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ORIGINAL ARTICLE

Safety, tolerability, pharmacodynamics and pharmacokinetics of the soluble guanylyl cyclase activator BI 685509 in patients with diabetic kidney disease: A randomized trial

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Abstract

Aims: Albuminuria is associated with abnormalities in the nitric oxide (NO)–soluble guanylyl cyclase (sGC)–cyclic guanosine monophosphate pathway. We assessed safety and efficacy of the NO-independent sGC activator BI 685509 in patients with diabetic kidney disease and albuminuria.

Materials and methods: In this Phase Ib trial (NCT03165227), we randomized patients with type 1 or 2 diabetes, estimated glomerular filtration rate (eGFR) 20–75 mL/min/1.73 m^2 and urinary albumin:creatinine ratio (UACR) 200–3500 mg/g to oral BI 685509 (1 mg three times daily, $n = 20$; 3 mg once daily, $n = 19$; 3 mg three times daily, $n = 20$, after final titration) or placebo ($n = 15$) for 28 days. Changes from baseline in UACR in first morning void ($UACR_{FMV}$) and 10-hour ($UACR_{10h}$) urine (3 mg once daily/three times daily only) were assessed.

Results: Baseline median eGFR and UACR were 47.0 mL/min/1.73 m^2 and 641.5 mg/g, respectively. Twelve patients had drug-related adverse events (AEs; 16.2%: BI 685509, $n = 9$; placebo, $n = 3$), most frequently hypotension (4.1%: BI 685509, $n = 2$; placebo, $n = 1$) and diarrhoea (2.7%: BI 685509, $n = 2$; placebo, $n = 0$). Four patients experienced AEs leading to study discontinuation (5.4%: BI 685509, $n = 3$; placebo, $n = 1$). Placebo-corrected mean $UACR_{FMV}$ decreased from baseline in the 3-mg once-daily (28.8%, $P = 0.23$) and three-times-daily groups (10.2%, $P = 0.71$) and increased in the 1-mg three-times-daily group (6.6%, $P = 0.82$); changes were not significant. $UACR_{10h}$ decreased by 35.3% (3 mg once daily, $P = 0.34$) and 56.7% (3 mg three times daily, $P = 0.09$); ≥50.0% of patients ($UACR_{10h}$ 3 mg once daily/three times daily) responded (≥20% UACR decrease from baseline).

Conclusions: BI 685509 was generally well tolerated. Effects on UACR lowering merit further investigation.

KEYWORDS
clinical trial, diabetic nephropathy, dose-response relationship, pharmacodynamics, pharmacokinetics, Phase I-II study

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1 | INTRODUCTION

Diabetic kidney disease (DKD) occurs in up to 40% of patients with diabetes,[1,2] and is the most common cause of chronic kidney disease (CKD) globally,[2] leading to approximately 40% of all cases of end-stage kidney disease (ESKD).[3] DKD is characterized by progressive kidney injury, leading to estimated glomerular filtration rate (eGFR) decline, increased cardiovascular morbidity and mortality,[4–7] and impaired quality of life.[4,8] From a therapeutic perspective, treatments approved for preventing or delaying DKD progression were, until recently, limited to renin-angiotensin-aldosterone system (RAAS) blockers.[9–11] Fortunately, within the past 2 years, sodium-glucose cotransporter-2 (SGLT2) inhibitors have been approved for the treatment of DKD,[12] with evidence extending to people with nondiabetic CKD,[13] and a novel nonsteroidal mineralocorticoid antagonist, finerenone, also reduced DKD risk.[14] Despite the use of these therapies, patients still have a high residual risk of DKD progression.[15–17] In addition, existing therapies have well-established side-effect profiles, including hypotension and hyperkalaemia in the case of RAAS inhibitors.[9,18] The identification of DKD treatments that can safely reduce residual DKD risk is therefore a major priority.

An emerging therapeutic class that may complement existing DKD treatment targets soluble guanylyl cyclase (sGC), which plays an important role in the renal nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signalling pathway.[19] sGC is the primary receptor for NO,[20] and is expressed in the renal vasculature and neuroendocrine cells, thereby contributing to the regulation of renal perfusion and renin release.[21] sGC is activated by NO and promotes cGMP production from guanosine triphosphate.[20,22] cGMP then acts on downstream effector targets, including cGMP-regulated protein kinases, phosphodiesterases and ion-gated channels, to regulate physiological processes.[23] For example, NO/cGMP has important physiological effects on renal blood flow and has anti-inflammatory, antifibrotic, and antiproliferative effects on vascular and nonvascular compartments of the kidney.[24] Importantly, NO-sGC-cGMP pathway dysfunction has been linked with elevated CKD risk.[22,24]

