (NC)
Day 245 (5880 h after first dose)	9	16 (16-4,096)	0 <sup>b</sup>	NC

Abbreviations: ADA, anti-drug antibody; NC, not calculated; q1w, once weekly.

<sup>a</sup>Only eight subjects were tested at this time point.

<sup>b</sup>Only two subjects were tested at this time point.

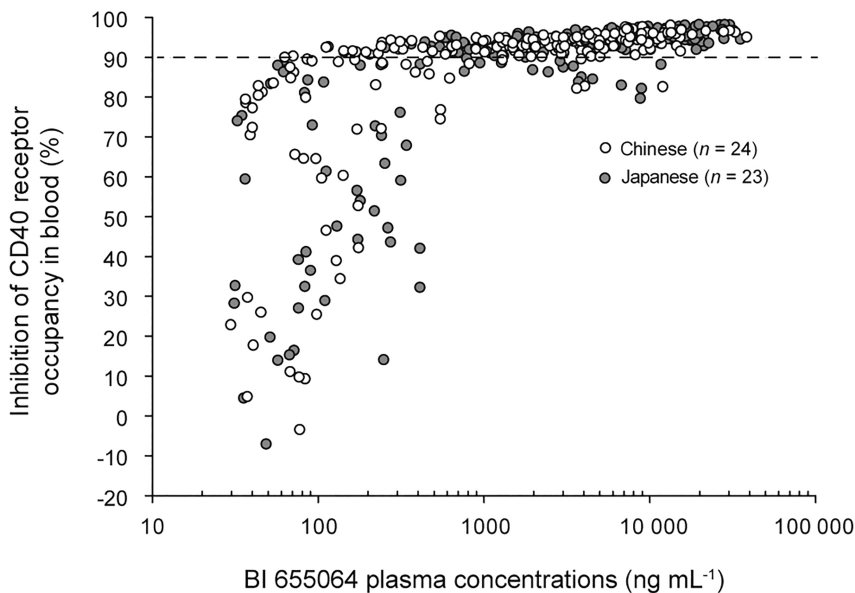


**FIGURE 3** Mean (±SD) inhibition of CD40 receptor occupancy over time following single-dose administration to Chinese and Japanese subjects in study 1 and following multiple-dose administration to Chinese subjects in study 2. SD, standard deviation. Note: For study 2, a drop in the unstained raw data values was observed. The calculation of the inhibition of CD40 receptor occupancy is based on ratios of fluorescence values from stained vs unstained samples. Therefore, small deviations in staining intensity of the unstained samples can result in large effects on the calculated percent inhibition results in certain instances

subjects (Figure 3). The duration of 90% inhibition increased with increasing BI 655064 dose (120 mg 24-168 hours, 180 mg 12-432 hours, 240 mg 12-648 hours).

A direct relationship was observed between BI 655064 plasma concentrations and inhibition of CD40 RO in study 1. Ninety percent

inhibition of CD40 RO was achieved with BI 655064 plasma concentrations  $\geq 400$  ng mL<sup>-1</sup>. Furthermore, there was no apparent difference in the relationship between BI 655064 plasma concentrations and inhibition of CD40 RO between Chinese and Japanese subjects (Figure 4).



**FIGURE 4** Relationship between BI 655064 plasma concentrations and inhibition of CD40 receptor occupancy following single-dose administration to Chinese and Japanese subjects in study 1. Dotted line indicates 90% inhibition

In study 2, the subject with a preexisting ADA and boosted response, most probably due to participation in study 1, was excluded from the PD evaluation. Preliminary investigations suggest that ADAs may interfere with the results of the PD assay format, most probably due to the use of the FITC-labelled BI 655064 assay reagent. Following q1w s.c. administration of 240 mg BI 655064 over 4 weeks, 90% inhibition of CD40 RO was observed in the BI 655064 treatment group, with inhibition decreasing substantially between 1848 and 3192 hours after the first dose. In the placebo treatment group, inhibition of CD40 RO declined from baseline over time (Figure 3).

