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ASi in CKD group; Tuttle, Katherine R.; Hauske, Sibylle J.; Canziani, Maria Eugenia; Caramori, Maria Luiza; Cherney, David; Cronin, Lisa; Heerspink, Hiddo J.L.; Hugo, Christian; Nangaku, Masaomi

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Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial

Katherine R Tuttle, Sibylle J Hauske*, Maria Eugenia Canziani, Maria Luiza Caramori, David Cherney, Lisa Cronin, Hiddo J L Heerspink, Christian Hugo, Masaomi Nangaku, Ricardo Correa Rotter, Arnold Silva, Shimoli V Shah, Zhichao Sun, Dorothea Urbach, Dick de Zeeuw, Peter Rossing*, on behalf of the ASi in CKD group†*

Summary

Background Excess aldosterone accelerates chronic kidney disease progression. This phase 2 clinical trial assessed BI 690517, an aldosterone synthase inhibitor, for efficacy, safety, and dose selection.

Methods This was a multinational, randomised, controlled, phase 2 trial. People aged 18 years or older with an estimated glomerular filtration rate (eGFR) of 30 to less than 90 mL/min/1·73 m², a urine albumin to creatinine ratio (UACR) of 200 to less than 5000 mg/g, and serum potassium of 4·8 mmol/L or less, taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, were enrolled. Participants were randomly assigned (1:1) to 8 weeks of empagliflozin or placebo run-in, followed by a second randomisation (1:1:1:1) to 14 weeks of treatment with once per day BI 690517 at doses of 3 mg, 10 mg, or 20 mg, or placebo. Study participants, research coordinators, investigators, and the data coordinating centre were masked to treatment assignment. The primary endpoint was the change in UACR measured in first morning void urine from baseline (second randomisation) to the end of treatment. This study is registered with ClinicalTrials.gov (NCT05182840) and is completed.

Findings Between Feb 18 and Dec 30, 2022, of the 714 run-in participants, 586 were randomly assigned to receive BI 690517 or placebo. At baseline, 33% (n=196) were women, 67% (n=390) were men, 42% (n=244) had a racial identity other than White, and mean participant age was 63·8 years (SD 11·3). Mean baseline eGFR was 51·9 mL/min/1·73 m² (17·7) and median UACR was 426 mg/g (IQR 205 to 889). Percentage change in first morning void UACR from baseline to the end of treatment at week 14 was –3% (95% CI –19 to 17) with placebo, –22% (–36 to –7) with BI 690517 3 mg, –39% (–50 to –26) with BI 690517 10 mg, and –37% (–49 to –22) with BI 690517 20 mg monotherapy. BI 690517 produced similar UACR reductions when added to empagliflozin. Investigator-reported hyperkalaemia occurred in 10% (14/146) of those in the BI 690517 3 mg group, 15% (22/144) in the BI 690517 10 mg group, and 18% (26/146) in the BI 690517 20 mg group, and in 6% (nine of 147) of those receiving placebo, with or without empagliflozin. Most participants with hyperkalaemia did not require intervention (86% [72/84]). Adrenal insufficiency was an adverse event of special interest reported in seven of 436 study participants (2%) receiving BI 690517 and one of 147 participants (1%) receiving matched placebo. No treatment-related deaths occurred during the study.

Interpretation BI 690517 dose-dependently reduced albuminuria with concurrent renin–angiotensin system inhibition and empagliflozin, suggesting an additive efficacy for chronic kidney disease treatment without unexpected safety signals.

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*Contributed equally

†ASi in CKD group listed in the appendix (pp 3–24)

University of Washington, Seattle, WA, USA (K R Tuttle MD); **Providence Inland Northwest Health, Spokane, WA, USA** (K R Tuttle); **Boehringer Ingelheim International, Ingelheim am Rhein, Rheinland-Pfalz, Germany** (S J Hauske MD); **Vth Department of Medicine, University Medical Centre Mannheim, Heidelberg University, Heidelberg, Germany** (S J Hauske); **Universidade Federal de São Paulo, São Paulo, Brazil** (M E Canziani MD); **Cleveland Clinic Foundation, Cleveland, OH, USA** (M L Caramori MD); **University of Minnesota, Minneapolis, MN, USA** (M L Caramori); **Toronto General Hospital, Toronto, ON, Canada** (D Cherney PhD); **Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA** (L Cronin MD, S V Shah MD, Z Sun PhD); **University Medical Centre Groningen, Groningen, Netherlands** (H J L Heerspink PhD, D de Zeeuw MD); **The George Institute for Global Health, Sydney, NSW, Australia** (H J L Heerspink); **Universitätsklinikum Carl Gustav Carus Dresden, Medizinische Klinik und Poliklinik III, Dresden, Germany** (C Hugo MD); **University of Tokyo Hospital, Tokyo, Japan** (M Nangaku PhD); **Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico**

Introduction

More than 800 million people worldwide live with chronic kidney disease.[1] The prevalence of chronic kidney disease is projected to progressively increase in parallel with diabetes, hypertension, obesity, and the ageing population.[2] First-line standard-of-care for chronic kidney disease includes renin–angiotensin system (RAS) inhibition, in the form of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and SGLT2 inhibitors.[3] Risk-based therapy for people with chronic kidney disease and type 2 diabetes who have residual albuminuria includes a non-steroidal mineralocorticoid receptor antagonist (MRA).[3] Despite the use of these therapies, people with chronic kidney disease are at risk of progression to kidney failure and cardiovascular complications, limiting their quality of life and life expectancy.[2–4]

Aldosterone accelerates chronic kidney disease progression.[5,6] The deleterious effects of aldosterone are mediated through multiple mechanisms resulting in inflammation and fibrosis, leading to glomerular, tubulointerstitial, and vascular injury to the kidney.[7] Although ACE inhibitors, ARBs, and non-steroidal

(R C Rotter MD); **Boise Kidney and Hypertension, Suite, Nampa, ID, USA** (A Silva MD); **Synexus Helderberg Clinical Research Centre, Cape Town, South Africa** (D Urbach MD); **Steno Diabetes Centre Copenhagen, Herlev, Denmark** (P Rossing MD); **Department of Clinical Medicine University of Copenhagen, Copenhagen, Denmark** (P Rossing)

Correspondence to: Dr Katherine R Tuttle, Providence Inland Northwest Health, Spokane, WA 99204, USA **katherine.tuttle@providence.org**

See Online for appendix

Research in context

Evidence before this study

Renin–angiotensin system (RAS) inhibitors are an established standard-of-care for the treatment of chronic kidney disease. More recently, SGLT2 inhibitors have been shown to reduce the progression of chronic kidney disease and risk of kidney failure when added to RAS inhibition across a broad range of patients with chronic kidney disease. However, RAS inhibition does not fully block the effects of aldosterone on the kidney. Aldosterone synthase inhibitors directly lower aldosterone production and, thereby, might more completely inhibit its deleterious effects. BI 690517 is a potent, highly selective aldosterone synthase inhibitor in development for chronic kidney disease treatment. We searched PubMed on Oct 5, 2023, for articles published in the past 5 years, with no language restrictions, using the search terms "aldosterone synthase inhibitor" AND "chronic kidney disease". No studies investigating aldosterone synthase inhibition in patients with chronic kidney disease were identified; other drugs in the aldosterone synthase inhibitor class have been shown to substantially lower blood pressure in patients with resistant (baxdrostat) or uncontrolled hypertension (lorundrostat), although these trials did not examine these drugs specifically in patients with chronic kidney disease.

