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Safety and Effectiveness of Bexagliflozin in Patients with Type 2 Diabetes Mellitus and Stage 3a/3b Chronic Kidney Disease

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Abstract

Rationale and Objective: Hyperglycemia exacerbates the progression of chronic kidney disease (CKD), but most glucose-lowering therapies do not address morbidities associated with CKD. Sodium-glucose cotransporter-2 (SGLT2) inhibitors offer potential benefits to patients with diabetes and CKD, but their effectiveness may be diminished with impaired kidney function. We aimed to evaluate the safety and effectiveness of bexagliflozin, a novel SGLT2 inhibitor, in patients with type 2 diabetes and CKD.

Study Design: Phase 3, double-blind, placebo-controlled, multi-center, multi-national, randomized trial

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Author Contributions: designed the study: ASA, MWF, YDH; trained investigators on the protocol procedures and reviewed subject data: SR, CB, CT, PS; directed clinical trial operation: TT, WZhang; analyzed the data: WZhou. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Prior Presentation: Results from this trial were presented as an oral abstract during the High Impact Clinical Trials session at ASN Kidney Week 2018 in San Diego, CA.

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Setting and Participants: 54 sites across 4 countries. Patients with CKD stage 3a or 3b, type 2 diabetes mellitus, and a hemoglobin A1c between 7.0% −10.5% and eGFR 30–59 ml/min/1.73 m^2 who were taking oral hypoglycemic agents for 8 weeks.

Interventions: Bexagliflozin, 20 mg daily versus placebo, for 24 weeks.

Outcomes: Primary outcome was the change in percent hemoglobin A_{1c} from baseline to week 24 weeks. Secondary endpoints included changes in body weight, systolic blood pressure, albuminuria and hemoglobin A_{1c} stratified by CKD stage.

Results: 312 patients across 54 sites were analyzed. Bexagliflozin lowered hemoglobin A1c by 0.37% [95% CI 0.20, 0.54]; p <0.001 compared to placebo. Patients with CKD stage 3a (eGFR 45 to < 60) and 3b (eGFR 30 to < 45) experienced reductions in hemoglobin A1c of 0.31% (p = 0.007) and 0.43% (p = 0.002), respectively. Bexagliflozin lowered body weight (1.61 kg, p < 0.001), systolic blood pressure (3.8 mmHg, p = 0.02), fasting plasma glucose (0.76 mmol/L, p = 0.003) and albuminuria (geometric mean ratio reduction of 20.1%, p = 0.03). The frequency of adverse events was not detectably different across treatment groups.

Limitations: Not designed to evaluate impact of treatment on long-term kidney disease and cardiovascular outcomes.

Conclusions: Bexagliflozin reduces hemoglobin A_{1c} in patients with diabetes and stage 3a/3b CKD and appears to be well tolerated. Additional observed benefits included reduction in body weight, systolic blood pressure, and albuminuria.

Funding: Trial was sponsored by Theracos Sub, LLC.

Trial Registration: ClinicalTrials.gov NCT02836873

Plain Language Summary:

Hyperglycemia accelerates the progression of chronic kidney disease (CKD). Few oral glucose-lowering therapies are effective for patients with diabetes and CKD, especially in stage 3b CKD. This study reports results from a phase 3, randomized, controlled trial comparing bexagliflozin, a novel sodium-glucose cotransporter-2 inhibitor, to placebo, in patients with stage 3a and 3b CKD. Patients treated with bexagliflozin had significantly lower hemoglobin A1c levels, body weight, systolic blood pressure, and albuminuria. Adverse events were similar between treatment groups. Bexagliflozin may be a safe and effective agent for the treatment of hyperglycemia in patients with stage 3a and 3b CKD.

Keywords

Type 2 diabetes; SGLT2 inhibitor; chronic kidney disease; renal impairment; bexagliflozin

Introduction

Type 2 diabetes mellitus is one of the leading causes of morbidity and mortality worldwide.[1–3] Chronic kidney disease (CKD) develops in over 1/3 of diabetic patients.[4,5] Tight glycemic control and agents that block the renin-angiotensin-aldosterone axis can delay progression of macrovascular and microvascular complications of diabetes.[6,7] As

kidney function and estimated glomerular filtration rate (eGFR) worsen, oral anti-diabetic treatment options become increasingly limited.[8–11] Thus, novel oral therapies that can be used safely and effectively in patients with diabetes and CKD are needed.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of oral antidiabetic medications that reduce hyperglycemia by decreasing renal proximal tubular reabsorption of glucose, thereby inducing glucosuria.[12] Agents in this class lower hemoglobin A_{1c} and decrease body weight and blood pressure; some members of the class have been shown to improve cardiovascular and kidney outcomes.[13–16] However, relatively few studies have been reported for the CKD population,[17,18] and SGLT2 inhibitors have generally not been effective in reducing hemoglobin A_{1c} in patients with stage 3 CKD.[19,20] To date, no SGLT2 inhibitor has been approved for the management of type 2 diabetes in patients with stage 3b CKD.

Bexagliflozin is an SGLT2 inhibitor with high potency and high selectivity for the SGLT2 transporter. It elicits a prominent and predictable glucosuria in experimental models.[21] In previous clinical trials, bexagliflozin has demonstrated hemoglobin A_{1c} lowering comparable to other members of the SGLT2 inhibitor class in subjects with type 2 diabetes who have eGFR > 60 mL min^{-1} per 1.73 m^2 (ClinicalTrials.gov NCT02715258, NCT02769481, NCT02956044). The current study was intended to determine if the glucose-lowering benefit of bexagliflozin could be extended safely into populations of diabetic patients with more moderately impaired kidney function, with particular emphasis on those with eGFR less than 45 mL min^{-1} per 1.73 m^2.

Methods

Study Design

Data were collected in a phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, parallel group trial intended to evaluate the safety and effectiveness of bexagliflozin in patients with type 2 diabetes mellitus, KDIGO (kidney disease improving global outcomes) CKD stage 3a/3b,[22] and inadequate glycemic control (with hemoglobin A1c ≥ 7.0%). The study was conducted between September 2016 and January 2018 at 54 investigational sites in the United States, Spain, France and Japan. Patients who met the inclusion and exclusion criteria were enrolled in a 1-week, placebo run-in period. After run-in, eligible patients were randomized in a 1:1 ratio to receive bexagliflozin (20 mg) or placebo for 24 weeks in an outpatient setting, with a final study visit at week 26. Randomization was stratified by screening hemoglobin A_{1c} level (7.0% to 8.5% or 8.6% to 10.5%), insulin-treated or non-insulin treated status, and stage 3a CKD (eGFR 45 to < 60 mL min^{-1} per 1.73 m^2) or stage 3b CKD (eGFR 30 to < 45 mL min^{-1} per 1.73 m^2) classification. Randomization and study drug allocation were performed via a central interactive web response system. Investigators, patients and the sponsor team remained blinded to allocation groups for the duration of the trial. Allocation codes were maintained by a designated statistician not involved in study operations.

This study was sponsored by Theracos Sub, LLC and coordinated by the Translational Medicine Group at Massachusetts General Hospital (Boston, MA). The study protocol

and statistical analysis plan were developed by the MGH Translational Medicine Group. The trial was registered with ClinicalTrials.gov (NCT02836873) and is part of an ongoing phase 3 development program involving multiple clinical trials. Prior to study initiation the study protocol, informed consent documents and all subject recruitment information were approved by a central institutional review board (IRB) for investigational sites in the US and by ethics committees for investigational sites in other countries. The study conduct adhered to the principles set forth in the Declaration of Helsinki. All patients provided written informed consent. A Data and Safety Monitoring Board reviewed unblinded aggregate data periodically.