Targeting the NO-sGC-cGMP axis, therefore, is an area of therapeutic interest, especially because sGC activation is associated with kidney protection in experimental models.[22,24] Our aim was to examine the safety, tolerability, pharmacodynamic (PD), and pharmacokinetic (PK) characteristics of BI 685509—a potent, NO-independent activator of sGC[25] —in patients with DKD. Furthermore, given the strong association between albuminuria lowering and protection against DKD,[26] we also explored the impact of BI 685509 on urinary albumin:creatinine ratio (UACR) in the trial cohort.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a multinational, randomized, double-blind, placebo-controlled, Phase Ib study (NCT03165227 registered on ClinicalTrials.gov) of three BI 685509 dose groups (with different titration regimens and different maximum doses) in patients with DKD being treated with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) over 28 days, that ran from 6 November 2017, to 10 December 2019. Screening, enrolment, and subsequent study visits occurred at 35 sites in five countries (Belgium, Canada, Czech Republic, Germany, and the United States). Eligible participants were patients aged ≥18 years with type 1 or type 2 diabetes mellitus, eGFR ≥20 and <75 mL/min/1.73 m^2, and UACR ≥200 and <3500 mg/g. The principal exclusion criteria were: treatment with SGLT2 inhibitors, phosphodiesterase inhibitors, nitrates or riociguat after screening or within five half-lives before randomization; treatment with rosiglitazone, repaglinide, or uridine diphosphate-glucuronosyltransferase inhibitors or inducers; any laboratory values more than three times the upper limit of normal at screening; nondiabetic kidney disease; the presence of other medical conditions, such as symptomatic orthostatic dysregulation, heart failure, arrhythmias, coronary heart disease, or cancer; surgery or trauma with significant blood loss in the previous 3 months; blood donation within 4 weeks before the first study drug dose; chronic alcohol or drug abuse; and, in women, childbearing potential.

The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guideline and with applicable regulatory requirements and standard operating procedures of the study sponsor. All participants provided written informed consent. Protocol amendments made after the start of the trial are listed in the Supplementary Methods in Data S1.

2.2 | Randomization and masking

Patients were assigned in a 4:1, double-blind fashion to receive either BI 685509 or placebo according to a randomization plan using interactive response technology via a validated system and verified by a trial-independent statistician. To support dose escalation decisions, access to blinded PK results was given to the Dose Escalation Committee and supporting functions during the clinical part of the trial and before database closure for this trial. These PK results were masked such that they could not be assigned to individual patients. Patients were enrolled in the lowest dose group first. Only after completion of enrolment in this dose group, and after receiving confirmation from the study's Dose Escalation Committee that the next dose group was open for enrolment, were patients enrolled in the next dose group. Within each dose group, BI 685509 was uptitrated in two steps after 7 and 14 days of treatment. Patients who did not tolerate an uptitration could return to the previous dose step and proceed with that dose regimen until the end of the treatment period. After 28 days of treatment, all patients entered a 7-day wash-out period without study medication.

2.3 | Procedures

Patients received 0.5 mg oral BI 685509 tablets (Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany) or placebo for

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28 days. The BI 685509 dosage schedules were: 1–3 mg/d in one to three divided doses, $n = 20$; 1–3 mg once daily, $n = 19$; or 1–3 mg three times daily, $n = 20$. Within these dose ranges, doses were uptitrated at Days 8 and 15. Doses after final titration were 1 mg three times daily, 3 mg once daily, and 3 mg three times daily. The trial medication was taken with food, except on days (morning intake) when the study protocol required fasting. Patients were instructed to take their trial medication with a glass of water immediately before or during breakfast, lunch and/or dinner, depending on the dose regimen. If patients were instructed to take the trial medication twice daily (in the morning at breakfast and in the evening at dinner), there had to be ≥6 hours between doses. If patients took the medication three times daily (at breakfast, lunch, and dinner), there had to be ≥3 hours between doses. Patients were asked to bring all remaining trial medication and empty package material with them to study visits to assess adherence to the regimen. Adherence was based on tablet counts (tablets taken/tablets that should have been taken). Throughout the study, all patients continued with their existing ACE inhibitor/ARB therapy, antidiabetic and all background medications, keeping doses as stable as possible.

Vital signs (diastolic blood pressure [DBP], systolic blood pressure [SBP], and pulse rate) were measured during the screening period and on Days 1, 8, and 15 of the randomized phase and at the end of treatment with an electronic sphygmomanometer. Measurements were taken before dosing and approximately 30, 120, 180, and 240 minutes after dosing (Protocol Amendment 6). The blood pressure (BP) measurement was performed three times at each timepoint. Twenty-four-hour ambulatory BP monitoring was conducted once during the screening period and twice during the randomized phase (Days 15–17 and Days 26–28). Monitoring started at the same time each morning, approximately 30 minutes before medication. Measurements were taken every 20 minutes throughout the day and night. Patients rested for 5 minutes before medication and for 5 minutes before the monitor was removed to allow seated BP measurements to be recorded.