Added value of this study

This phase 2 trial assessed the use of BI 690517, a novel aldosterone synthase inhibitor, as a monotherapy at doses of 3 mg, 10 mg, and 20 mg once per day and in combination with the SGLT2 inhibitor empagliflozin 10 mg once per day in participants who had chronic kidney disease with or without type 2 diabetes. Placebo-corrected reductions in the urine albumin to creatinine ratio (UACR) were 37–40% on BI 690517 treatment, with a plateau of the dose response at 10 mg both as a monotherapy and when combined with empagliflozin, suggesting an additive efficacy. Reductions in the UACR of 30% were reached by 51–70% of participants receiving BI 690517 10 mg. The incidence of hyperkalaemia was higher with BI 690517 compared with placebo, although medical intervention and treatment discontinuation were infrequent.

Implications of all the available evidence

This is the first major phase 2 clinical trial prospectively testing aldosterone synthase inhibition as monotherapy and combined with SGLT2 inhibition, in addition to background treatment with RAS inhibition, for chronic kidney disease with or without type 2 diabetes. Aldosterone synthase inhibition together with SGLT2 inhibition produced clinically meaningful improvements in albuminuria and represents a promising combination therapy for chronic kidney disease to be tested in large-scale clinical trials.

MRAs provide benefit for chronic kidney disease, they do not fully block the effects of aldosterone and increase the risk of hyperkalaemia.[8–15] Aldosterone synthase inhibitors directly lower aldosterone production and, thereby, could enhance therapeutic effectiveness.[7,13,14,16,17] BI 690517 is a potent, highly selective aldosterone synthase inhibitor in development for chronic kidney disease treatment. This phase 2, placebo-controlled, double-blind study assessed the efficacy and safety of multiple oral doses of BI 690517 alone or combined with an SGLT2 inhibitor in people with chronic kidney disease, with or without type 2 diabetes, receiving stable background therapy with an ARB or ACE inhibitor.

Methods

Study design

This multinational (including countries from Argentina, Australia, Belgium, Bulgaria, Brazil, Canada, Czech Republic, China, Finland, Germany, Greece, Hong Kong, Hungary, India, Italy, Japan, South Korea, Malaysia, Mexico, Norway, the Philippines, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Türkiye, and the USA), randomised, controlled, phase 2 trial investigated three doses of BI 690517, alone or combined with the SGLT2 inhibitor empagliflozin, in addition to an ARB or ACE inhibitor, for the treatment of chronic kidney disease. Participants were recruited from hospitals, research institutes, and universities. The study design (appendix p 41) and methods of this clinical trial have been previously described.[18] The trial was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was reviewed and approved by institutional review boards or ethics committees overseeing human studies at all research sites. All participants provided written informed consent before the study procedures commenced. This trial is registered with ClinicalTrials.gov (NCT05182840).

Participants

People aged 18 years or older who had a diagnosis of chronic kidney disease, with or without type 2 diabetes, were eligible for inclusion if their estimated glomerular filtration rate (eGFR) was 30 to less than 90 mL/min/1·73 m², their urine albumin to creatinine ratio (UACR) was between 200 and 5000 mg/g, and their serum potassium was 4·8 mmol/L or less. The main exclusion criteria were chronic kidney disease associated with type 1 diabetes, infection, or malignancy; acute kidney injury within the previous 30 days before screening; clinical indication for an MRA; or current or planned SGLT2 inhibitor or SGLT1/2 inhibitor treatment. Participants received the maximum tolerated dose of an ARB or ACE inhibitor, initiated at least

4 weeks before screening. A full list of the inclusion and exclusion criteria is provided in the appendix (pp 28–30).

Randomisation and masking

Participants were randomly assigned (1:1) by a computer-generated algorithm to receive either empagliflozin 10 mg once per day or matched placebo orally for an 8-week run-in period and during the full trial duration. After 8 weeks of the run-in period, participants underwent a second computer-generated random assignment (1:1:1:1) to receive either BI 690517 3 mg, 10 mg, or 20 mg once per day, or placebo orally for a 14-week treatment period, with a follow-up visit 4 weeks after drug washout at week 18. Participant random assignment occurred in a stratified manner, on the basis of prognostic variables (eGFR <45 or ≥45 mL/min/1·73 m² and UACR ≤750 or >750 mg/g), to ensure a balance of participants between treatment groups. Diabetes status was used as a capping factor for recruitment (70% of patients who were diabetic), but not used for random assignment. Participants were recruited, enrolled, and assigned to study treatment according to the randomisation algorithm by research coordinators and investigators who followed up the participants throughout the trial at the participating sites. They and the data coordinating centre were masked to treatment assignment. Random assignment was done centrally using an interactive response technology. To randomly assign the study participants, the masked investigator called the central interactive response technology system. The vendor providing this system received the randomisation list from the sponsor's internal unmasked randomisation group. The sponsor's standard validated random number generating system was used to generate the randomisation schedules. These schedules were verified by a trial-independent statistician. People directly involved in the conduct and analysis of the trial had no access to the randomisation schedule. During conduct of the trial, treatment assignment was masked to participants, investigators, and the sponsor.

Procedures and outcomes

The primary endpoint was the change from baseline (second random assignment) in UACR measured in first morning void urine ($UACR_{FMV}$) after 14 weeks of study treatment. Secondary endpoints included the proportion of participants with absolute decreases of 15% or more and 30% or more in $UACR_{FMV}$ from baseline to 14 weeks. Baseline UACR was derived as the average of all non-missing measurements at weeks –2, –1, and 0 before the second random assignment. Similarly, week 14 UACR was derived as the average of all non-missing measurements at weeks 12, 13, and 14. This approach provided UACR values at baseline, and weeks 6, 10, and 14 for the efficacy analysis.

Additional endpoints after 14 weeks of study treatment included changes from baseline in eGFR, serum potassium, blood pressure, and markers of target engagement (plasma aldosterone) and selectivity (serum cortisol). Safety endpoints included adverse event and serious adverse event reporting, adrenocorticotropic hormone challenge tests to assess cortisol response, and hyperkalaemia based on the site investigators' judgement. Adverse events of special interest included potential severe drug-induced liver injury, events leading to lower limb amputation, ketoacidosis, Cushing's syndrome, and adrenal insufficiency. Adrenal insufficiency could be reported if morning serum cortisol was less than 496·6 nmol/L on the basis of the investigator's judgement, and irrespective of other symptoms. Three analyses were conducted for serum potassium including: (1) a placebo-corrected mean change; (2) a placebo-corrected median change; and (3) a post-hoc analysis based on central laboratory measurements only (sensitivity analysis).