The required sample size for the study was calculated using a two-group t-test assuming two-sided significance of 0.05, placebo-corrected mean reduction of hemoglobin A_{1c} of 0.4% in the treatment arm and a standard deviation of 1%. Under these assumptions, a sample size of 133 patients per arm was estimated to yield 90% power to detect a treatment difference between the bexagliflozin and placebo arms. This sample size determination was based on the assumptions at a specific time point of week 24, without consideration of correlated repeated measurements. The goal was to recruit 300 participants, comprising a minimum of 135 subjects in each CKD stage, to account for a potential loss of approximately 12% of subjects due to early withdrawal.

Patient Population

CKD stage and eGFR were calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation.[23] To be eligible, a prospective participant was required to have been a diabetic man or non-pregnant woman of age ≥ 20 years, either treatment naïve or currently managed by a regimen of approved hypoglycemic agents that had not changed in the preceding 8 weeks; have a baseline eGFR between 30 and 59 mL min^{-1} per 1.73 m^2; and have a body mass index (BMI) ≤ 45 kg m^{-2}. Disqualifying conditions included a diagnosis of type I diabetes mellitus, the presence of a hemoglobinopathy that could interfere with A_{1c} measurement, or a history of > 1 episode of symptomatic hypoglycemia per week; patients were also excluded if they had a history of cancer not in remission for > 3 years, a myocardial infarction, stroke, or hospitalization for unstable angina/heart failure within 3 months of screening, use of an SGLT2 inhibitor within 3 months of screening, or had prior kidney replacement therapy (dialysis or transplant).

All participants were instructed to continue their existing anti-diabetic regimens for the duration for the study. Investigators were directed to prescribe additional medication for hyperglycemia at any time if deemed medically necessary. If a patient had an episode of 3 consecutive days of fasting serum glucose ≥ 270 mg dL^{-1} from week 1 to week 6, ≥ 240 mg dL^{-1} from week 7 to week 12, or ≥ 200 mg dL^{-1} from week 12 to week 24 or had fasting serum glucose ≥ 250 mg dL^{-1} associated with severe clinical signs or symptoms of hyperglycemia, the prescription of additional medication, dictated by the medical judgement of the site principal investigator, was permitted.

Outcomes

The primary endpoint was the change in percent hemoglobin A_{1c} from baseline to week 24. Additional endpoints included the change from baseline to week 24 of fasting plasma glucose, body weight, blood pressure and urine albumin to creatinine ratio, as well as the change in percent hemoglobin A_{1c} within the subgroups defined by stage 3a or stage 3b CKD at baseline. The proportion of patients that achieved a hemoglobin $A_{1c} < 7\%$, or of patients with baseline BMI ≥25 kg m^{-2} that achieved ≥5% reduction of body weight was also documented.

Safety

Safety monitoring included assessments of vital signs, physical examinations, electrocardiograms, urinalyses, and blood specimens. In addition, histories of adverse events and changes in concomitant medication use were recorded. Samples for laboratory testing were processed at regional central facilities. Adverse events of special interest were prospectively defined based on available safety data and regulatory information. Patients were provided with glucometers to measure and upload serum glucose values and were instructed to keep a daily glucose dairy for review during study visits. Suspected acute kidney injury (AKI) was addressed via a standard monitoring protocol using creatinine-based KDIGO definitions (Supplementary Figure 1).[24] Urinary tract infection was defined as a positive urinalysis for leukocyte esterase and/or nitrites plus symptoms and/or a culture of 10^5 colony forming units of one bacterial species. All suspected major adverse cardiac events (MACE) were forwarded to a cardiovascular endpoint committee for blinded adjudication based on prospectively defined event definitions.

Statistical Analysis

Effectiveness analyses were performed in an intention-to-treat (ITT) manner. The primary outcome of change in percent hemoglobin A_{1c} from baseline to week 24 was analyzed using a mixed-effect model repeated measures (MMRM) analysis of covariance (ANCOVA) to generate an estimate of treatment difference at 24 weeks. The model included region, insulin-treated status, baseline eGFR, treatment, visit, treatment-by-visit interaction, and the baseline hemoglobin A_{1c} value as fixed effect covariates. An unstructured covariance matrix was assumed. Data from Weeks 6, 12, and 24 were used in the model. A last observation carried forward method was used to impute hemoglobin A_{1c} values after rescue medication. Secondary continuous outcomes were analyzed using all available data at each week. Similar to the primary outcome, MMRM analysis (with additional baseline value of the outcome as a fixed effect covariate) was utilized. Proportion of hemoglobin $A_{1c}<7\%$ was analyzed using mixed-effects logistic regression for repeated measures assuming an unstructured covariance matrix, using the same covariates as the primary outcome. Urine albumin to creatinine ratio (UACR) data were log transformed prior to analysis. Change in log transformed UACR from baseline to week 24 was analyzed by ANCOVA model. The fixed effect included region, baseline hemoglobin A_{1c} value, insulin-treated status, baseline eGFR, and treatment group. The log transformed baseline UACR values were used as covariate as well. The adjusted geometric mean ratio of relative change from baseline in UACR and the 95 % CI by treatment group were calculated as the antilog of the LS mean and 95 % CI of

log transformed values, converted to percentages. The effect of group assignment on early withdrawal was assessed by Kaplan Meier analysis.

All patients who took at least one dose of double-blind study medication were included in the safety analysis. An interim analysis was not performed. All analyses were performed using SAS version 9.3 (Cary, NC).

Results

Demographics

A total of 312 patients (157 in the bexagliflozin arm and 155 in the placebo arm) were included in the final analysis. (Figure 1). At baseline, 166 participants had CKD stage 3a and 146 had CKD stage 3b. Normoalbuminuria (< 30 mg g^{-1} UACR) was observed in 116/312 (37%) patients, microalbuminuria (30–299 mg g^{-1} UACR) in 118/312 (38%) and macroalbuminuria (≥ 300 mg g^{-1} UACR) in 78/312 (25%). The mean duration of diabetes as assessed by medical history was nearly 16 years, and the mean (SD) baseline hemoglobin A_{1c} was 7.98% (0.798). Approximately 56% of patients were prescribed insulin as part of their regimen for glycemic control. The mean (SD) age was 69.6 (8.32) years, 116/312 (37%) were women and 171/312 (55%) self-described as white or Caucasian. The mean (SD) baseline BMI was 30.2 (5.87) kg m^{-2} and the mean SBP (SD) was 137 (14.5) mm Hg. Baseline characteristics, including variables used to stratify randomization (Table 1), and early withdrawal rates (Supplementary Figure 2) were similar between treatment groups. Frequently used concomitant baseline medications are presented in Table 2.

Change in Hemoglobin A_{1c} from Baseline to Week 24

Subjects treated with bexagliflozin had a mean reduction in hemoglobin A_{1c} of 0.61% whereas those treated with placebo had a mean reduction of 0.24%, yielding a placebo-corrected reduction of 0.37% [95% CI 0.20, 0.54]; p <0.001 (Figure 2). Rescue medication was provided to 26 patients, (9 in the bexagliflozin arm and 17 in the placebo arm). Including observed values after the administration of rescue medication, subjects treated with bexagliflozin had a mean reduction in hemoglobin A_{1c} of 0.59% whereas those treated with placebo had a mean reduction of 0.31%, a placebo-corrected reduction in hemoglobin A_{1c} of 0.28% [95% CI 0.10, 0.46]; p = 0.003.