## 4 | DISCUSSION

The two phase 1 studies described here evaluated the safety, PK and PD of BI 655064 after administration of SRDs of 80-240 mg BI 655064 and multiple dosing with 240 mg BI 655064 q1w over 4 weeks in healthy East Asian subjects, and were conducted to support integration of East Asian subjects into a phase 2 clinical trial.

BI 655064 showed good overall tolerability following administration of single s.c. doses of 80-240 mg and multiple dosing of 240 mg q1w over 4 weeks in healthy East Asian subjects. The observed AE profiles were consistent with results from similar studies conducted in a Western population.<sup>11,12</sup> In general, the proportion of subjects with AEs was similar or lower than that observed in subjects who received placebo. Overall, a higher proportion of Chinese subjects reported any AE compared with Japanese subjects (59.4 vs 3.1%). The difference was observed for subjects receiving BI 655064 as well as those receiving placebo. The lower frequency of AEs reported in Japanese subjects has also been observed in other single- and multiple-dose studies reported in the literature comparing Japanese healthy volunteers with other ethnicities.<sup>14-17</sup> However, the proportion of Chinese subjects reporting AEs was comparable to that

observed in a similar SRD study performed in a Western population, where 41% of subjects reported AEs following BI 655064 s.c. or i.v. administration.<sup>12</sup>

BI 655064 exhibited nonlinear, saturable kinetics with higher doses of BI 655064, resulting in slower clearance and disproportionately higher plasma exposure (AUC and  $C_{max}$ ). Clearance reached a minimum of 0.514-0.713 mL min<sup>-1</sup> at the 240 mg dose level. The observed BI 655064 PK profile in East Asian subjects is comparable to the profile observed in a Western population<sup>11,12</sup> and is consistent with other compounds exhibiting nonlinear PK, possibly due to a target-mediated pathway.<sup>18,19</sup>

The individual BI 655064 exposures from Caucasian, Japanese and Chinese populations were compared as shown in Supporting Information Figure S1; large variability was observed within and across ethnicities in  $C_{max}$  and AUC<sub>0-168</sub> after a single dose (Supporting Information Figures S1A and 1B, respectively) and multiple doses of BI 655064 (Supporting Information Figures S1C and 1D, respectively). Despite the large variability, there were no apparent differences in BI 655064 exposure (AUC,  $C_{max}$ ) following SRD administration over a 80-240 mg dose range or following multiple dosing in East Asian subjects compared with the exposure observed in a Western population (Supporting Information, Figure S1).<sup>11,12</sup>

A trend towards decreasing BI 655064 exposure with increasing body weight and BMI was observed. BI 655064 exposure (AUC,  $C_{max}$ ) in Japanese subjects was generally higher than in Chinese subjects across the 80-240 mg dose range in study 1. This may be due to the correlation between BI 655064 exposure and body weight, given that Japanese subjects had a lower baseline body weight than the Chinese subjects enrolled into study 1 (Table 1). Since the number of subjects is limited per dose group, further investigation with a larger number of subjects is needed to show the effect of covariates quantitatively, such as body weight and smoking history.

Ninety percent inhibition of CD40 RO was achieved with doses of BI 655064  $\geq 120$  mg in this East Asian population, and a direct relationship between BI 655064 plasma concentration and inhibition of CD40 RO was observed. Higher doses of BI 655064 may be required to achieve  $>90\%$  CD40 RO in patients with LN, as inflammation in LN is not only driven by B cells, but also monocytes, macrophages, dendritic cells and kidney resident cells (including mesangial cells, podocytes and proximal tubule cells), which all express CD40.<sup>20,21</sup>

In study 2, the placebo group showed a decline in CD40 RO inhibition (from 0 at baseline to  $<-100\%$  at the last sampling time point), which was associated with an unusual decline in the fluorescence intensities of the unstained samples. The decline occurred in both treatment groups and the reason for this is not known (no deviations observed in sample stability, assay conduct or sample integrity). Therefore, CD40 RO data from study 2 should be interpreted with caution.