Statistical analysis

The adjusted effect of log-transformed UACR from baseline to week 14 was estimated using a mixed model for repeated measures (MMRM). The MMRM estimates and their corresponding covariance matrix were used to evaluate the dose–response relationship of BI 690517 alone and combined with empagliflozin by examining the fitness of models via the multiple comparison procedures modelling approach, which was performed in participants who received empagliflozin and empagliflozin-matching placebo. The percentage change from baseline of $UACR_{FMV}$ was calculated on the basis of the back-transformation of adjusted mean of change from baseline in log-transformed UACR from MMRM using the following formula: exp(adjusted mean of change from baseline log[UACR])–1, in which exp(adjusted mean of change from baseline log[UACR]) corresponds to the adjusted geometric mean of change from baseline in log-transformed UACR. The primary MMRM analysis of UACR included data from all patients before dose down-titration of study treatment or discontinuation. As a result, 481 (82%) of 586 randomly assigned patients were included in the primary $UACR_{FMV}$ analysis. The percentage of randomly assigned patients included in the analysis ranged from 88% for placebo and 84% for BI 690517 3 mg compared with 79% for BI 690517 10 mg and 77% for BI 690517 20 mg. This relationship between BI 690517 dose and the proportion of analysable participants indicates that some of the missing data were not missing at random. The primary and sensitivity MMRM model analyses for UACR, as well as the analyses of the percentage of participants who had a 30% or higher or 15% or higher reduction in UACR, were stratified according to the random assignment stratum. The MMRM model used for UACR also included treatment and planned visit as fixed effects, participant as a random effect, baseline UACR as a covariate, and the interaction between baseline and visit and the interaction between treatment and visit. An unstructured covariance matrix was used.

Background therapy (empagliflozin or respective placebo) was included as a fixed effect in the analysis that included participants on both background therapies. The primary efficacy analysis was based on the full analysis set. The full analysis set included all patients randomly assigned at the second randomisation who had at least one baseline measurement of UACR at week –2, –1, or 0 and at least one post-baseline measurement.

Safety analyses were descriptive and included all treated participants, with a focus on treatment-emergent adverse events. Study baseline refers to the time of the second random assignment. Unless otherwise specified, analyses presented from this baseline are for participants randomly assigned to receive BI 690517 or matching placebo. The analyses assessed the effects of BI 690517 when combined with empagliflozin or its matched placebo, on top of RAS inhibition.

Subgroup and sensitivity analyses of the primary and secondary endpoints were performed for MMRM estimates of change from baseline in log transformed $UACR_{FMV}$ at week 14 for BI 690517 alone and for combination with empagliflozin. The subgroups included age, sex, race, ethnicity, geographical region, BMI, presence of diabetes, eGFR, UACR, glycated haemoglobin, blood pressure, and presence of cardiovascular disease.

Adjusted multiple imputation using Markov Chain Monte Carlo regression was implemented to impute missing data with a monotone missing pattern as the sensitivity analysis for primary $UACR_{FMV}$ analysis. The statistical analysis plan describes the statistical model that was used for the exploratory analysis of the decline in eGFR and explains how this model dealt with missing data. However, descriptive statistics of the proportion of patients with a decline were found to adequately describe the result, therefore it was not included here.

Descriptive statistics and logistic regression were used for the proportional UACR responses. Analyses for secondary endpoints included multiple imputation,

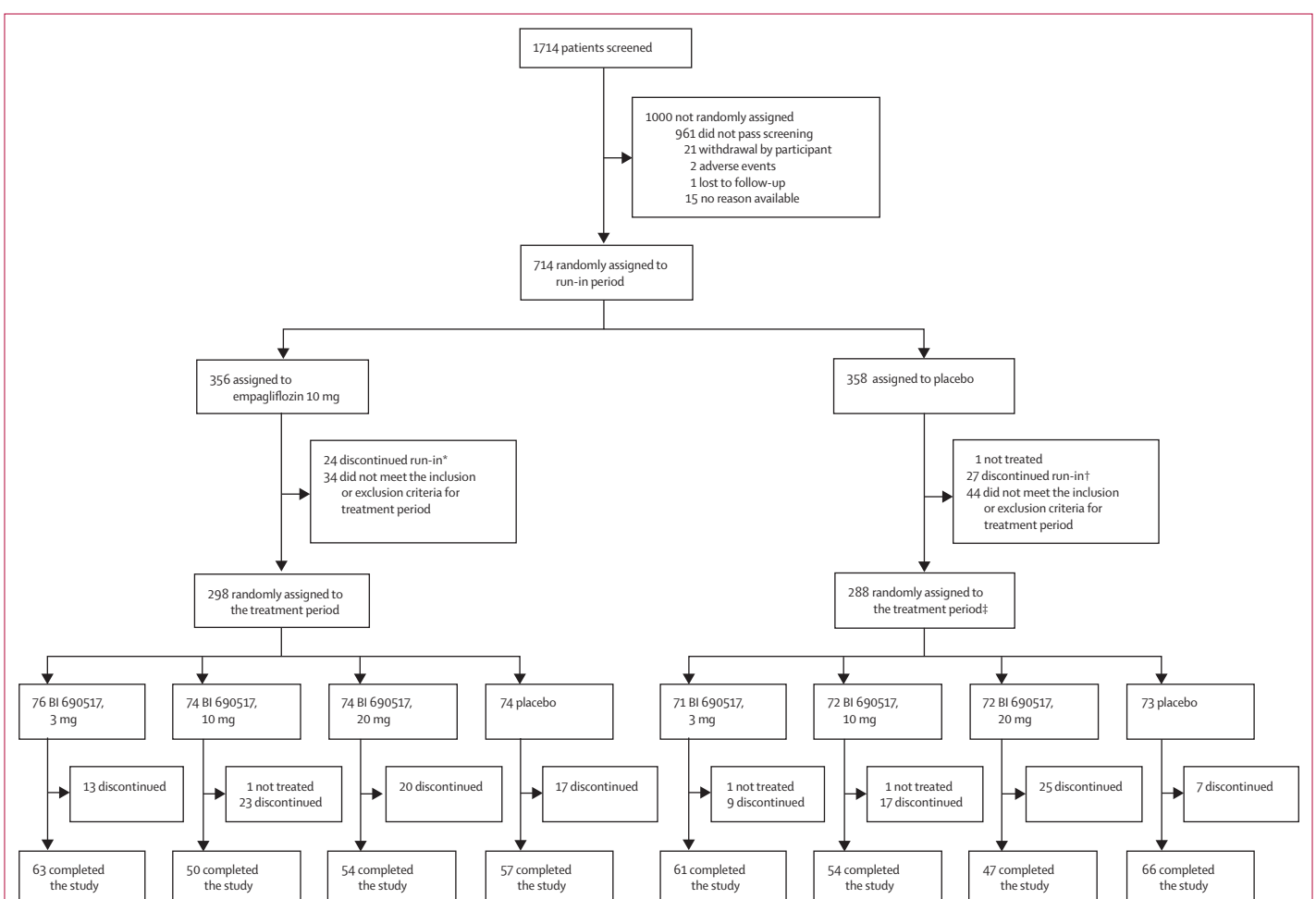

Figure 1: **CONSORT flow diagram**

*Reasons included adverse events (n=5), change of residence (n=1), burden of study procedures (n=2), other reasons (ie, non-compliance and participant decision; n=14), and no reason available (n=2). †Reasons included adverse events (n=5), burden of study procedures (n=2), other reasons (ie, non-compliance, participant decision, and death; n=18), and no reason available (n=2). ‡Two patients were randomly assigned to the treatment period without completing the run-in period.