The full schedule of study measurements and timing of assessments performed is available in the Supplementary Methods in Data S1. Electronic case report forms were used for all patients. All clinical data were captured using an electronic data capture system. The trial site personnel entered and edited the data via a secure network with secure access features, and a complete electronic audit trail was maintained. The investigators approved the data using an electronic signature to confirm the accuracy of the data recorded. The investigators permitted trial-related monitoring, audits and review by institutional review boards or independent ethics committees and regulatory inspection, and provided direct access to all source data.

2.4 | Outcomes

The primary study endpoint was the proportion of patients with drug-related adverse events (AEs) during the 28-day double-blind period and 7-day follow-up period. AEs were coded using the Medical Dictionary for Regulatory Activities version 22.1.

Secondary PD endpoints were changes from baseline in log-transformed UACR, measured in a morning void urine sample ($UACR_{FMV}$) and a 10-hour urine collection ($UACR_{10h}$), after approximately 28 days of trial treatment. Whenever possible, collected urine was stored at approximately 4–8°C until sample processing. Post hoc PD analyses were conducted to determine placebo-corrected changes from baseline in $UACR_{FMV}$, $UACR_{10h}$, eGFR, and BP.

PK endpoints calculated for BI 685509 and its primary metabolite, BI 685144 included: peak plasma concentration (C_{max}) and time to C_{max} (t_{max}); and steady-state area under the plasma concentration–time curve over a dosing interval τ ($AUC_{\tau,ss}$), terminal half-life ($t_{½,ss}$), apparent clearance (CL/F_{ss}), and apparent volume of distribution during the terminal phase (V_z/F_{ss}). For quantification of analyte plasma concentrations of BI 685509 and its primary metabolite, BI 685144, approximately 3 mL blood was drawn from an antecubital or forearm vein into a potassium ethylenediaminetetraacetic acid-anticoagulant blood-drawing tube at the times indicated in the schedule of study measurements (Supplementary Methods in Data S1). BI 685509 and BI 685144 concentrations in plasma were determined by a validated liquid chromatography tandem mass spectrometry assay.

2.5 | Statistical analysis

For this exploratory trial, it was planned to include a total of 75 patients. The planned sample size was not based on a power calculation. Rather, the size of 25 patients per dose group (20 on active treatment, and five on placebo) is commonly used in multiple-rising dose trials of the current type and was considered sufficient to detect major differences between the various treatment groups and placebo regarding the primary endpoint and for the exploratory evaluation of PD and PK characteristics.

The primary endpoint was analysed using descriptive statistics to compare active dose groups to placebo. Secondary endpoints were analysed descriptively and with a restricted maximum-likelihood, estimation-based, mixed-effect model for repeated measures analysis (MMRM; $UACR_{FMV}$) or analysis of covariance (ANCOVA; $UACR_{10h}$). The MMRM analysis included treatment and visit as discrete fixed effects, baseline as a continuous fixed effect, and interaction between visit and treatment, and interaction between visit and baseline. The ANCOVA model included treatment as a fixed classification effect and baseline as a covariate.

For the MMRM analysis of secondary PD endpoints, the Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors. An unstructured (co)variance structure was used to model within-patient measurements. Adjusted mean values and treatment contrasts were presented together with 95% confidence intervals (CIs) and *P* values. Response rate (proportion of responders) was summarized by treatment. A responder was defined as a patient whose percentage change from baseline in UACR was ≥20%; this response-definition cut-off was selected because the stepwise uptitration of

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TABLE 1 Baseline demographics and laboratory characteristics of participants

