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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

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Abstract

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](https://clinicaltrials.gov/ct2/show/study/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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