complete case analysis, missing as non-responder, and last observation carried forward. Specifically for multiple imputation, Markov Chain Monte Carlo regression was used to impute non-monotone missing data to create the monotone missing pattern. Regression method was used for imputation. Missing $UACR_{FMV}$ values at a visit were imputed by treatment and randomisation stratum using the imputation model with baseline $UACR_{FMV}$ and previous $UACR_{FMV}$ measurements. The odds ratios (ORs), 95% CIs, and p values were calculated on the basis of the logistic regression of binary outcome adjusting for treatment and random assignment stratification as covariates. Further details on the statistical methods are available in the appendix (pp 25–27) and the statistical analysis plan.

To establish the sample size, assuming a 15% discontinuation rate, 552 participants was the minimum number needed to be assigned at the second randomisation for at least 480 participants (≥60 per study group) to complete the treatment period. Thereby, at week 14, the resultant study data had 90% power to detect a 30% change in the $UACR_{FMV}$ (assuming an SD in log-transformed UACR of 0·67), with the null hypothesis of no dose relationship rejected at a one-sided α value of 5%. The power calculation for this study was based on 10 000 simulations using R version 4.0.2.

Role of the funding source

Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy, as well as intellectual property considerations.

Results

Between Feb 18 and Dec 30, 2022, of the 714 run-in participants, 586 were randomly assigned to receive BI 690517 or placebo (figure 1). Of these, 33% (n=196) were

	BI 690517 placebo + placebo (N=73)	BI 690517 3 mg + placebo (N=71)	BI 690517 10 mg + placebo (N=72)	BI 690517 20 mg + placebo (N=72)	BI 690517 placebo + empagliflozin (N=74)	BI 690517 3 mg + empagliflozin (N=76)	BI 690517 10 mg + empagliflozin (N=74)	BI 690517 20 mg + empagliflozin (N=74)
Gender								
Women	18 (25%)	20 (28%)	23 (32%)	27 (38%)	31 (42%)	27 (36%)	30 (41%)	20 (27%)
Men	55 (75%)	51 (72%)	49 (68%)	45 (63%)	43 (58%)	49 (64%)	44 (59%)	54 (73%)
Age, years	62·3 (11·4)	64·4 (11·8)	64·8 (9·9)	64·3 (10·7)	63·4 (10·3)	65·4 (11·2)	64·4 (12·3)	61·8 (12·2)
Race								
American Indian or Alaska Native	1 (1%)	2 (3%)	2 (3%)	3 (4%)	2 (3%)	0	2 (3%)	1 (1%)
Asian	16 (22%)	23 (32%)	15 (21%)	19 (26%)	19 (26%)	17 (22%)	27 (36%)	20 (27%)
Black or African American	10 (14%)	3 (4%)	9 (13%)	9 (13%)	10 (14%)	9 (12%)	6 (8%)	7 (9%)
Native Hawaiian or other Pacific Islander	1 (1%)	0	0	0	0	0	0	0
White	44 (60%)	42 (59%)	45 (63%)	40 (56%)	42 (57%)	49 (64%)	35 (47%)	45 (61%)
Multiple	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	4 (5%)	1 (1%)
Diabetes	49 (67%)	48 (68%)	52 (72%)	47 (65%)	51 (69%)	67 (88%)	46 (62%)	54 (73%)
BMI, kg/m^2	30·4 (6·0)	30·5 (5·0)	30·3 (5·2)	29·5 (5·3)	29·5 (5·2)	30·3 (5·8)	29·6 (5·3)	29·4 (5·9)
HbA_{1c}, %	7·0 (1·4)	6·8 (1·2)	6·9 (1·3)	6·9 (1·3)	7·0 (1·3)	7·1 (1·2)	6·9 (1·4)	7·1 (1·3)
eGFR, mL/min/1·73 m^2	54·6 (18·7)	51·8 (16·4)	56·1 (20·9)	51·6 (16·0)	49·6 (17·5)	50·3 (16·7)	50·2 (17·9)	51·5 (17·1)
UACR, mg/g	396 (205–909)	464 (176–1168)	372 (212–777)	456 (293–886)	348 (147–983)	464 (229–1036)	398 (188–817)	434 (237–828)
Systolic blood pressure, mm Hg	133·9 (15·9)	134·8 (18·7)	135·0 (15·1)	136·1 (16·2)	132·7 (13·9)	134·4 (16·4)	131·7 (13·1)	131·8 (16·0)
Diastolic blood pressure, mm Hg	80·2 (11·4)	78·5 (9·1)	75·9 (8·7)	77·4 (9·0)	76·9 (10·7)	76·4 (9·2)	77·1 (9·4)	75·6 (8·6)
Serum potassium, mmol/L	4·31 (0·44)	4·26 (0·38)	4·22 (0·56)	4·40 (0·40)	4·29 (0·46)	4·37 (0·41)	4·29 (0·36)	4·29 (0·37)
Serum aldosterone, pmol/L	180·0 (144·9)	187·9 (172·7)	191·5 (263·1)	145·1 (120·6)	148·0 (123·1)	160·2 (118·9)	163·2 (145·5)	137·2 (107·7)
Morning serum cortisol, nmol/L	305·68 (114·29)	299·60 (102·49)	293·29 (126·99)	305·64 (97·11)	308·02 (123·69)	321·04 (97·09)	300·24 (107·70)	314·02 (98·94)
Medications								
ARB*†	49 (67%)	41 (58%)	56 (78%)	51 (71%)	49 (66%)	55 (72%)	55 (74%)	49 (66%)
ACE inhibitor*†	25 (34%)	29 (41%)	14 (19%)	21 (29%)	24 (32%)	23 (30%)	18 (24%)	24 (32%)
GLP-1 receptor agonists	7 (10%)	4 (6%)	4 (6%)	3 (4%)	5 (7%)	10 (13%)	6 (8%)	11 (15%)

Data are n (%), mean (SD), or median (IQR). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. eGFR=estimated glomerular filtration rate. RAS=renin–angiotensin system. UACR=urine albumin to creatinine ratio. *Stable background therapy with at least one medication of this class. †Values do not add up to 100% (N=586) because two participants did not receive a RAS inhibitor and the data for one participant are missing.