Participants with stage 3a CKD that were treated with bexagliflozin had a mean reduction in hemoglobin A_{1c} of 0.65% whereas those treated with placebo had a mean reduction of 0.34%, a placebo-corrected reduction of 0.31% [95% CI 0.09, 0.53]; p = 0.007. Participants in stage 3b CKD that were treated with bexagliflozin had a mean reduction in hemoglobin A_{1c} of 0.59% whereas those treated with placebo had a mean reduction of 0.16%, a placebo-corrected reduction of 0.43% [95% CI 0.16, 0.69]; p = 0.002 (Figure 2). The magnitudes of the reduction in hemoglobin A_{1c} in the bexagliflozin arm were similar between the stage 3a and stage 3b populations, but the placebo effect was more pronounced in the stage 3a population, leading to an apparent increase in treatment effect in those with more severe kidney disease.

Other Endpoints at 24 Weeks

Change in hemoglobin A_{1c} over time is reported in Figure 3A. At 24 weeks, bexagliflozin increased the proportion of patients who achieved hemoglobin $A_{1c} < 7\%$ (34% vs. 22%; $p = 0.007$). The treatment effect was apparent as early as 6 weeks ($p = 0.001$) and the trend continued for the entire course of 24 weeks with an odds ratio of 2.26 favoring bexagliflozin treatment (Figure 3B). Bexagliflozin treatment over 24 weeks resulted in an average 1.61 kg body weight reduction compared to placebo (95% CI 1.00, 2.22; $p < 0.001$). The body weight reduction was consistent throughout the 24-week treatment period (Figure 3C). More bexagliflozin-treated patients with baseline BMI ≥ 25 kg m^{-2} had a ≥ 5% decrease in body weight compared to placebo (19% vs. 9%, $p = 0.03$). Bexagliflozin lowered SBP by 3.8 [95% CI 0.6, 7.1] mm Hg ($p = 0.02$; Figure 3D) and decreased fasting plasma glucose by 0.76 [95% CI 0.26, 1.26] mmol/L ($p = 0.003$; Figure 3E). A decrease in diastolic blood pressure of 3.0 mm Hg was observed in bexagliflozin-treated patients, though this was not meaningfully different from those who received placebo (2.1 mm Hg). At week 24, those treated with bexagliflozin had a relative reduction in geometric mean ratio of UACR of 20.1% [95% CI 2.52%, 34.56%]; $p = 0.03$ (Figure 3F).

Safety Endpoints

Overall, treatment emergent adverse events were reported for 214 patients (109 [69%] bexagliflozin vs. 105 [68%] placebo). Serious adverse events were reported for 20 patients (11 [7%] bexagliflozin vs. 9 [6%] placebo). An adverse event led to withdrawal from the study for 5 patients (1 [1%] bexagliflozin vs. 4 [3%] placebo) and discontinuation of study drug for 11 patients (4 [3%] bexagliflozin vs. 7 [5%] placebo). No patients died during the study period (Table 3).

Hypoglycemia was the most common adverse event of interest (39 [25%] bexagliflozin vs. 38 [25%] placebo), followed by diuretic effects (18 [11%] bexagliflozin vs. 5 [3%] placebo), urinary tract infections (11 [7%] bexagliflozin vs. 5 [3%] placebo) and AKI (8 [5%] bexagliflozin vs. 6 [4%] placebo). All AKI events were stage I AKI. Stage II/III AKI or a need for kidney replacement therapy was not reported. AKI events did not lead to any withdrawals. New malignancies were uncommon (3 [2%] bexagliflozin vs. 4 [3%] placebo). There were five genital mycotic infections in the bexagliflozin arm, one amputation in the bexagliflozin arm, and seven falls/fractures in the bexagliflozin arm (compared to six in the placebo arm). There were 2 adjudicated MACE events, both in the bexagliflozin arm. There were no cases of diabetic ketoacidosis (DKA) in either arm (Table 3).

Kidney Function Tests

Kidney function tests and changes from baseline values are displayed in Figure 4. A slight increase in serum creatinine concentration and decrease in eGFR affected subjects assigned to the bexagliflozin arm throughout the treatment period. An increase in creatinine of 0.08 mg dL^{-1} and a decrease of eGFR of 2.41 mL min^{-1} per 1.73 m^2 were observed at week 24. Two weeks after the end of the treatment period, the eGFR for the bexagliflozin arm had increased to near-baseline values (net increase from baseline 1.37 mL min^{-1} per 1.73 m^2).

Discussion

Bexagliflozin is a novel member of the SGLT2 inhibitor class currently in phase 3 development. In earlier studies in patients with eGFR > 60 mL min^{-1} per 1.73 m^2, bexagliflozin demonstrated good safety and efficacy, with hemoglobin A_{1c} reductions comparable to those of the already approved members of the class (ClinicalTrials.gov NCT02715258, NCT02769481, NCT02956044). In the current study, we aimed to examine the impact of bexagliflozin in patients with significant kidney impairment to determine if hemoglobin A_{1c} lowering efficacy was preserved, despite a reduction in eGFR. In a study population consisting of predominantly older individuals with inadequately controlled diabetes and CKD stage 3a/3b, exposure to bexagliflozin produced a statistically significant and clinically meaningful decrease in hemoglobin A_{1c}. The effect was more marked in the sub-population with eGFR between 30 and < 45 (CKD stage 3b), an outcome that was ascribed to a larger placebo effect on hemoglobin A_{1c} in participants with an eGFR between 45 and 60 (CKD stage 3a). Similar positive, short-term effects on body weight, systemic blood pressure, albuminuria and eGFR have been reported for other drugs in the class.[13,15] However, to the best of our knowledge, no previous study has reported a statistically significant A_{1c} lowering effect in diabetic patients with stage 3b CKD.

As eGFR declines, less serum glucose is filtered by the glomerulus. SGLT2 inhibitors are expected to have diminished capacity to increase urinary glucose excretion and lower plasma glucose concentration in the setting of kidney failure.[12,17] In the current study, the absolute decrease in hemoglobin A_{1c} observed for subjects in the bexagliflozin arm was consistent with or better than expectations based on eGFR,[25] and persisted after being controlled for placebo effect and the contribution of rescue medications. In contrast to the data of the current study, data from studies of other SGLT2 inhibitors in subjects with CKD stage 3a/3b have failed to show A_{1c} lowering effects.[19,20] Further study is needed to determine the properties of SGLT2 inhibitors that allow for persistent effectiveness in lowering hemoglobin A_{1c} at lower eGFR. There may also be other transport mechanisms that influence SGLT2 inhibitor action. For example, in mice, the glucosuric effect of empagliflozin has been shown to be dependent on active transport of empagliflozin into the proximal tubule by the organic anion transporter OAT3.[26] The structure-activity relationship for SGLT2 inhibitors and OAT3 transport has not been elucidated in humans.

The changes in eGFR and albuminuria observed in this study were consistent with reports from studies of other SGLT2 inhibitors and of renin-angiotensin-aldosterone axis inhibitors that have demonstrated kidney protective effects.[5,13,15] Long term assessments of the effects of empagliflozin and canagliflozin have reported an initial reduction in eGFR within weeks of exposure to study drug, followed by a prolonged plateau in eGFR and an increase in eGFR following the end of the treatment period. The net effect was a reduction in long-term GFR decline compared to placebo. We observed a similar initial decrease in eGFR followed by a plateau over 24 weeks, with an appropriate rebound after the end of the treatment period in this study. A plausible mechanism for eGFR reduction invokes tubulo-glomerular feedback mediated by an increased delivery of solute in the form of sodium chloride to the macula densa, resulting from the osmotic diuresis produced by SGLT2 inhibition. The effect of the reduced filtration rate, combined with the possible beneficial influence

of lower glucotoxicity, may account for the renoprotective action of SGLT2 inhibitors. A sustained reduction of eGFR has been documented in studies of ACE inhibitors and angiotensin receptor blockers that have since been incorporated in practice guidelines for the management of diabetic patients with CKD.[22] Other SGLT2 inhibitors have shown the prompt reduction in albuminuria[16] observed in this study. Whether this effect on albuminuria is secondary to reduced filtration has not been established.