Nearly all East Asian subjects enrolled into these studies had a positive, treatment-emergent ADA response. While the incidence was high, the ADA responses were predominately observed at the end of the follow-up periods in these studies, where BI 655064 plasma concentrations were near the lower limit of assay quantification and BI 655064 had largely been eliminated, therefore the effect of ADAs on BI 655064 PK could not be evaluated. In previous studies conducted in a Western population, the ADA response was modest, with titres being relatively low and highly variable (2-640).<sup>11</sup> Higher incidences of ADAs in East Asian subjects compared with Caucasian subjects have been observed with other monoclonal antibodies, including adalimumab<sup>22,23</sup> and efalizumab.<sup>24,25</sup>

In study 2, the ADA titres were relatively low (1-64), except for the subject who had previously received BI 655064 in study 1 and had a preexisting ADA response at baseline in study 2. This subject had a significantly boosted ADA response during study 2 but showed no safety findings related to the presence of ADAs. A neutralising ADA assay is not currently available, therefore no conclusion could be drawn about whether ADAs were neutralising or not. Boosted ADA responses have also been reported following re-exposure with the humanised anti-CD52 monoclonal antibody alemtuzumab.<sup>26</sup>

In these studies, an impact of ADA on PK and the PD assays cannot be excluded. The cause for the high incidence of ADA responses observed is not known, but could be due to the expression of CD40 on dendritic cells.<sup>27</sup> In a recent clinical trial with BI 655064 in patients with RA with an inadequate response to methotrexate, the incidence of ADAs was low (6/44 patients) and all ADA titres were  $\leq 8$ .<sup>3</sup>

In conclusion, the BI 655064 PK and safety profiles in East Asian male subjects were consistent with those observed in previous studies conducted in a Western population, therefore no adjustments to the BI 655064 dosing recommendations are warranted for future clinical studies. A high incidence of ADAs was observed in this East Asian population, therefore future clinical trials should monitor the immunogenicity profiles of patients co-administering BI 655064 with other immunosuppressants (ie, methotrexate), which may reduce the incidence of ADA responses, as seen with other biologics in RA.<sup>28-30</sup>

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## COMPETING INTERESTS

F.H. and C.G. are employees of Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA. Y.T. is an employee of Nippon Boehringer Ingelheim Co. Ltd, Kobe, Japan. N.Y. is an employee of Nippon Boehringer Ingelheim Co. Ltd, Tokyo, Japan. E.B. is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. S.J.P. is an employee of Boehringer Ingelheim International GmbH, Ingelheim, Germany. J.S. is an employee of Boehringer Ingelheim International GmbH, Biberach, Germany. I.-J.J. is an employee of the Seoul National University Hospital Clinical Trials Center, South Korea.

## CONTRIBUTORS

Y.T., C.G., E.B., N.Y., S.P., I.-J.J. and J.S. were involved the conception and design of the studies included in this report. I.-J.J. was responsible for the acquisition of the data. All authors were all involved in the analysis and interpretation of the results of the studies. All authors collaborated in the writing of the manuscript and made the decision to submit the manuscript for publication.

## DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (eg, study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: [https://trials.boehringer-ingelheim.com/transparency\\_policy.html](https://trials.boehringer-ingelheim.com/transparency_policy.html). Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical Study Reports and Related Clinical Documents can be requested via this link: [https://trials.boehringer-ingelheim.com/trial\\_results/clinical\\_submission\\_documents.html](https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html) All such requests will be governed by a Document Sharing Agreement. Bona fide, qualified scientific and medical researchers may request access to de-identified,

analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use <https://clinicalstudydatarequest.com> to request access to study data.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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