Table 1: **Participant demographics and characteristics by treatment group at baseline**

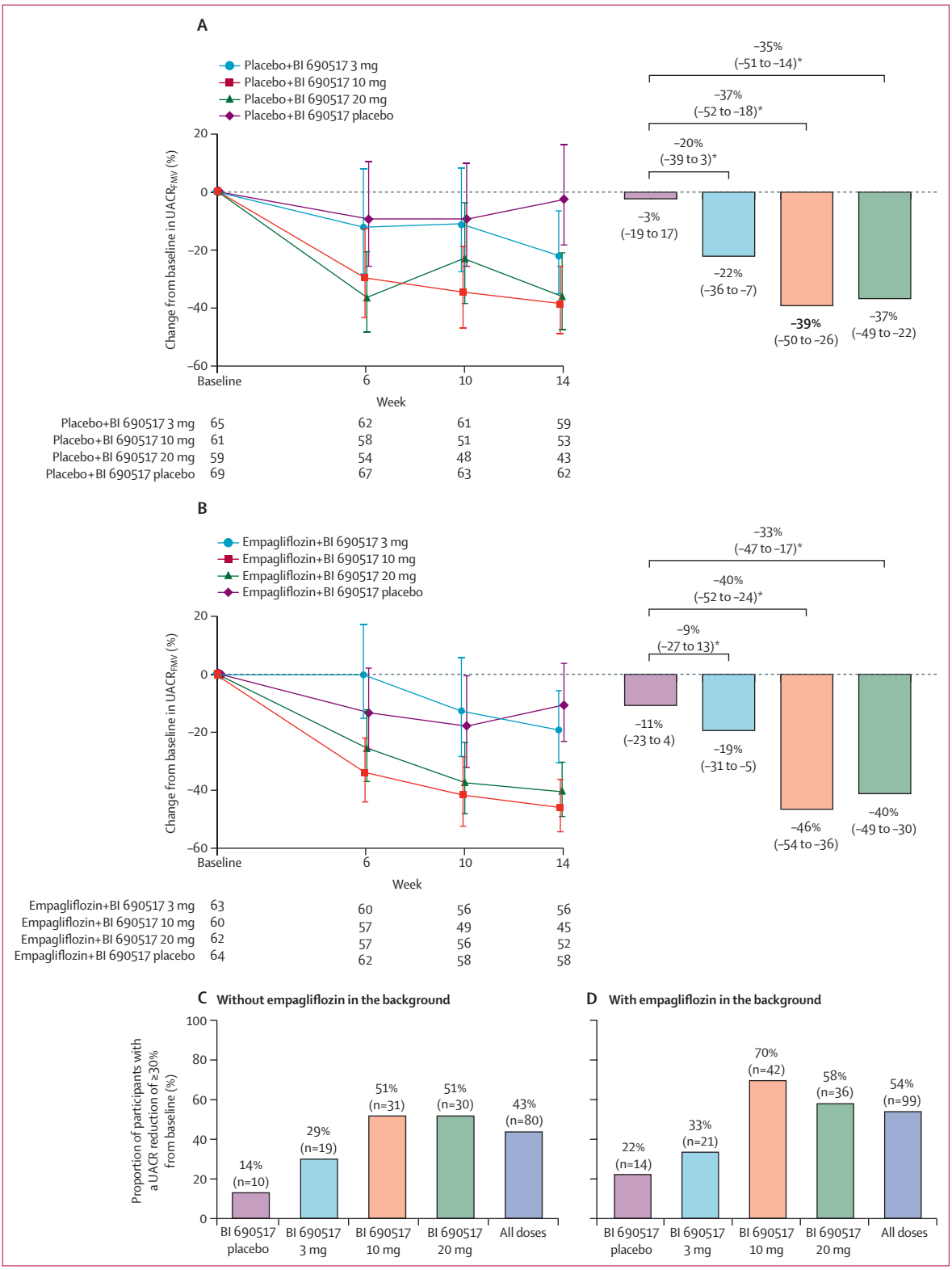

***Figure 2*: Change from baseline in UACR$_{FMV}$ over the study treatment period and at end of treatment**

(A) Percentage change (95% CI) from baseline in UACR$_{FMV}$ over the course of study treatment in participants on BI 690517 monotherapy (line graphs) and at end of treatment at week 14 (bar graphs). (B) Percentage change (95% CI) from baseline in UACR$_{FMV}$ over the course of study treatement in participants on BI 690517 when added to empagliflozin (line graphs) and at end of treatment at week 14 (bar graphs). (C) Proportion of participants on BI 690517 monotherapy with a UACR reduction of 30% or more from baseline to end of treatment at week 14. (D) Proportion of participants on BI 690517 when added to empagliflozin therapy with a UACR reduction of 30% or more from baseline to end of treatment at week 14. FMV=first morning void. UACR=urine albumin to creatinine ratio. *Placebo-corrected percentage.

