# Aldosterone synthase inhibition with or without background sodium-glucose cotransporter-2 inhibition in CKD: a Phase II clinical trial

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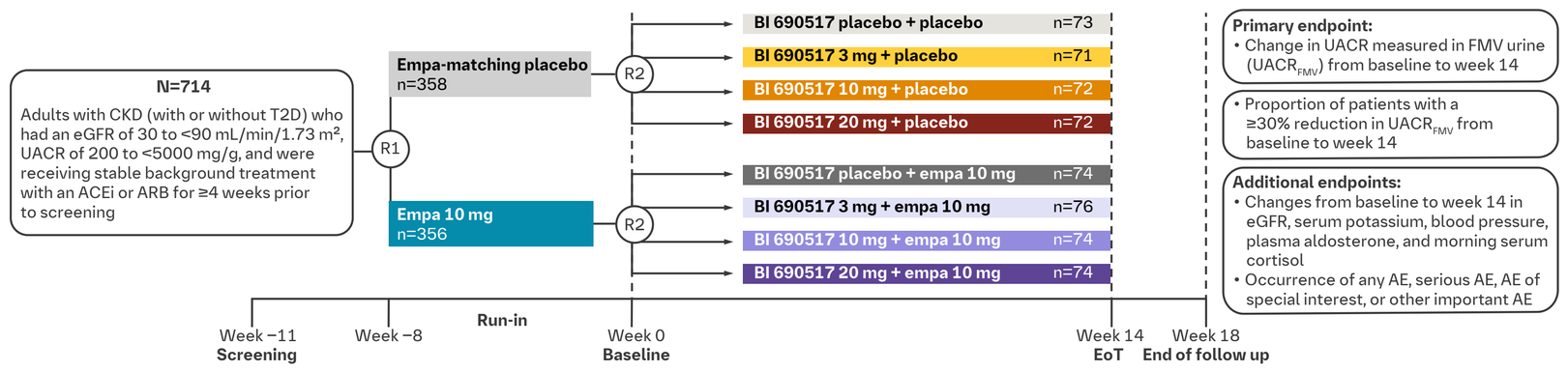
**Aim: To assess the efficacy and safety of an aldosterone synthase inhibitor, BI 690517, when given in addition to RAAS inhibitors with or without empagliflozin in participants with CKD**

## Introduction

- People with CKD remain at high risk of progression despite treatment with ACEis, ARBs, and SGLT2 inhibitors[1]
- Aldosterone excess accelerates CKD progression[2]
- ACEis and ARBs do not fully block the effects of aldosterone and increase risk of hyperkalemia[3]
- SGLT2 inhibitors may add benefit to other CKD treatments, while possibly mitigating hyperkalemia risk[4]
- AS inhibitors directly lower aldosterone production, and thereby, may improve therapeutic efficacy for CKD[5]

## Methods

### Figure 1. Study design[6]




Measurements from the R2 baseline assessed AS inhibitor effects vs placebo without considering effects from empagliflozin, which would have been established during the 8-week run-in and were not part of the presented assessment.