Reduction in body weight and SBP were observed in patients treated with bexagliflozin. These findings may be due to caloric wasting and proximal tubular diuretic effects that result from increased urinary glucose excretion. Other proposed mechanisms involve concurrent increased urinary sodium excretion, uric acid excretion and effects attributable to interactions with the renin-aldosterone and sympathetic nervous systems.[25] While outside the direct scope of this trial, long-term study of other SGLT2 inhibitors have shown a cardiovascular mortality benefit.[13,14] Further study is needed to elucidate the interactions and mechanisms behind this clinical observation, given the positive effects SGLT2 inhibitors have demonstrated towards cardiac risk factors, such as weight, blood pressure, kidney function, and glycemic control.

In general, bexagliflozin was well-tolerated but increased adverse events in the categories of urinary tract infection and genital mycotic infections were found in this study. These findings have been previously attributed to SGTL2 inhibition. The findings of mild volume depletion, weight loss and reduction in systolic blood pressure reported here are consistent with the expected osmotic diuresis and caloric wasting induced by SGLT2 inhibition. Similarly, the elevation of serum creatinine concentration, described as acute kidney injury, is consistent with the pharmacology of the SGLT2 inhibitor class and the expected effect of natriuresis on glomerular filtration rate. Other serious adverse events were rare and included two MACE events in the bexagliflozin arm, one amputation in the bexagliflozin arm, and seven falls/fractures in the bexagliflozin arm (compared to six in the placebo arm).

This trial should be interpreted in the context of its limitations. The number of patients in this trial was too small to evaluate changes in frequency of rare adverse events. Although the short-term kidney and blood pressure findings are encouraging, this study was not specifically powered or designed to evaluate reno- or vaso-protective effects. Larger trials evaluating cardiovascular outcomes of bexagliflozin are ongoing.

Patients with diabetes and mild to moderate kidney failure have fewer treatment options compared to those with preserved kidney function. Bexagliflozin appears to be beneficial for intensification of glycemic control for patients in this vulnerable condition. Additional therapeutic advantages of bexagliflozin include reduction in body weight, systolic blood pressure and albuminuria. The results of this study support the conduct of additional investigations on the renoprotective potential of bexagliflozin for the management of diabetic kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing:

Individual participant data will not be publically available. Other supporting documents (study protocol, statistical analysis plan, informed consent form, clinical study report, analytic code) will not be available. Study design is available on clinicaltrials.gov (NCT02836873).

List of Abbreviations:

CKD	chronic kidney disease
SGLT2	sodium-glucose cotransporter-2
eGFR	estimated glomerular filtration rate
IRB	institutional review board
BMI	body mass index
SBP	systolic blood pressure
UACR	urine albumin to creatinine ratio
AKI	acute kidney injury
MACE	major adverse cardiac event
MMRM	mixed-effect model repeated measures
ANCOVA	analysis of covariance model
KDIGO	kidney disease improving global outcomes
DKA	diabetic ketoacidosis
MDRD	modification of diet in renal disease

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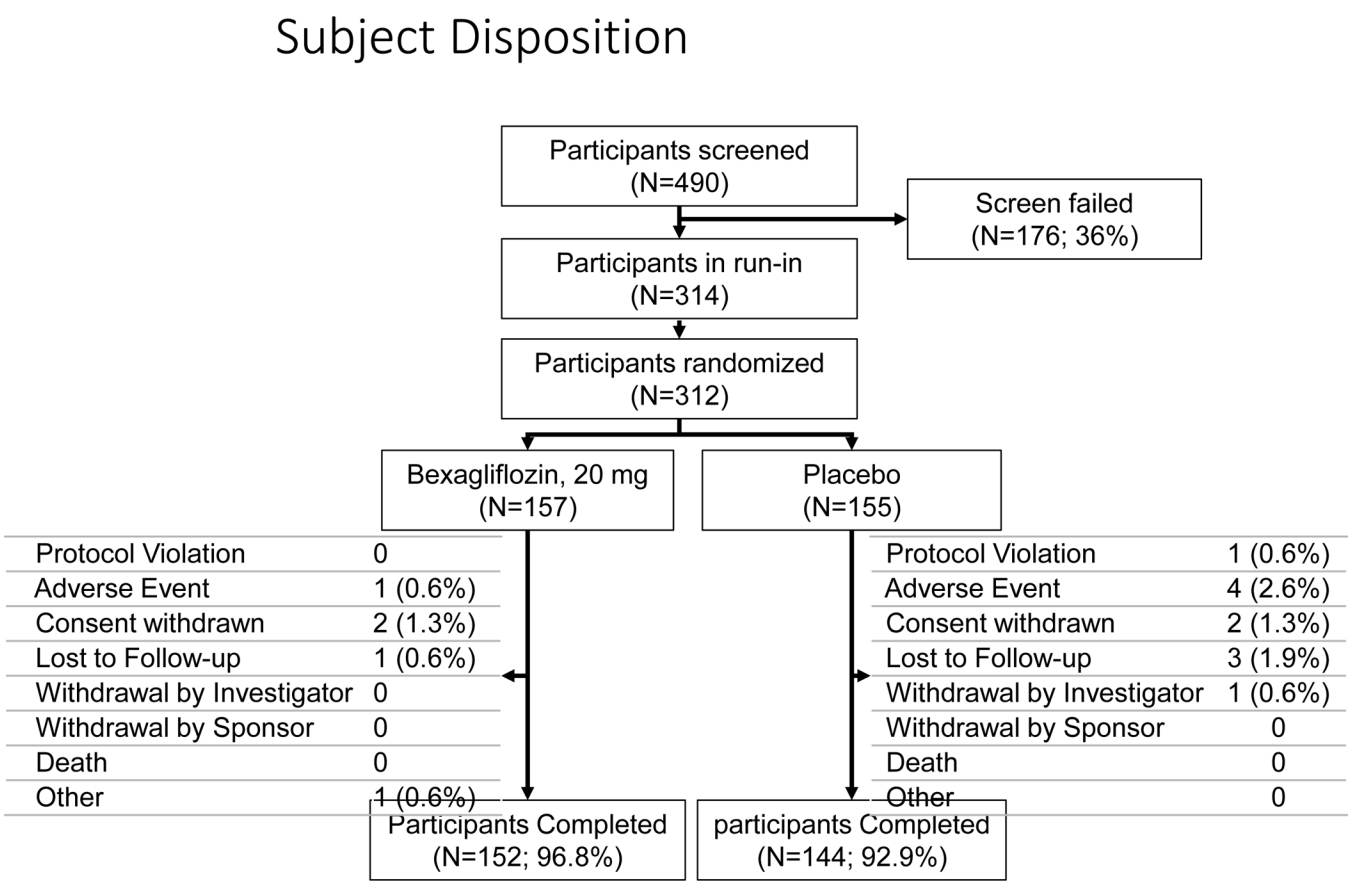


Figure 1:
CONSORT flow chart of patient disposition.