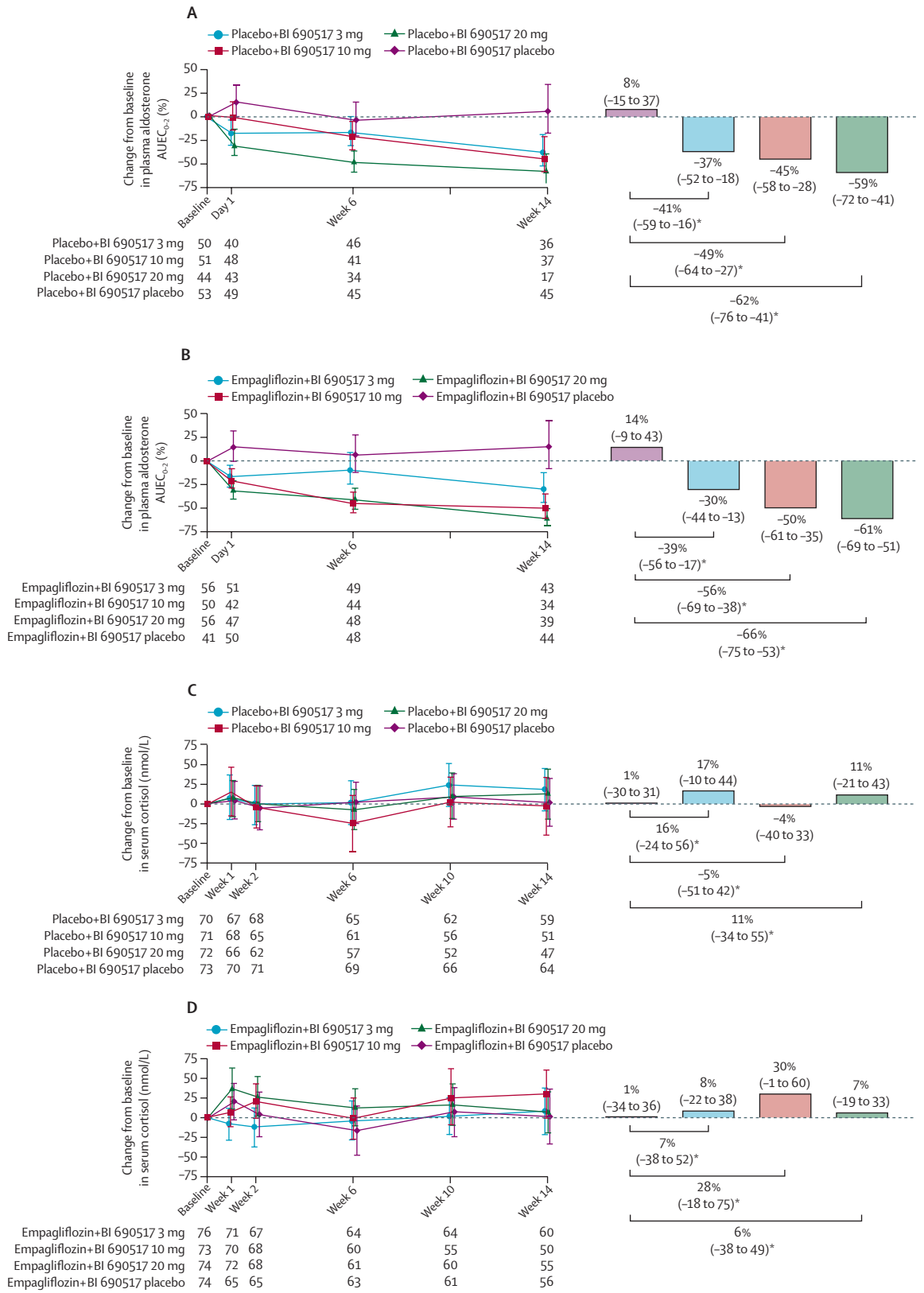

***Figure 3*: Change from baseline in plasma aldosterone exposure and morning serum cortisol concentration over the study treatment period and at the end of treatment**

(A) Percentage change (95% CI) from baseline in plasma aldosterone exposure as $AUEC_{0-2}$ over the course of study treatment in participants on BI 690517 monotherapy (line graphs) and at end of treatment at week 14 (bar graphs). (B) Percentage change (95% CI) from baseline in plasma aldosterone as $AUEC_{0-2}$ over the course of study treatment in participants on BI 690517 when added to empagliflozin (line graphs) and at end of treatment at week 14 (bar graphs). (C) Mean (95% CI) change from baseline in morning serum cortisol over the course of study treatment in participants on BI 690517 monotherapy (line graphs) and at end of treatment at week 14 (bar graphs). (D) Mean (95% CI) change from baseline in morning serum cortisol over the course of study treatment in participants on BI 690517 when added to empagliflozin (line graphs) and at end of treatment at week 14 (bar graphs). Week 14 was the end of treatment. $AUEC_{0-2}$=area under the effect curve within 2 h of administration. *Placebo-corrected change.

women, 67% (n=390) were men, and 42% (n=244) had a racial identity other than White (table 1; appendix pp 31–32). At baseline, the mean participant age was 63·8 years (SD 11·3), mean systolic blood pressure was 133·8 mm Hg (15·7), mean serum potassium was 4·31 mmol/L (0·43), mean eGFR was 51·9 mL/min/1·73 m² (17·7), and the median UACR was 426 mg/g (IQR 205–889). The mean systolic blood pressure was 133·8 mm Hg (15·7), and 13% (36/288) of participants with BI 690517 alone and 17% (51/298) with BI 690517 in combination with empagliflozin had a systolic blood pressure of less than 120 mm Hg at baseline. Participants were taking either an ARB (n=405 [69%]) or an ACE inhibitor (n=178 [30%]). However, two participants were not recorded as receiving a RAS inhibitor and one had missing data. A total of 71% (n=414) of participants had type 2 diabetes. Demographics and clinical characteristics were similar between the dose groups at baseline.

Among the participants who received BI 690517 monotherapy, the percentage change in $UACR_{FMV}$ from baseline to end of treatment at week 14 was –3% (95% CI –19 to 17) with placebo, –22% (–36 to –7) with BI 690517 3 mg, –39% (–50 to –26) with BI 690517 10 mg, and –37% (–49 to –22) with BI 690517 20 mg (figure 2A). In those who received BI 690517 and empagliflozin, the percentage change in $UACR_{FMV}$ was –11% (–23 to 4) with placebo, –19% (–31 to –5) with BI 690517 3 mg, –46% (–54 to –36) with BI 690517 10 mg, and –40 (–49 to –30) with BI 690517 20 mg (figure 2B). A reduction in $UACR_{FMV}$ was observed from week 6 to week 14 (appendix p 42). Results of the subgroup analyses and sensitivity analyses for missing data were congruent with the main results, with BI 690517 10 mg and 20 mg being consistently superior to placebo (appendix pp 43–54).

In the BI 690517 10 mg dose group, a 30% or higher UACR reduction from baseline was observed in 51% (31/61; OR *vs* placebo 6·09; 95% CI 2·64–14·08) of participants on monotherapy and 70% (42/60; OR *vs* placebo 8·42; 3·73–19·02) of those also receiving empagliflozin (figure 2C and D). Across the BI 690517 doses, the largest response rate for a 15% or higher reduction in UACR from baseline was observed in the BI 690517 10 mg dose group also receiving empagliflozin, with an OR versus placebo of 6·08 (2·73–13·57; appendix p 55). Results of the sensitivity analyses for missing data were consistent with the main results (appendix pp 33–38).

BI 690517 reduced plasma aldosterone exposure (area under the curve) dose-dependently up to –62% (95% CI –76 to –41) without empagliflozin and –66% (95% CI –75 to –53) with empagliflozin compared with placebo at the highest dose of BI 690517 (20 mg) by week 14 (figure 3). In both the BI 690517 monotherapy and BI 690517 combined with empagliflozin groups, at all doses, there were no decreases observed compared with placebo in morning serum cortisol concentrations by week 14 (figure 3).