	BI 685509 1 mg three times daily[a] ($n = 20$)	BI 685509 3 mg once daily[a] ($n = 19$)	BI 685509 3 mg three times daily[a] ($n = 20$)	Placebo ($n = 15$)	Total ($N = 74$)
Sex, n (%)					
Male	13 (65)	12 (63)	15 (75)	13 (87)	53 (72)
Female	7 (35)	7 (37)	5 (25)	2 (13)	21 (28)
Race, n (%)					
White	16 (80)	14 (74)	15 (75)	14 (93)	59 (80)
Black or African American	4 (20)	4 (21)	4 (20)	1 (7)	13 (18)
Asian	0	1 (5)	1 (5)	0	2 (3)
Age, mean (SD), years	67.1 (9.3)	67.3 (8.7)	66.1 (7.2)	72.5 (8.7)	68.0 (8.7)
BMI, mean (SD), kg/m^2	29.8 (3.6)	32.3 (3.5)	33.0 (5.1)	32.4 (5.0)	31.9 (4.4)
Blood pressure (seated), adjusted mean (SD), mmHg					
Systolic	147.5 (12.4)[b]	141.9 (11.8)	145.9 (14.8)[c]	137.5 (15.6)[d]	N/D
Diastolic	78.1 (8.0)[b]	79.0 (5.4)	75.7 (7.5)[c]	73.5 (10.1)[d]	N/D
Baseline eGFR, mean (SD), mL/min/1.73 m^2	43.2 (12.2)	45.7 (11.1)	49.1 (16.8)	47.2 (13.1)	46.2 (13.4)
Screening UACR, mean (SD), mg/g	987.6 (855.4)	662.5 (464.8)	1171.8 (688.4)	774.3 (437.2)	910.7 (666.2)
Smoking history, *n* (%)					
Never	12 (60)	13 (68)	7 (35)	9 (60)	41 (55)
Current	1 (5)	0	4 (20)	1 (7)	6 (8)
Former	7 (35)	6 (32)	9 (45)	5 (33)	27 (37)
Alcohol history, *n* (%)					
Never	12 (60)	10 (53)	10 (50)	8 (53)	40 (54)
Current	6 (30)	8 (42)	6 (30)	4 (27)	24 (32)
Former	2 (10)	1 (5)	4 (20)	3 (20)	10 (14)
Diabetes history, *n* (%)					
Type 1 diabetes	3 (15.0)	1 (5.3)	0	0	4 (5.4)
Type 2 diabetes	17 (85.0)	18 (94.7)	20 (100)	15 (100)	70 (94.6)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; N/D, not determined; SD, standard deviation; UACR, urinary albumin: creatinine ratio.
[a]Dose after final titration.
[b]$n = 19$.
[c]$n = 18$.
[d]$n = 14$.

BI 685509 meant that patients in the higher dose groups received target doses for relatively short periods of time, and studies of other interventions[26] indicate that maximum UACR-lowering effects cannot be expected.

The PK variables were assessed using descriptive statistics and were calculated based on actual sampling times using WinNonlin software (professional network version 8.1; Pharsight Corporation, Mountain View, California) or SAS version 9.4 or later (SAS Institute Inc., Cary, North Carolina) by means of noncompartmental analysis and according to the sponsor's relevant standard operating procedure.

3 | RESULTS

3.1 | Baseline characteristics and adherence

Of the 219 patients screened, 75 were randomized, of whom 74 received at least one dose of study medication (Figure S1, Data S1). Of these 74 patients, 67 (90.5%) completed treatment. Seven patients (9.5%) prematurely discontinued trial medication: four (5.4%) due to an AE (BI 685509 groups, $n = 3$ [5.1%]; placebo, $n = 1$ [6.7%]), and three (4.1%) for other reasons (BI 685509 groups, $n = 2$ [3.4%]; placebo, $n = 1$ [6.7%]).

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TABLE 2 Treatment-emergent adverse events[a]

	BI 685509 1 mg three times daily[b] ($n = 20$)	BI 685509 3 mg once daily[b] ($n = 19$)	BI 685509 3 mg three times daily[b] ($n = 20$)	Placebo ($n = 15$)	Total ($N = 74$)
Any AE	8 (40.0)	7 (36.8)	9 (45.0)	7 (46.7)	31 (41.9)
Diarrhoea	1 (5.0)	1 (5.3)	2 (10.0)	1 (6.7)	5 (6.8)
Headache	2 (10.0)	1 (5.3)	0 (0.0)	1 (6.7)	4 (5.4)
Drug-related AEs[c]	3 (15.0)	1 (5.3)	5 (25.0)	3 (20.0)	12 (16.2)
Hypotension	0 (0.0)	1 (5.3)	1 (5.0)	1 (6.7)	3 (4.1)
Diarrhoea	1 (5.0)	0 (0.0)	1 (5.0)	0 (0.0)	2 (2.7)
Other significant AEs[d]	0 (0.0)	1 (5.3)	2 (10.0)	1 (6.7)	4 (5.4)
AEs leading to discontinuation of study drug	1 (5.0)	0 (0.0)	2 (10.0)	1 (6.7)	4 (5.4)
AEs of severe intensity	1 (5.0)	0 (0.0)	1 (5.0)	0 (0.0)	2 (2.7)
Syncope	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Hypotension	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.4)
Serious AEs	2 (10.0)	0 (0.0)	1 (5.0)	0 (0.0)	3 (4.1)
Required (or prolonged) hospitalization	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.4)
Other medically important serious event	2 (10.0)	0 (0.0)	1 (5.0)	0 (0.0)	3 (4.1)

Note: Data are n (%) of patients.
Abbreviation: AE, adverse event.
[a]Patients may be counted in more than one category.
[b]Dose after final titration.
[c]Investigator assessed.
[d]According to International Conference on Harmonization E3.