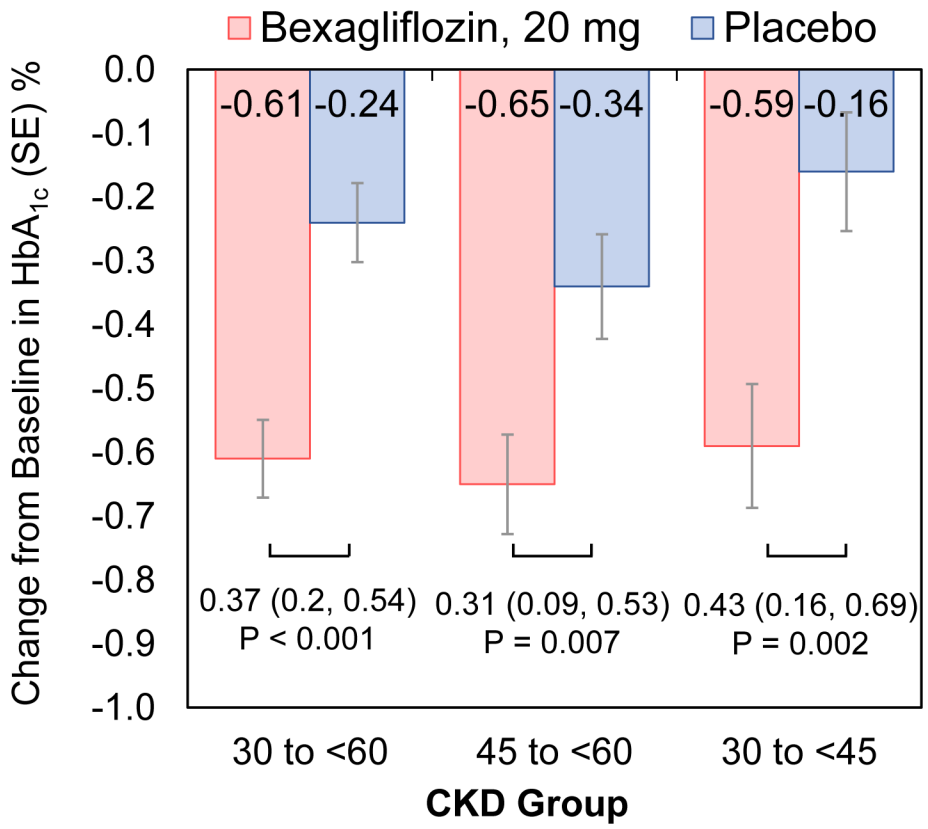


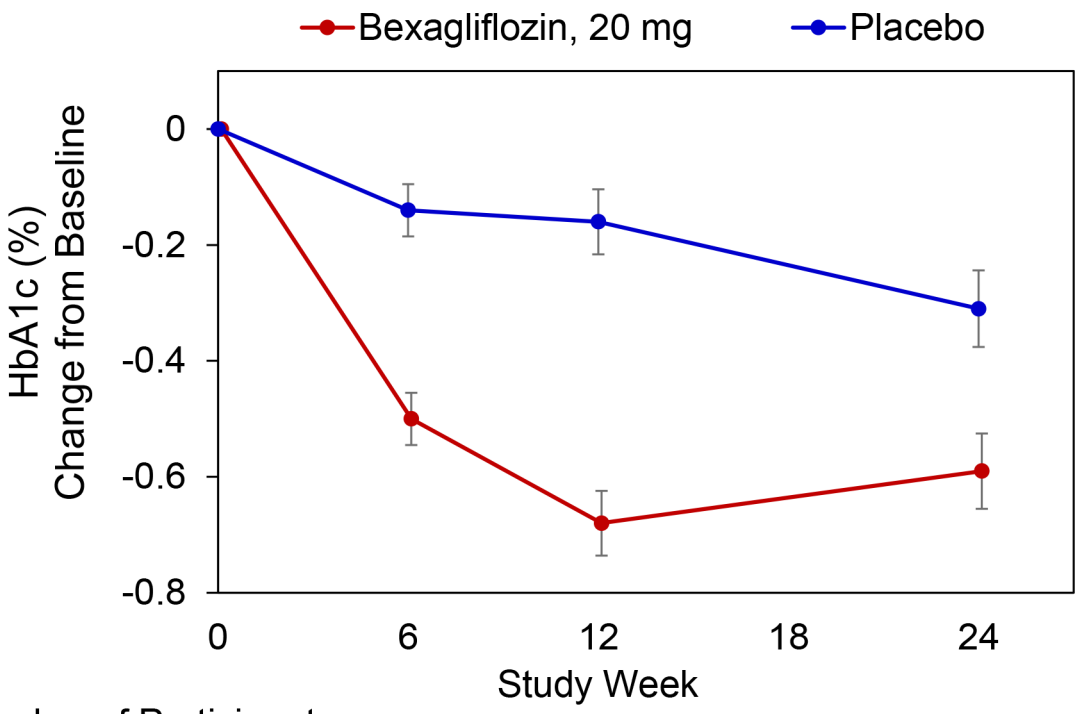
Figure 2:

Estimated mean change from baseline in hemoglobin A_{1c} by treatment and kidney function group at week 24

Key: HbA_{1c} (hemoglobin A_{1c}), SE (standard error), CKD (chronic kidney disease)

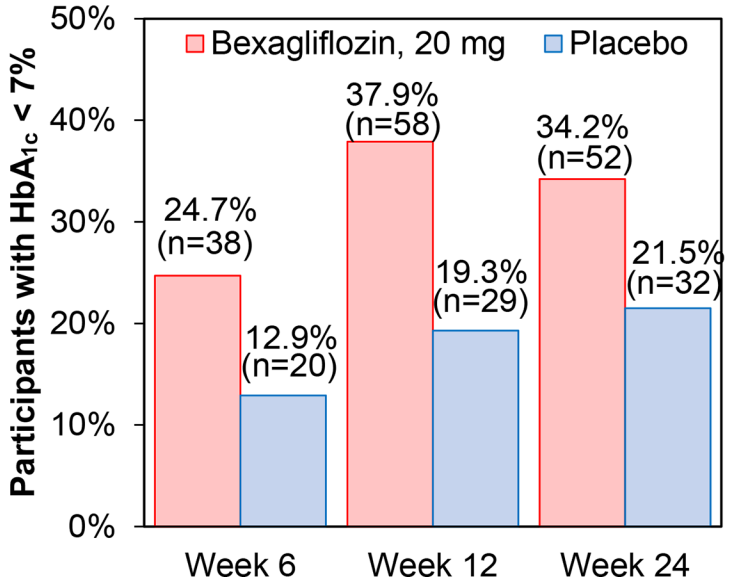
The analysis used a mixed-effects repeated measures model that included region, insulin-treated status, baseline eGFR, treatment, visit, treatment-by-visit interaction, and the baseline hemoglobin A_{1c} value as a fixed effect covariate. An unstructured covariance matrix was assumed. Data from Weeks 6, 12, and 24 were used in the model. The last post-baseline observation before rescue medication was carried forward.