	Participants on BI 690517 monotherapy		Participants on BI 690517 plus empagliflozin	
	Change	Placebo-corrected change	Change	Placebo-corrected change
Serum potassium, mmol/L				
BI 690517 placebo	0·01 (–0·09 to 0·10)	..	0·07 (–0·03 to 0·17)	..
BI 690517, 3 mg	0·25 (0·12 to 0·38)	0·25 (0·08 to 0·41)	0·12 (0·00 to 0·23)	0·05 (–0·10 to 0·20)
BI 690517, 10 mg	0·34 (0·17 to 0·50)	0·33 (0·15 to 0·51)	0·39 (0·22 to 0·55)	0·32 (0·13 to 0·50)
BI 690517, 20 mg	0·33 (0·17 to 0·48)	0·32 (0·15 to 0·49)	0·31 (0·17 to 0·45)	0·24 (0·08 to 0·41)
eGFR, mL/min/1·73 m²				
BI 690517, placebo	–1·17 (–3·04 to 0·70)	..	–0·69 (–2·39 to 1·01)	..
BI 690517, 3 mg	–3·51 (–5·67 to –1·35)	–2·34 (–5·15 to 0·47)	–1·64 (–3·34 to 0·06)	–0·95 (–3·33 to 1·43)
BI 690517, 10 mg	–4·75 (–7·35 to –2·16)	–3·59 (–6·68 to –0·50)	–3·04 (–5·11 to –0·97)	–2·35 (–4·98 to 0·28)
BI 690517, 20 mg	–4·13 (–6·32 to –1·94)	–2·96 (–5·80 to –0·11)	–4·40 (–7·56 to –1·24)	–3·71 (–7·21 to –0·21)
Systolic blood pressure, mm Hg				
BI 690517, placebo	1·09 (–3·35 to 5·53)	..	2·47 (–1·30 to 6·23)	..
BI 690517, 3 mg	–2·80 (–8·15 to 2·56)	–3·89 (–10·73 to 2·95)	–4·56 (–7·94 to –1·17)	–7·02 (–12·02 to –2·02)
BI 690517, 10 mg	–0·72 (–5·18 to 3·74)	–1·81 (–8·10 to 4·48)	–5·34 (–10·04 to –0·64)	–7·81 (–13·69 to –1·92)
BI 690517, 20 mg	–4·94 (–9·44 to –0·43)	–6·03 (–12·44 to 0·38)	–5·78 (–9·37 to –2·19)	–8·25 (–13·40 to –3·09)
Diastolic blood pressure, mm Hg				
BI 690517, placebo	–0·62 (–2·90 to 1·67)	..	–0·17 (–2·41 to 2·07)	..
BI 690517, 3 mg	–1·90 (–4·35 to 0·55)	–1·28 (–4·60 to 2·03)	–1·25 (–3·73 to 1·22)	–1·08 (–4·41 to 2·24)
BI 690517, 10 mg	2·15 (–0·22 to 4·52)	2·77 (–0·52 to 6·05)	–3·58 (–6·12 to –1·04)	–3·41 (–6·75 to –0·07)
BI 690517, 20 mg	–1·55 (–4·01 to 0·90)	–0·94 (–4·31 to 2·43)	–1·22 (–3·57 to 1·14)	–1·05 (–4·26 to 2·17)

Data are mean (95% CI). eGFR=estimated glomerular filtration rate.

Table 2: **Change from baseline in additional endpoints up to week 14**

With BI 690517 monotherapy, the placebo-corrected mean change in serum potassium from baseline was 0·25 mmol/L (95% CI 0·08–0·41) with BI 690517 3 mg, 0·33 mmol/L (0·15–0·51) with BI 690517 10 mg, and 0·32 mmol/L (0·15–0·49) with BI 690517 20 mg (table 2; appendix p 56). Placebo-corrected increases in mean serum potassium with BI 690517 combined with empagliflozin were smaller in most dose groups (table 2; appendix p 56). Median increases in serum potassium were lower across all dose groups of BI 690517 when given along with empagliflozin (appendix p 39).

Small decreases in eGFR from baseline to week 14 of study treatment were observed in response to BI 690517 with or without concurrent empagliflozin (table 2). With BI 690517 monotherapy, the proportion of participants with a decrease in eGFR of 30% or more from baseline to week 14 was 3% each with BI 690517 placebo (two of 73) and BI 690517 3 mg (two of 71) and 10 mg (two of 72), and 6% (four of 72) with BI 690517 20 mg. Among those that received BI 690517 combined with empagliflozin, the proportion of participants with a decrease in eGFR of 30% or higher from baseline to week 14 was 3% (two of 74) with BI 690517 placebo, 1% (one of 76) with BI 690517 3 mg, 3% (two of 74) with BI 690517 10 mg, and 4% (three of 74) with BI 690517 20 mg. Changes in eGFR over time from the first random assignment to empagliflozin or its matched placebo for the run-in period are shown in the appendix (p 57). BI 690517 with empagliflozin resulted in larger decreases in placebo-corrected mean systolic and diastolic blood pressures compared with BI 690517 monotherapy across most dose groups (table 2; appendix pp 58–59). Investigator-reported hypotension and orthostatic hypotension were infrequent adverse events (table 3; appendix p 40).

BI 690517 had an acceptable safety profile with and without empagliflozin (table 3; appendix p 40). A total of four deaths occurred during the treatment period, none of which were considered related to the study treatment by investigators. There were no cases of severe drug-induced liver injury or ketoacidosis.

The occurrence of hyperkalaemia was higher in the pooled BI 690517 20 mg group (18% [26/146]) than the 10 mg (15% [22/144]) and 3 mg groups (10% [14/146]). No fatal hyperkalaemia events occurred. Most participants with hyperkalaemia did not require treatment (86% [72/84]). A total of six participants of 436 (1%) receiving BI 690517 had a serum potassium of 6 mmol/L or more during the treatment period (two participants with BI 690517 3 mg, three participants with BI 690517 10 mg, and one participant with BI 690517 20 mg) compared with one participant of 147 (1%) receiving placebo. The rate of discontinuation for hyperkalaemia was 4% (17/436) in those treated with BI 690517, whereas there were none in the placebo group.

Protocol requirements mandated frequent cortisol testing during the trial and follow-up period. The mean morning serum cortisol at baseline was 306·1 nmol/L (SD 108·7) before the initiation of BI 690517, and no differences in cortisol concentrations were seen at week 14 (mean 310·9 nmol/L; SD 106·9) compared with baseline. Adrenal insufficiency was an adverse event of special interest reported in seven study participants of 436 (2%) receiving BI 690517 and one participant of 147 (1%) receiving matched placebo. A total of two asymptomatic participants receiving BI 690517 had morning serum cortisol concentrations of less than 82·8 nmol/L at the time of investigator-reported adrenal insufficiency.

	Pooled BI 690517, placebo (N=147)	Pooled BI 690517, 3 mg (N=146)	Pooled BI 690517, 10 mg (N=144)	Pooled BI 690517, 20 mg (N=146)
Any adverse event	79 (54%)	80 (55%)	88 (61%)	91 (62%)
Any serious adverse event	10 (7%)	7 (5%)	11 (8%)	11 (8%)
Adverse event of special interest	1 (1%)	1 (1%)	4 (3%)	4 (3%)
Adrenal insufficiency	1 (1%)	1 (1%)	3 (2%)	3 (2%)
Cushing's syndrome	0	0	0	0
Ketoacidosis	0	0	1 (1%)	0
Events leading to lower limb amputation	0	0	0	1 (1%)
Other important adverse events				
Investigator-reported hyperkalaemia	9 (6%)	14 (10%)	22 (15%)	26 (18%)
Hypotension	1 (1%)	1 (1%)	4 (3%)	2 (1%)
Orthostatic hypotension	1 (1%)	0	0	0
Acute kidney injury	1 (1%)	0	2 (1%)	4 (3%)

Pooled groups include participants who received BI 690517 either as monotherapy or in combination with empagliflozin.