Baseline characteristics in the four cohorts are shown in Table 1. Overall, 53 patients (71.6%) were male and 21 patients (28.4%) were female; the mean (standard deviation [SD]) age was 68.0 (8.7) years, and mean (SD) body mass index was 31.9 (4.4) kg/m^2. The majority of patients (94.6%) had type 2 diabetes mellitus. The mean (SD) eGFR values at baseline were similar in all the dose groups, ranging from 43.2 (12.2) to 49.1 (16.8) mL/min/1.73 m^2. The mean (SD) UACR values at screening varied among the dose groups and ranged from 662.5 (464.8) mg/g to 1171.8 (688.4) mg/g. Treatment adherence (correct intake of the trial drug 80–120% of the time over the entire treatment period) was 100%.

3.2 | Primary endpoint

Investigator-assessed, drug-related AEs occurred in 12 patients (16.2%; BI 685509, $n = 9$ [15.3%]; placebo, $n = 3$ [20.0%]) and were independent of study drug dose (Table 2). The most frequently reported drug-related AEs were hypotension (three patients, 4.1%: BI 685509, $n = 2$ [3.4%]; placebo, $n = 1$ [6.7%]) and diarrhoea (two patients, 2.7%: BI 685509, $n = 2$ [3.4%]; placebo, $n = 0$). Most AEs were of mild to moderate intensity. Severe, drug-related AEs (syncope and hypotension) occurred in two BI 685509-treated patients (2.7%). Further information regarding these drug-related AEs is shown in Table S1 in Data S1.

Treatment-emergent AEs (TEAEs) occurred in 31 of 74 patients (41.9%). The incidence of patients with at least one TEAE was similar in BI 685509-treated patients (36.8–45.0%) and placebo recipients (46.7%). Overall, the most frequently reported TEAEs were diarrhoea (five patients, 6.8%: BI 685509, $n = 4$ [6.8%]; placebo, $n = 1$ [6.7%]) and headache (four patients, 5.4%: BI 685509, $n = 3$ [5.1%]; placebo, $n = 1$ [6.7%]). AEs that led to study drug discontinuation occurred in four patients (5.4%): three BI 685509-treated patients ([5.1%], orthostatic intolerance; palpitations and dizziness; hypotension), and one placebo recipient ([6.7%] orthostatic intolerance). Two BI 685509-treated patients (1- to 3-mg once-daily group, $n = 1$ [mild hypotension]; 1- to 3-mg three-times-daily group, $n = 1$ [mild oedema, and moderate diarrhoea, urinary urgency, aggravated vertigo, and generalized weakness]) had an unplanned dose reduction (downtitration) and did not titrate to the highest planned dose. No deaths occurred during the trial.

3.3 | PD endpoints

In this analysis, a "responder" was defined as a patient with a decrease from baseline in UACR of ≥20%. For $UACR_{FMV}$, 15.8–27.8%

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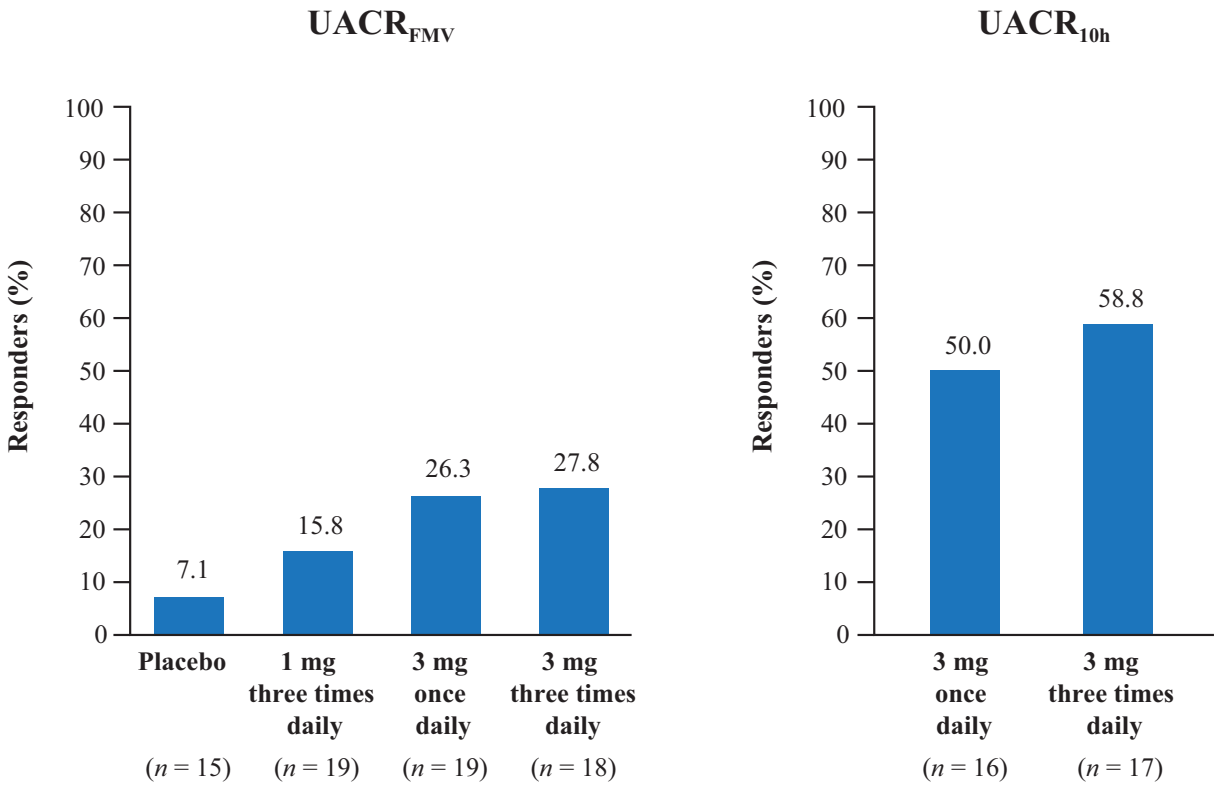