## Results

### Table 1. Demographics and baseline characteristics

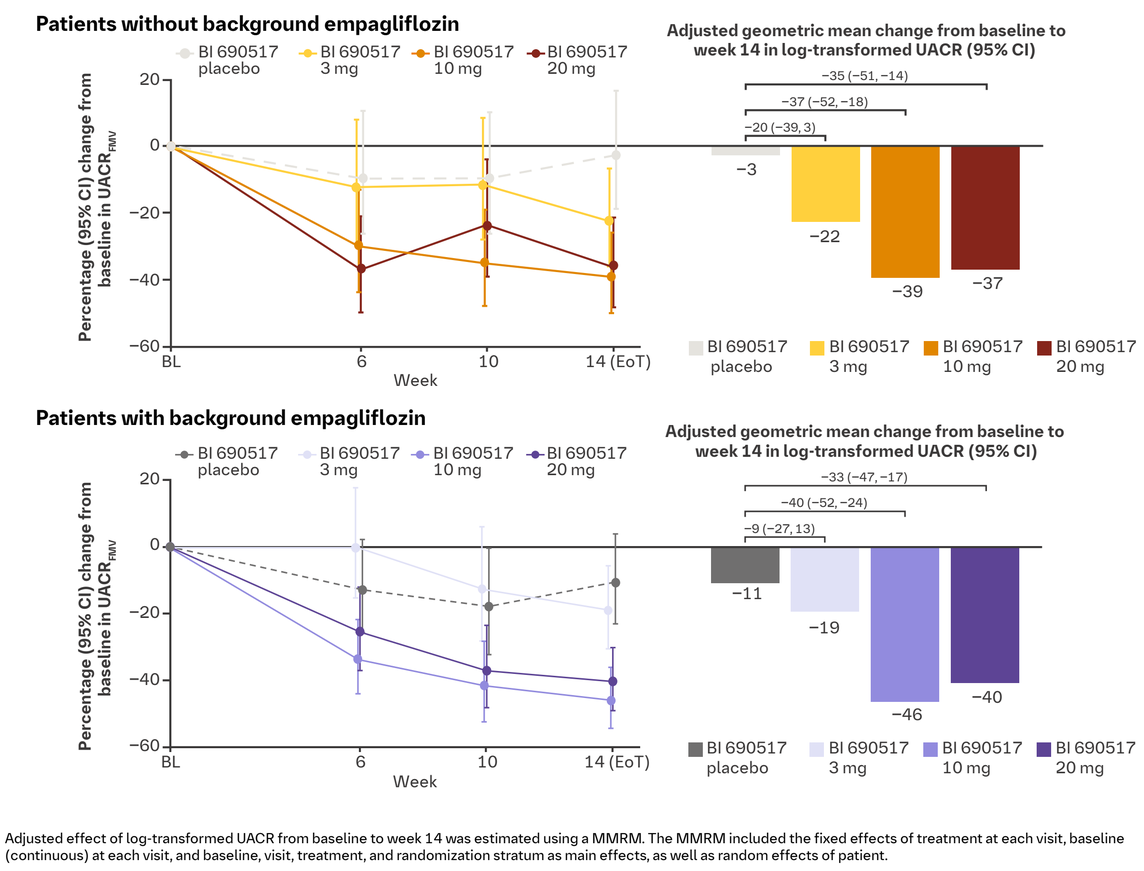
| Characteristic | BI 690517 placebo + placebo n=73 | BI 690517 3 mg + placebo n=71 | BI 690517 10 mg + placebo n=72 | BI 690517 20 mg + placebo n=72 | BI 690517 placebo + empa n=74 | BI 690517 3 mg + empa n=76 | BI 690517 10 mg + empa n=74 | BI 690517 20 mg + empa n=74 |
|---|---|---|---|---|---|---|---|---|
| **Women, n (%)** | 18 (25) | 20 (28) | 23 (32) | 27 (38) | 31 (42) | 27 (36) | 30 (41) | 20 (27) |
| **Age, years, mean (SD)** | 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) |
| **Diabetes, n (%)** | 49 (67) | 48 (68) | 52 (72) | 47 (65) | 51 (69) | 67 (88) | 46 (62) | 54 (73) |
| **eGFR, mL/min/1.73 m², mean (SD)** | 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, median (IQR)** | 396 (205–909) | 464 (176–1168) | 372 (212–777) | 456 (293–886) | 348 (147–983) | 464 (229–1036) | 398 (188–817) | 434 (237–828) |
| **BMI, kg/m², mean (SD)** | 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) |
| **SBP mmHg, mean (SD)** | 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) |
| **DBP, mmHg, mean (SD)** | 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, mean (SD)** | 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) |
| **Medications, n (%)** | | | | | | | | |
| ARB | 49 (67) | 41 (58) | 56 (78) | 51 (71) | 49 (66) | 55 (72) | 55 (74) | 49 (66) |
| ACEi | 25 (34) | 29 (41) | 14 (19) | 21 (29) | 24 (32) | 23 (30) | 18 (24) | 24 (34) |
| GLP-1 receptor agonists | 7 (10) | 4 (6) | 4 (6) | 3 (4) | 5 (7) | 10 (13) | 6 (8) | 11 (15) |

### Table 2. Safety and tolerability findings data for 14-week period following R2 randomization

| Characteristic | 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 + empa n=74 | BI 690517 3 mg + empa n=76 | BI 690517 10 mg + empa n=74 | BI 690517 20 mg + empa n=74 |
|---|---|---|---|---|---|---|---|---|
| **Any AE** | 37 (51) | 37 (53) | 40 (56) | 49 (68) | 42 (57) | 43 (57) | 48 (66) | 42 (57) |
| **Any serious AE** | 3 (4) | 3 (4) | 4 (6) | 6 (8) | 7 (10) | 4 (5) | 7 (10) | 5 (7) |
| **AEs of special interest** | 0 | 1 (1) | 1 (1) | 2 (3) | 1 (1) | 0 | 3 (4) | 2 (3) |
| Adrenal insufficiency | 0 | 1 (1) | 1 (1) | 2 (3) | 1 (1) | 0 | 2 (3) | 1 (1) |
| Cushing's syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Events leading to lower limb amputation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1) |
| Ketoacidosis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1) | 0 |
| **Other important AEs** | | | | | | | | |
| Hyperkalemia | 4 (6) | 8 (11) | 7 (10) | 17 (24) | 5 (7) | 6 (8) | 15 (21) | 9 (12) |
| Hypotension | 0 | 1 (1) | 0 | 0 | 1 (1) | 0 | 4 (6) | 2 (3) |
| Acute kidney injury | 1 (1) | 0 | 1 (1) | 2 (3) | 0 | 0 | 1 (1) | 2 (3) |