Table 3: **Adverse events summary**

Discussion

This study is, to the best of our knowledge, the first report of a clinical trial testing an aldosterone synthase inhibitor in addition to a randomly assigned treatment with an SGLT2 inhibitor and background RAS inhibition. Placebo-corrected UACR reductions were 37–40% on BI 690517 treatment with a plateau of the dose response at 10 mg, either as monotherapy or when combined with empagliflozin, suggesting additive efficacy. Hyperkalaemia occurred at a rate typical for a chronic kidney disease population, but most episodes did not require medical treatment or BI 690517 discontinuation. Lower aldosterone exposure and stable morning serum cortisol provided evidence of target engagement and selectivity for BI 690517.

The observed albuminuria reductions with BI 690517 are clinically relevant. Notably, at BI 690517 10 mg, 51% and 70% of participants met a UACR reduction of 30% or higher with monotherapy or with empagliflozin, respectively. On the basis of analyses assessing albuminuria change as a predictive indicator, these changes are projected to translate into risk reductions for clinical kidney disease events by at least 30%, even when the therapy is applied along with both RAS inhibition

and SGLT2 inhibition.[19–23] After an early decrease in eGFR after initiating BI 690517, eGFR stabilised and paralleled the respective placebo group during the study treatment period. Although the mechanisms that cause the reduction in albuminuria are unknown, intrarenal haemodynamic pathways might be involved, as reflected by the eGFR dip, and might complement anti-inflammatory and anti-fibrotic actions based on lower aldosterone exposure.[24,25] Since the BI 690517 effects on albuminuria are of a similar magnitude in the presence of an SGLT2 inhibitor, these data suggest that the methods of action of these drugs in the kidney might be complementary. Aldosterone synthase inhibition could be of benefit to those who cannot take SGLT2 inhibitors. However, based on the potential additive effects on efficacy combined with a postulated reduction in hyperkalaemia events, the combination of BI 690517 with an SGLT2 inhibitor appears to be promising.

Also noteworthy are the reductions in blood pressure with BI 690517, which were more pronounced with empagliflozin use across the dose groups. Other drugs in the aldosterone synthase inhibitor class substantially lower blood pressure in patients with resistant hypertension (baxdrostat) or uncontrolled hypertension (lorundrostat).[26,27] Although these studies enrolled participants not selected for chronic kidney disease, our data suggest that the anti-hypertensive effects of aldosterone synthase inhibition might also be present in a population with established kidney disease. In many patients with chronic kidney disease, several drugs are often needed to manage resistant hypertension.[3] Therefore, treatments that block aldosterone and also improve blood pressure control might offer additional benefits for kidney and cardiovascular protection, as long as hyperkalaemia is managed, as previously reported with spironolactone.[28]

Although BI 690517 was associated with higher rates of hyperkalaemia compared with placebo, most cases did not require medical intervention. Treatment discontinuation for hyperkalaemia was also infrequent. Dose-dependent increases in serum potassium concentrations were observed with BI 690517, but were possibly ameliorated in the presence of empagliflozin. The magnitude of potassium reduction by empagliflozin is in line with a 2022 meta-analysis including nearly 50 000 participants from six different SGLT2 inhibitor outcome trials.[29] Small decreases in potassium concentrations during these trials were associated with reductions in hyperkalaemia risk of approximately 20%, including subgroups that used MRAs.[29] Similar observations were made in the EMPEROR heart failure programme, where empagliflozin use resulted in no significant reduction in potassium concentrations during the study, but a significant reduction in the risk of hyperkalaemia.[30] Analyses from the FIDELITY study also support the hypothesis of a lower incidence of hyperkalaemia in participants receiving finerenone and an SGLT2 inhibitor at baseline compared with those without an SGLT2 inhibitor.[19] The observed potassium changes are consistent with the reported results from the aldosterone synthase inhibitors, baxdrostat and lorundrostat, despite differences in study populations.[26,27] However, hyperkalaemia events were reported as rare in these studies, which can possibly be attributed to study populations with a mostly preserved kidney function and lower hyperkalaemia risk.

Morning serum cortisol concentrations were stable up to week 14 compared with baseline with BI 690517 alone or combined with empagliflozin. The incidence of morning serum cortisol of less than 82·8 nmol/L was low, and no participants with cortisol in this range reported signs or symptoms. Larger scale studies are required to better understand the clinical significance of this finding. However, taken together, these findings support the selectivity of BI 690517 for aldosterone synthase.

A major strength of this study is the testing of a new chronic kidney disease therapy with a randomly assigned run-in treatment, rather than drop-in use, of an SGLT2 inhibitor in addition to a RAS inhibitor to show the potential for additive benefit of combination therapies. Limitations include the short study duration of a phase 2 trial that precludes the longer term assessment of efficacy and safety, with particular attention to potential risks of hyperkalaemia. Patients with chronic kidney disease who had a clinical indication for MRA treatment were excluded from study participation because of overlapping mechanisms of action with aldosterone synthase inhibition. Future research might reasonably consider comparative effectiveness studies of MRAs and aldosterone synthase inhibitors for various clinical indications. Although the albuminuria lowering effects of BI 690517 were consistent across various analyses, potential imbalances in covariates that were not measured could affect the results, especially considering the modest samples sizes. Additionally, the study population largely comprised participants who identify as White and men. Therefore, the results of this study might not represent those with different race and gender identities affected by chronic kidney disease. Future studies for the development of BI 690517 will focus on the enrolment of a more diverse population with chronic kidney disease.

In conclusion, the novel selective aldosterone synthase inhibitor, BI 690517, dose-dependently reduced albuminuria up to 10 mg daily with or without the SGLT2 inhibitor, empagliflozin, in addition to RAS inhibition in participants with chronic kidney disease. Using BI 690517 along with empagliflozin might offer the potential for additive kidney protection, while mitigating hyperkalaemia risk. Therefore, BI 690517 is a promising new therapy that can be tested, along with standard-of-care treatments such as RAS inhibition and SGLT2 inhibition, for a broad range of patients with chronic kidney disease, including those with and without

diabetes. Such a therapeutic strategy with aldosterone synthase inhibition warrants further study in a large phase 3 kidney disease outcomes trial.

Contributors

KRT, PR, SJH, LC, and DdZ were involved in study conceptualisation and the development of the methods. KRT, MEC, MLC, DC, HJLH, CH, MN, RCR, AS, DU, DdZ, and PR are members of the study Steering Committee and were involved with study supervision, participant recruitment, and data collection. SJH, LC, SVS, and ZS contributed to data curation and data analysis. KRT, PR, SJH, LC, SVS, and ZS had full access to and verified the data and contributed to data interpretation and visualisation. All authors provided critical review, revision, and approval of the manuscript, and were responsible for the decision to submit for publication.

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Data sharing

To ensure the independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. 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 after the publication of the primary manuscript and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major regulatory authorities. Researchers should use the https://vivli.org link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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