FIGURE 1 Proportion of patients responding to BI 685509, defined as a ≥20% decrease from baseline in UACR$_{FMV}$ (left panel) or UACR$_{10h}$ (right panel)

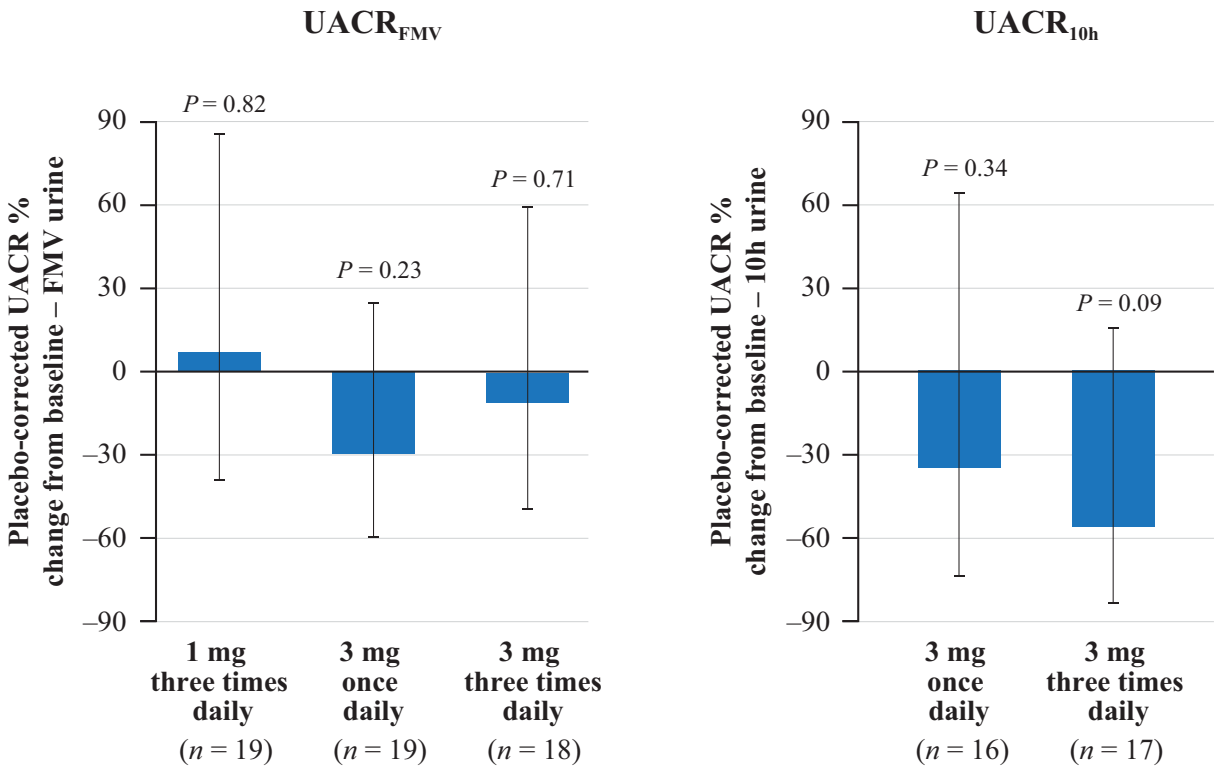

FIGURE 2 Placebo-corrected mean changes from baseline produced by BI 685509 in UACR$_{FMV}$ (left panel) and UACR$_{10h}$ (right panel) urine collections