A

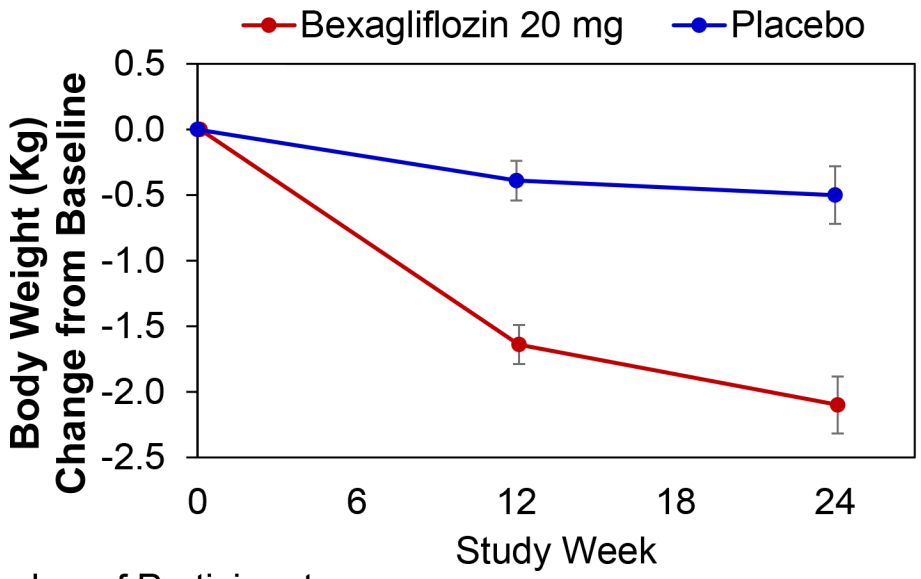


Number of Participants				
Placebo	155	155	150	149
Bexagliflozin	157	154	153	152

B Proportion of Participants Achieved $HbA_{1c} < 7\%$

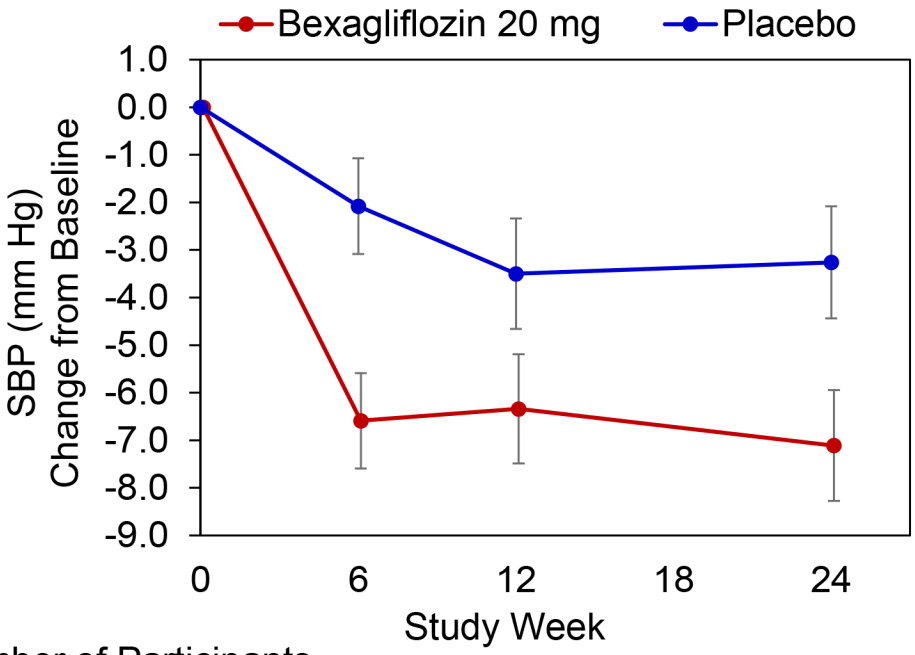


C Body Weight Change



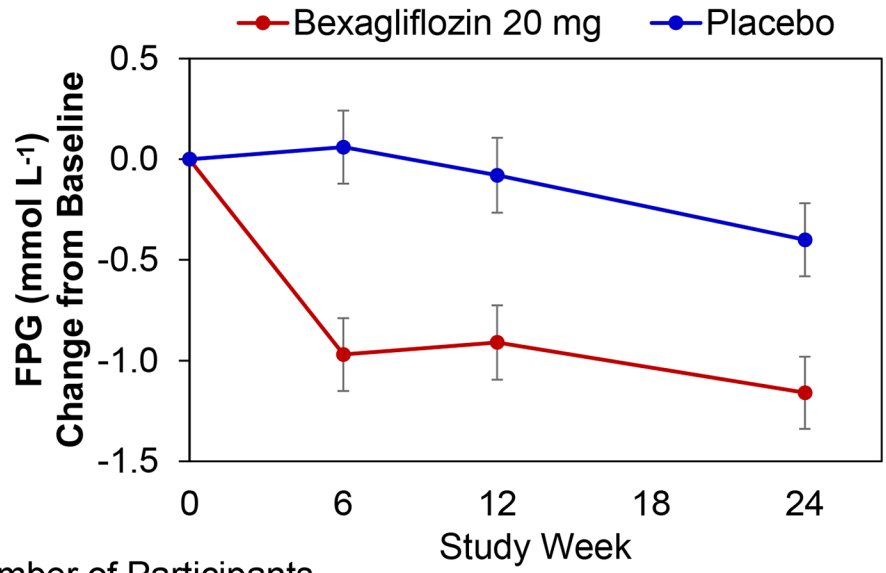
Number of Participants			
Placebo	155	150	149
Bexagliflozin	157	153	152

D SBP change from Baseline



Number of Participants				
Placebo	155	154	150	149
Bexagliflozin	157	155	153	152

E Fasting Plasma Glucose Change from Baseline



Number of Participants				
Placebo	155	154	150	149
Bexagliflozin	157	154	153	152

F Change in UACR

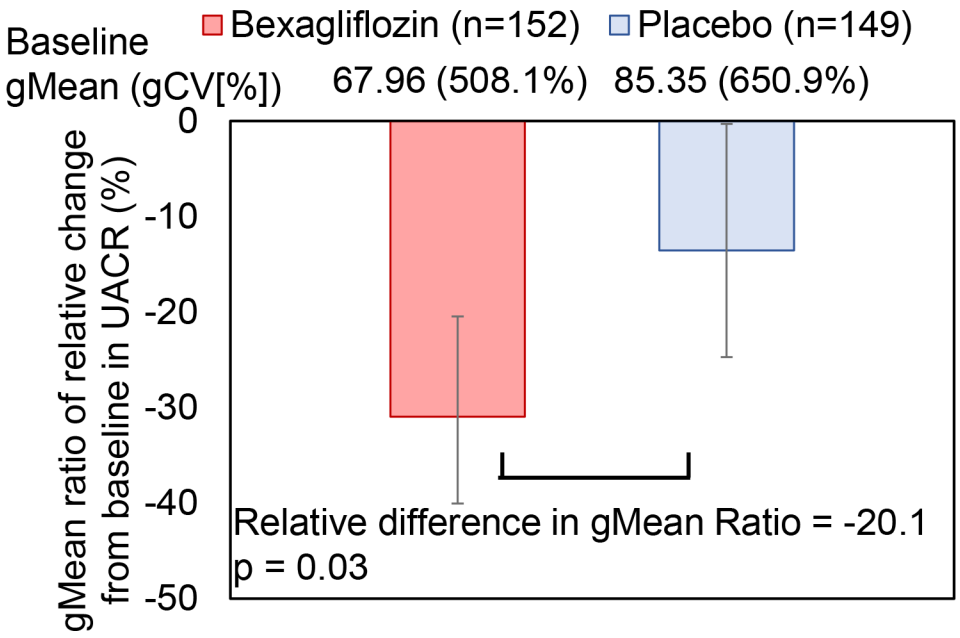


Figure 3:

Change over time of clinical outcomes by treatment group. Panels: (A) Change in hemoglobin A_{1c}, (B) Proportion of patients who achieved hemoglobin A_{1c} <7%, (C) Change in body weight, (D) Change in systolic blood pressure, (E) Change in fasting plasma glucose, and (F) Change in albuminuria (UACR) at week 24

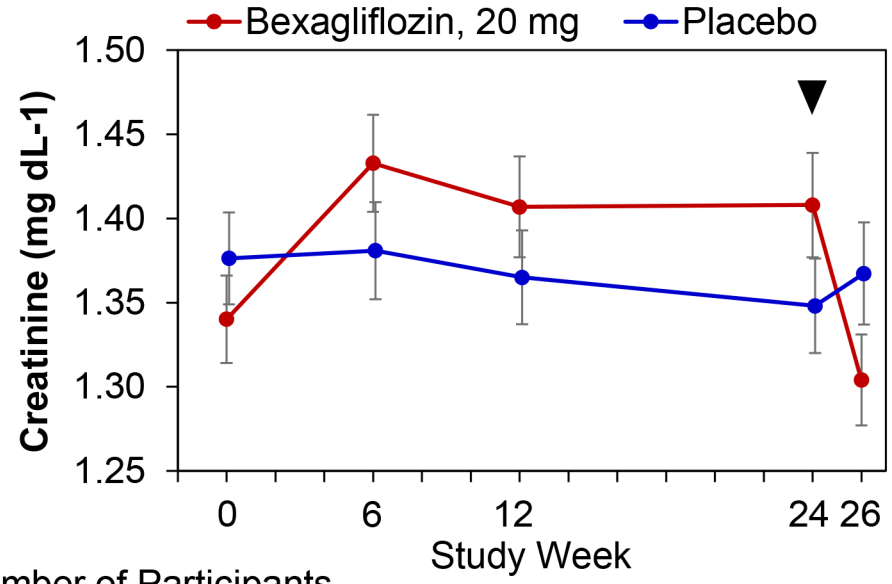
Key: HbA_{1c} (Hemoglobin A_{1c}), SBP (systolic blood pressure), FPG (fasting plasma glucose), UACR (urinary albumin-creatinine ratio), gMean (geometric mean), gCV (geometric coefficient of variation)

(A), (C), (D), (E): Estimated Mean (± SE) change from baseline in hemoglobin A_{1c} (%), body weight (kg), SBP (mm Hg), and fasting plasma glucose (mmol L^{-1}) for all subjects were summarized. The full model is a mixed-effects repeated measures analysis.

(B) Proportion of subjects with HbA1c < 7% over time was summarized using mixed-effects logistic regression for repeated measures analysis. An unstructured covariance matrix is assumed.

(F) Adjusted geometric mean ratios of relative change from baseline in UACR was calculated as (gmean of week 24 /gmean of baseline) and their 95% CIs calculated as the antilog of the least squares means and 95 % CI of change from baseline in log-transformed, are values minus 1, converted to percentage.

A Change in Creatinine



Number of Participants					
Placebo	155	154	149	147	142
Bexagliflozin	157	154	152	146	147

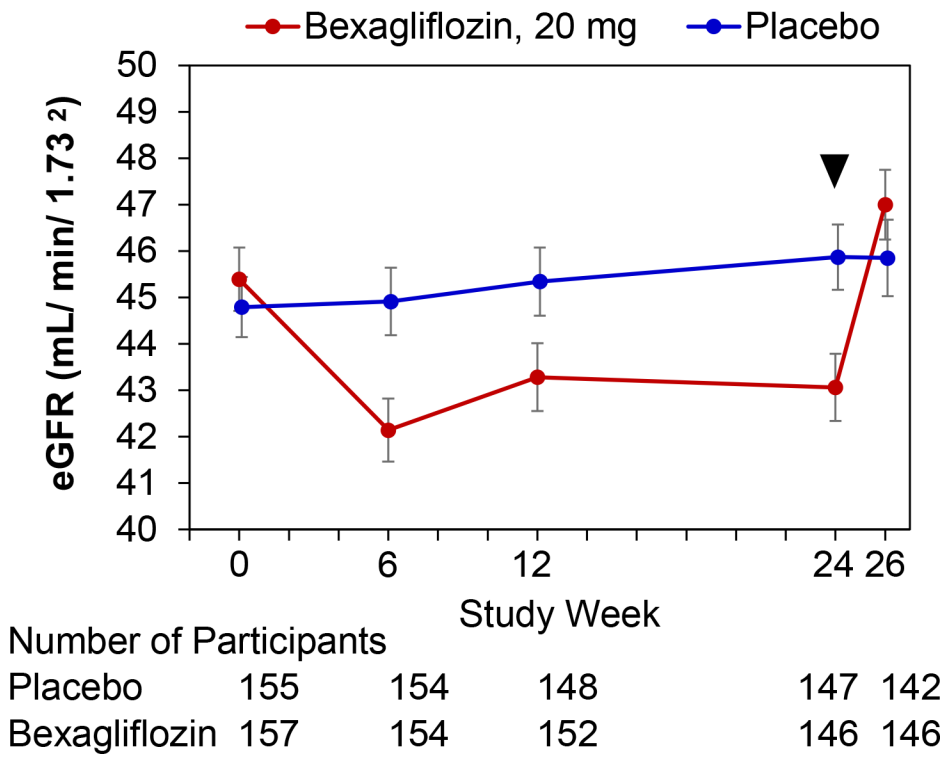


Figure 4:

Change in kidney function by treatment group.

Panels: (A) Change in creatinine, (B) Change in estimated glomerular filtration rate (eGFR). Bexagliflozin/placebo was dosed through week 24, with an arrow denoting last dose.

Table 1:

Baseline Characteristics by Randomization Status.

	Bexagliflozin, 20 mg (N=157)	Placebo (N=155)	Total (N=312)
Gender, n (%)			
Woman	65 (41.4)	51 (32.9)	116 (37.2)
Man	92 (58.6)	104 (67.1)	196 (62.8)
Age (years) Mean (SD)	69.3 (8.36)	69.9 (8.29)	69.6 (8.32)
Race, n (%)			
White	83 (52.9)	88 (56.8)	171 (54.8)
Black or African-American	9 (5.7)	6 (3.9)	15 (4.8)
Asian	61 (38.9)	59 (38.1)	120 (38.5)
Other	4 (2.5)	2 (1.3)	6 (1.9)
Country of Investigational Site			
France	12 (7.6)	16 (10.3)	28 (9.0)
Spain	34 (21.7)	31 (20.0)	65 (20.8)
USA	53 (33.8)	50 (32.3)	103 (33.0)
Japan	58 (36.9)	58 (37.4)	116 (37.2)
BMI, Mean (SD)	30.29 (5.988)	30.10 (5.774)	30.20 (5.874)
Body Weight (kg), Mean (SD)	82.90 (20.509)	82.59 (21.196)	82.75 (20.820)
SBP (mm Hg), Mean (SD)	135.9 (14.25)	137.6 (14.75)	136.8 (14.50)
Hemoglobin A_{1c} (%), Mean (SD)	8.01 (0.786)	7.95 (0.812)	7.98 (0.798)
Hemoglobin A_{1c} Group, n (%)			
7.0 to 8.5%	124 (79.0)	123 (79.4)	247 (79.2)
8.6 to 10.5%	33 (21.0)	32 (20.6)	65 (20.8)
Fasting Plasma Glucose (mmol L^{-1}), Mean (SD)	8.61 (2.525)	8.63 (2.246)	8.62 (2.387)
Subjects in eGFR Sub-group at Baseline, n (%)[1]			
Stage 3a CKD: eGFR 45 to <60	86 (54.8)	80 (51.6)	166 (53.2)
Stage 3b CKD: eGFR 30 to <45	71 (45.2)	75 (48.4)	146 (46.8)
eGFR (mL min^{-1} per 1.73 m^2), Mean (SD)	45.44 (8.565)	44.78 (8.085)	45.11(8.323)
eGFR (mL min^{-1} per 1.73 m^2), Mean (SD) Sub-group			
eGFR 45 to <60: Stage 3a CKD	51.76 (5.307)	51.27 (4.404)	51.52 (4.884)
eGFR 30 to <45: Stage 3b CKD	37.79 (4.572)	37.87 (4.629)	37.83 (4.586)
UACR Group, n (%)			
Normoalbuminuria (UACR<30 mg g^{-1})	61 (38.9)	55 (35.5)	116 (37.2)