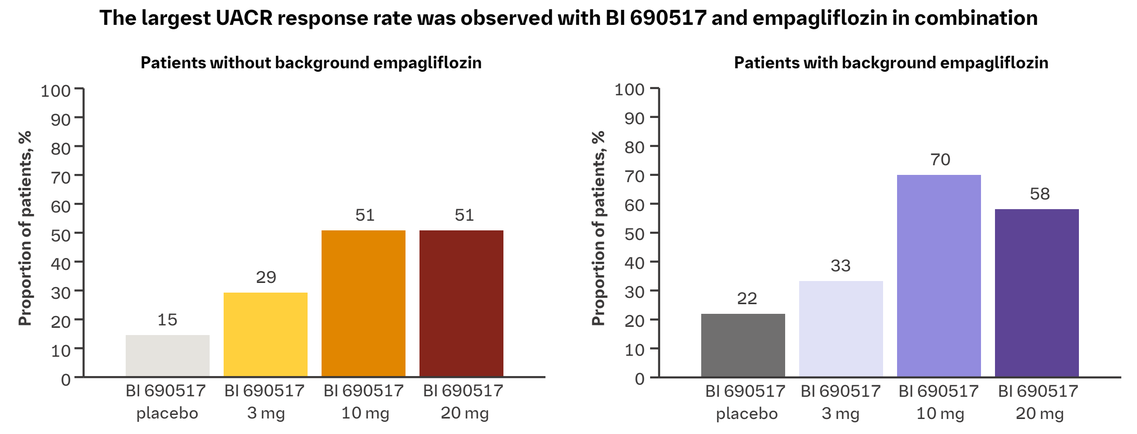
- Most cases of hyperkalemia did not require treatment (86%)
- 6 participants (1%) on BI 690517 had a serum potassium >6 mEq/L vs 1 participant (1%) on placebo
- Discontinuation rate for hyperkalemia was 4% with BI 690517 vs 0% for placebo

### Figure 2. Primary endpoint: UACR$_{FMV}$ percentage change from baseline to week 14

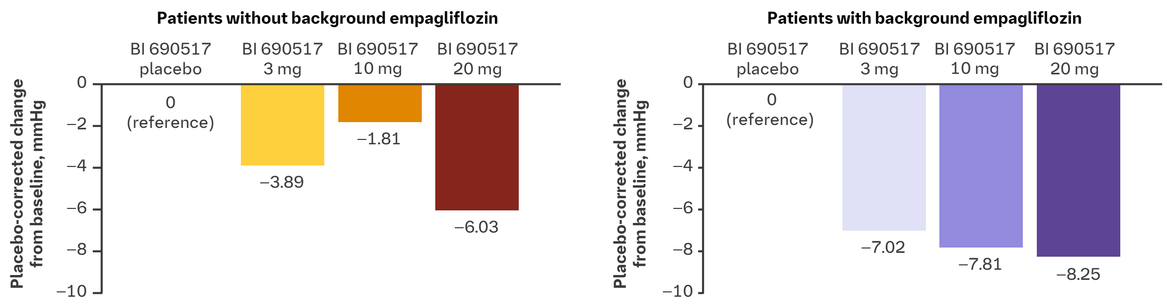



Adjusted effect of log-transformed UACR from baseline to week 14 was estimated using a MMRM. The MMRM included the fixed effects of treatment at each visit, baseline (continuous) at each visit, and baseline, visit, treatment, and randomization stratum as main effects, as well as random effects of patient.

### Figure 3. Proportion of patients with UACR reduction ≥30% from baseline




### Figure 4. Placebo-corrected change from baseline in SBP




- More pronounced SBP changes were observed with BI 690517 in combination with empagliflozin vs placebo background
- Additional endpoint data (change in eGFR, SBP, plasma aldosterone, serum cortisol, and serum potassium) are available in the interactive version of this poster (see QR code/link below)

## Conclusions

- **In participants with CKD, the selective AS inhibitor BI 690517 reduced albuminuria by up to 40% (placebo-corrected) in a dose-dependent manner**
- **Albuminuria reductions occurred with or without concurrent SGLT2 inhibition, suggesting additive effects of BI 690517 and empaglifozin**
- **BI 690517 was generally well tolerated with no unexpected safety finding**
- **AS inhibition is a promising new therapy that may add benefit to SGLT2 inhibition for CKD with or without T2D**
- **This therapeutic strategy will be tested further in a Phase III clinical trial (EASi-KIDNEY™)[7]**

Scan the QR code or click on the link for an interactive device-friendly version of this poster

https://bit.ly/4c6YFAI

### References

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7. EASi-KIDNEY™: https://www.ctsu.ox.ac.uk/research/easi-kidney

### Abbreviations

ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AS, aldosterone synthase; BL, baseline; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; empa, empagliflozin; EoT, end of treatment; f/u, follow up; FMV, first morning void; GLP-1, glucagon-like peptide; IQR, interquartile range; MMRM, mixed model for repeated measure; R, randomization; SBP, systolic blood pressure; SD, standard deviation; SGLT2, sodium-glucose co-transporter; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio

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### Data sharing 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. 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, typically, 1 year after the approval has been granted by major Regulatory Authorities or after termination of the development program. 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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