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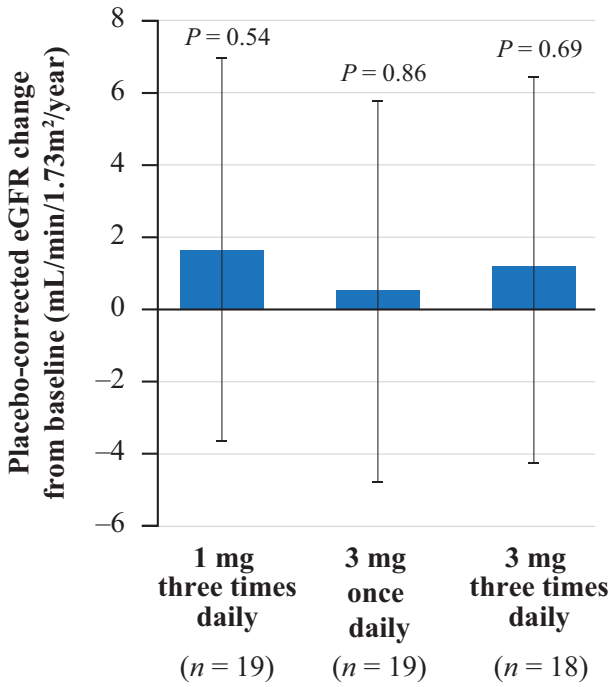

FIGURE 3 Placebo-corrected mean BI 685509-induced changes in eGFR from baseline

of BI 685509-treated patients ($n = 3$–5 per dose group), compared with 7.1% of placebo recipients ($n = 1$), were responders. For $UACR_{10h}$, ≥50% of patients treated with BI 685509 1 to 3 mg once daily or 1 to 3 mg three times daily (i.e., 8–10 patients per dose group), compared with 0% of placebo recipients, were classified as responders (Figure 1).

Placebo-corrected mean changes from baseline in $UACR_{FMV}$ after approximately 28 days of trial treatment were 6.6% in the BI 685509 1 mg three-times-daily group ($P = 0.82$), −28.8% in the BI 685509 1- to 3-mg once-daily group ($P = 0.23$) and −10.2% in the BI 685509 1- to 3-mg three-times-daily group ($P = 0.71$; Figure 2). Placebo-corrected mean changes from baseline in $UACR_{10h}$ after approximately 28 days of trial treatment were −35.3% in the BI 685509 1- to 3-mg once-daily group ($P = 0.34$) and −56.7% in the BI 685509 1- to 3-mg three-times-daily group ($P = 0.09$; Figure 2). $UACR_{10h}$ was not tested in the BI 685509 1-mg three-times-daily group. During the study, adjusted mean changes from baseline in eGFR revealed no statistically significant effects (placebo-corrected mean changes from baseline in eGFR in all BI 685509 dose groups were $P \geq 0.54$; Figure 3).

Regarding seated BP, the only statistically significant placebo-corrected mean changes from baseline were −9.4 (95% CI −18.2, −0.5) mmHg in seated SBP in the first BI 685509 dose group (1 mg three times daily; $P = 0.04$) and +5.7 (95% CI 0.6, 10.8) mmHg in seated DBP in the third BI 685509 dose group (3 mg three times daily; $P = 0.03$, Figure S2 in Data S1). No statistically significant, placebo-adjusted mean changes from baseline were noted in 24-hour, day-time, or night-time ambulatory BP in any of the three BI 685509 dose groups (Table S2 and Figures S3-S5 in Data S1).

3.4 | PK endpoints

The variability of PK characteristics ranged from moderate to high for all dose groups, with a geometric coefficient of variation for C_{max} of 39.71–212.0% (Table S3, Data S1). After administration on Days 1 and 28, BI 685509 was rapidly absorbed (median $t_{max,ss}$ 0.50–1.02 hours), and apparent geometric mean $t_{½,ss}$ was 14.4–15.0 hours. After multiple dosing of BI 685509, V_z/F_{ss} was 182–216 L and CL/F_{ss} was 140–175 mL/min. The ratio of C_{max} for the metabolite (BI 685144) relative to the parent compound (BI 685509) was 0.105 to 0.126. Systemic exposure to BI 685144 (metabolite) was <13% of that to BI 685509 at all doses tested.

4 | DISCUSSION

In this placebo-controlled, multiple-dose, Phase 1b trial, our first major observation was that rising oral doses of BI 685509 were generally well tolerated, with no imbalance in the proportion of patients with AEs. This includes the most frequent drug-related AEs, hypotension and diarrhoea, which were observed in similar proportions of BI 685509-treated patients and placebo recipients; however, the number of events was too small to draw a conclusion. Overall, most AEs were of mild to moderate intensity. Ultimately, while larger trials are required to determine the AE profile of BI 685509, no specific safety concerns were identified in this Phase Ib trial.