	Bexagliflozin, 20 mg (N=157)	Placebo (N=155)	Total (N=312)
Microalbuminuria (≥ 30 and <300 mg g^{-1})	65 (41.4)	53 (34.2)	118 (37.8)
Macroalbuminuria (≥ 300 mg g^{-1})	31 (19.7)	47 (30.3)	78 (25.0)
Duration of Diabetes, Mean (SD) (years)	15.54 (9.198)	16.28 (8.977)	15.91 (9.082)
Anti-diabetic Treatment, n (%)			
Insulin	86 (54.8)	88 (56.8)	174 (55.8)
Alpha Glucosidase Inhibitors	8 (5.1)	2 (1.3)	10 (3.2)
Biguanides	57 (36.3)	73 (47.1)	130 (41.7)
Dipeptidyl Peptidase 4 Inhibitors	71 (45.2)	59 (38.1)	130 (41.7)
Glucagon-like Peptide-1 Receptor Agonists	16 (10.2)	11 (7.1)	27 (8.7)
Meglitinides	11 (7.0)	12 (7.7)	23 (7.4)
Sulfonylureas	35 (22.3)	34 (21.9)	69 (22.1)
Thiazolidinediones	13 (8.3)	10 (6.5)	23 (7.4)
Combination Oral Agents	6 (3.8)	6 (3.9)	12 (3.8)

Abbreviations: BMI = body mass index; CKD = chronic kidney disease; SBP = systolic blood pressure; SD = standard deviation; UACR = Urine Albumin-to-Creatinine Ratio. eGFR = estimated glomerular filtration rate.

Table 2:

Frequently Used Concomitant Medications

	Bexagliflozin 20 mg (N=157), n (%)	Placebo (N=155), n (%)	Total (N=312), n (%)
Any Concomitant Medication	157 (100)	154 (99.4)	311 (99.7)
Drugs Used in Diabetes	149 (94.9)	149 (96.1)	298 (95.5)
Insulin	89 (56.7)	91 (58.7)	180 (57.7)
Non-Insulin	125 (79.6)	126 (81.3)	251 (80.4)
Alpha Glucosidase Inhibitors	8 (5.1)	2 (1.3)	10 (3.2)
Biguanides	57 (36.3)	73 (47.1)	130 (41.7)
Dipeptidyl Peptidase 4 Inhibitors	71 (45.2)	61 (39.4)	132 (42.3)
Glucagon-like Peptide-1 Receptor Agonists	17 (10.8)	13 (8.4)	30 (9.6)
Meglitinides	12 (7.6)	12 (7.7)	24 (7.7)
Sulfonylureas	35 (22.3)	37 (23.9)	73 (23.1)
Thiazolidinediones	13 (8.3)	10 (6.5)	23 (7.4)
Combination Oral Agents	6 (3.8)	6 (3.9)	12 (3.8)
Lipid Modifying Agents	133 (84.7)	120 (77.4)	253 (81.1)
Agents Acting on the Renin-Angiotensin System	113 (72.0)	117 (75.5)	230 (73.7)
Antithrombotic Agents	93 (59.2)	102 (65.8)	195 (62.5)
Drugs for Gastric Acid Related Disorders	66 (42.0)	75 (48.4)	141 (45.2)
Diuretics	65 (41.4)	66 (42.6)	131 (42.0)
Calcium Channel Blockers	58 (36.9)	67 (43.2)	125 (40.1)
Beta Blocking Agents	58 (36.9)	59 (38.1)	117 (37.5)
Analgesics	55 (35.0)	48 (31.0)	103 (33.0)
Antibacterials For Systemic Use	39 (24.8)	36 (23.2)	75 (24.0)
Antigout Agents	34 (21.7)	31 (20.0)	65 (20.8)
Antiinflammatory And Antirheumatic Agents	34 (21.7)	25 (16.1)	59 (18.9)
Antianemic Agents	26 (16.6)	24 (15.5)	50 (16.0)
Urologicals	23 (14.6)	24 (15.5)	47 (15.1)
Psycholeptics	20 (12.7)	23 (14.8)	43 (13.8)

Concomitant medication is any medication that the participant had been taking prior to enrollment and was expected to continue for some portion of the trial, as well as any medication other than the investigational product that was taken during the course of the trial. Medications are coded using WHO-DD version March 2016. Anatomical Therapeutic Chemical (ATC) classes and preferred terms are presented.

Table 3:

Adverse Events by Randomization Status

	Bexagliflozin N=157, n (%)	Placebo N=155, n (%)	Total N=312, n (%)
Subjects with any TEAEs	109 (69.4)	105 (67.7)	214 (68.6)
Total reports of TEAEs	562	533	1095
Subjects with any Treatment Related AEs [1]	60 (38.2)	42 (27.1)	102 (32.7)
Subjects with any Serious Adverse Event	11 (7.0)	9 (5.8)	20 (6.4)
Subjects with any Serious Treatment Related AEs [1]	1 (0.6)	0	1 (0.3)
Subjects with AEs Leading to Dosing Discontinuation [2]	4 (2.5)	7 (4.5)	11 (3.5)
Subjects with AEs Leading to Subject Discontinuation [3]	1 (0.6)	4 (2.6)	5 (1.6)
Subjects with AE Leading to Death	0	0	0
Subjects with any TEAE of interest	74 (47.1)	59 (38.1)	133 (42.6)
Hypoglycemia	39 (24.8)	38 (24.5)	77 (24.7)
Diuretic Effects	18 (11.5)	5 (3.2)	23 (7.4)
UTI	11 (7.0)	5 (3.2)	16 (5.1)
Acute Kidney Injury	8 (5.1)	6 (3.9)	14 (4.5)
Falls and Fractures	7 (4.5)	6 (3.9)	13 (4.2)
Hypotension Episode	6 (3.8)	5 (3.2)	11 (3.5)
Malignancies	3 (1.9)	4 (2.6)	7 (2.2)
Genital Mycotic Infection	5 (3.2)	0	5 (1.6)
Rash	0	3 (1.9)	3 (1.0)
Acid-Base Disorder	1 (0.6)	0	1 (0.3)
Syncope	1 (0.6)	0	1 (0.3)
Amputation	1 (0.6)	0	1 (0.3)
MACE (adjudicated)	2 (1.3)	0	2 (0.6)

Key: TEAE=Treatment-Emergent Adverse Events; AE=Adverse Event. UTI=Urinary Tract Infection; MACE=Major Adverse Cardiac Event

[1] AEs are considered treatment-related if the causality is definite, probable, possible or missing.

[2] Permanent discontinuation of study drug due to AE.

[3] Subject withdrew due to AE.