Reduced albuminuria is an important surrogate marker of protection against DKD progression.[26] Other kidney-protective therapies, such as RAAS inhibitors and SGLT2 inhibitors, reduce UACR and the risk of clinical renal outcomes, in part by reducing glomerular pressure,[27,28] although other pathways are probably also involved. In previous experimental studies, sGC activation reduced albuminuria without affecting renal perfusion or measures of GFR,[29] suggesting a neutral effect on haemodynamics and glomerular hypertension. This reduction in markers of kidney injury, without impacting kidney haemodynamics, suggests that these therapies may be protective, principally by impacting mechanisms related to suppressing inflammation and/or fibrosis, at least in experimental models of CKD.[30] Consistent with these previous studies was the observation that, compared with placebo, BI 685509 tended to reduce $UACR_{10h}$ from baseline after 28 days of treatment in patients with DKD, although between-group differences did not reach statistical significance. Moreover, in the higher dose groups, ≥50% of patients were responders, defined as a ≥20% decrease from baseline in $UACR_{10h}$, a magnitude of UACR lowering that is associated with benefits on other clinical kidney variables.[26,31] Assessment of the significance of the changes in albuminuria observed in this preliminary analysis, and impact on long-term tolerability, should be a focus of future large-scale studies, with longer follow-up duration. For PK characteristics, the BI 685509 PK profile in patients with DKD was characterized by rapid absorption and biphasic elimination; limited accumulation was observed after multiple dosing. In addition, in a multiple-rising-dose study of BI 685509 in healthy volunteers, a close to dose-proportional

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increase in exposure and limited accumulation were observed (unpublished data).

While the mechanisms responsible for lowering UACR are not known,[32] beyond changes in glomerular pressure, the characteristic BP reduction with these therapies may also contribute. Previous preclinical work with other sGC activators outside the kidney has suggested that these agents may be of benefit by reducing cardiovascular risk, potentially on the basis of improved BP control.[29,30,32] In this trial, we did observe a reduction in SBP at the 1-mg three-times-daily dose, although interestingly, DBP increased at the higher dose of 3 mg three times daily. Given that no consistent changes in BP were observed, ultimately, larger adequately powered trials are required to further elucidate any haemodynamic effects of sGC activators and to ascertain whether differential BP effects are dependent on dose and/or frequency of drug administration.

This study has important limitations. The sample size in each group was small and intended to assess the safety profile of BI 685509. Because of the limited number of participants and short follow-up time, as expected, UACR levels were variable, making it challenging to draw definite conclusions about changes in albuminuria in response to BI 685509. The small sample size also makes it impossible to draw firm conclusions about effects on other PD characteristics, such as BP and eGFR, which will be captured in larger dedicated trials that are due to be completed soon. For example, two large Phase II studies of BI 685509 are ongoing in patients with DKD (NCT04750577, $N = 238$) and CKD (NCT04736628, $N = 240$).

In conclusion, BI 685509 was generally well tolerated and exhibited acceptable PK and PD profiles in patients with DKD. The main aim of the present analysis was to establish the safety profile of BI 685509; however, the study provided some initial insights into the potential impact on haemodynamics and the kidney that should be investigated in future studies. The impact of BI 685509 on the proportion of participants who were responders, based on $UACR_{10h}$, suggests a beneficial effect for BI 685509 on UACR lowering. Further studies with BI 685509 in patients with CKD are warranted.

AUTHOR CONTRIBUTIONS

David Z. I. Cherney, Dick de Zeeuw, and Arne Wenz were involved in study design, monitoring of study progress, data analysis, and manuscript writing and revision. Hiddo J. L. Heerspink was involved in study design, data collection, data analysis, and manuscript writing and revision. Jose Cardona was involved in data conduct and manuscript writing and revision. Marc Desch and Masaomi Nangaku were involved in manuscript writing and revision. Friedrich Schulze was involved in study design, data analysis, and manuscript writing and revision.

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CONFLICT OF INTEREST STATEMENT

David Z. I. Cherney has received honoraria from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Eli Lilly, Janssen, Maze, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk Otsuka, Prometic, Sanofi, and Yeungene, and operational funding for clinical trials from AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi. Dick de Zeeuw has served on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mitsubishi Tanabe, and Travere Pharmaceuticals; on Steering Committees and/or as a speaker for AbbVie and Janssen; and on Data Safety and Monitoring Committees for Bayer, for which honoraria were paid to the institution and consultant/speaker. Hiddo J. L. Heerspink has received grants from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Chinook, Dimerix, Eli Lilly, Gilead, Goldfinch Bio, Janssen, Merck, Mitsubishi Tanabe, Novo Nordisk, and Travere Pharmaceuticals, and payment or honoraria for speaking from AstraZeneca. Jose Cardona has nothing to declare. Marc Desch, Arne Wenz, and Friedrich Schulze are employees of Boehringer Ingelheim. Masaomi Nangaku has received scholarship from Bayer, Chugai, Daiichi Sankyo, Kyowa Kirin, Mitsubishi Tanabe, Takeda, and Torii, research grants from Bayer and JT Pharmaceuticals, and honoraria/speaking fees from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, JT Pharmaceuticals, Kyowa Kirin, and Mitsubishi Tanabe.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on Vivli-Center for Global Clinical Research Data, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Please visit Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information.

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SUPPORTING INFORMATION

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

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