Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD

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Rationale & 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 decreased 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, multicenter, multinational, randomized trial.

Setting & Participants: 54 sites across 4 countries. Patients with CKD stage 3a or 3b, type 2 diabetes mellitus, and hemoglobin A_{1c} level of 7.0% to 10.5% and estimated glomerular filtration rate (eGFR) of 30 to 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 change in percent hemoglobin A_{1c} from baseline to week 24. Secondary end points included changes in body weight, systolic blood pressure, albuminuria, and hemoglobin A_{1c} level stratified by CKD stage.

Results: 312 patients across 54 sites were analyzed. Bexagliflozin lowered hemoglobin A_{1c} levels by 0.37% (95% CI, 0.20%-0.54%); $P < 0.001$ compared to placebo. Patients with CKD stages 3a (eGFR, 45-<60 mL/min/1.73 m^2) and 3b (eGFR, 30-<45 mL/min/1.73 m^2) experienced reductions in hemoglobin A_{1c} levels of 0.31% ($P = 0.007$) and 0.43% ($P = 0.002$), respectively. Bexagliflozin decreased body weight (1.61 kg; $P < 0.001$), systolic blood pressure (3.8 mm Hg; $P = 0.02$), fasting plasma glucose level (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 the impact of treatment on long-term kidney disease and cardiovascular outcomes.

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

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Type 2 diabetes mellitus is one of the leading causes of morbidity and mortality worldwide.[1-3] Chronic kidney disease (CKD) develops in more than one-third of patients with diabetes.[4,5] Tight glycemic control and agents that block the renin-angiotensin-aldosterone axis can delay the progression of macrovascular and microvascular complications of diabetes.[6,7] As kidney function and estimated glomerular filtration rate (eGFR) worsen, oral antidiabetic 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} (HbA_{1c}) levels 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 HbA_{1c} levels 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 HbA_{1c} lowering comparable to other members of the SGLT2 inhibitor class in individuals with type 2 diabetes who have eGFRs > 60 mL/min/1.73 m^2 (ClinicalTrials.gov-registered trials NCT02715258, NCT02769481, and NCT02956044). The current study was intended to determine whether the glucose-lowering benefit of bexagliflozin could be extended safely into populations of patients with diabetes with lower kidney function, with particular emphasis on those with eGFR < 45 mL/min/1.73 m^2.

Methods

Study Design

Data were collected in a phase 3, multicenter, multinational, 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 stages 3a/3b,[22] and inadequate glycemic control ($HbA_{1c} \geq 7.0\%$). 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 randomly assigned 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 HbA_{1c} level (7.0%-8.5% or 8.6%-10.5%), insulin-treated or non–insulin-treated status, and stage 3a (eGFR, 45-<60 mL/min/1.73 m^2) or 3b CKD (eGFR, 30-<45 mL/min/1.73 m^2) classification. Randomization and study drug allocation were performed through 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 Massachusetts General Hospital 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. Before study initiation, the study protocol, informed consent documents, and all participant recruitment information were approved by a central institutional review board for investigational sites in the United States 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 2-group t test assuming 2-sided significance of 0.05, placebo-corrected mean reduction in HbA_{1c} level of 0.4% in the treatment arm and a standard deviation (SD) 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 participants in each CKD stage, to account for a potential loss of ~12% of participants due to early withdrawal.

Patient Population

CKD stage and eGFR were calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[23] To be eligible, a prospective participant was required to have been a diabetic man or nonpregnant woman 20 years or older, either treatment naive 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/1.73 m^2, and have body mass index (BMI) ≤ 45 kg/m^2. Disqualifying conditions included a diagnosis of type 1 diabetes mellitus, the presence of a hemoglobinopathy that could interfere with HbA_{1c} measurement, or a history of more than 1 episode of symptomatic hypoglycemia per week. Patients were also excluded if they had a history of cancer not in remission for more than 3 years; 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 prior kidney replacement therapy (dialysis or transplantation).

All participants were instructed to continue their existing antidiabetic 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 level ≥ 270 mg/dL from week 1 to week 6, ≥240 mg/dL from week 7 to week 12, or ≥200 mg/dL from week 12 to week 24 or had a fasting serum glucose level ≥ 250 mg/dL associated with severe clinical signs or symptoms of hyperglycemia, the prescription of additional medication, dictated by the medical judgment of the site principal investigator, was permitted.

Outcomes

The primary end point was change in percent HbA_{1c} level from baseline to week 24. Additional end points included change from baseline to week 24 of fasting plasma glucose level, body weight, blood pressure, and urinary albumin-creatinine ratio (UACR), as well as change in percent HbA_{1c} level within the subgroups defined by stage 3a or 3b CKD at baseline. The proportion of patients who achieved an HbA_{1c} level < 7% or of patients with baseline BMI ≥ 25 kg/m^2 who achieved ≥5% reduction in 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 diary for review during study visits. Suspected acute kidney injury (AKI) was addressed through a standard monitoring protocol using creatinine-based KDIGO definitions (Fig S1).[24] Urinary tract infection was defined as a urinalysis positive for leukocyte esterase and/or nitrites plus symptoms and/or a culture of 10^5 colony-forming units of 1 bacterial species. All suspected major adverse cardiac events (MACE) were forwarded to a cardiovascular end point committee for blinded adjudication based on prospectively defined event definitions.

Statistical Analysis

Effectiveness analyses were performed in an intention-to-treat manner. The primary outcome of change in percent HbA_{1c} level from baseline to week 24 was analyzed using a mixed-effect model repeated-measures 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 baseline HbA_{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 HbA_{1c} values after rescue medication. Secondary continuous outcomes were analyzed using all available data at each week. Similar to the primary outcome, mixed-effect model repeated-measures analysis (with additional baseline value of the outcome as a fixed effect covariate) was used. Proportion of $HbA_{1c} < 7\%$ was analyzed using mixed-effects logistic regression for repeated measures assuming an unstructured covariance matrix, using the same covariates as the primary outcome.

UACR data were log transformed before analysis. Change in log-transformed UACR from baseline to week 24 was analyzed using an ANCOVA model. The fixed effect included region, baseline HbA_{1c} value, insulin-treated status, baseline eGFR, and treatment group. Log-transformed baseline UACR value was used as a covariate as well. The adjusted geometric mean ratio of relative change from baseline in UACR and the 95% confidence interval (CI) by treatment group were calculated as the antilog of the least squares mean and 95% CI of log-transformed values, converted to percentages. The effect of group assignment on early withdrawal was assessed using Kaplan-Meier analysis.

All patients who took at least 1 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 (SAS Institute).

Results

Demographics

A total of 312 patients (157 in the bexagliflozin arm and 155 in the placebo arm) were included in the final analysis (Fig 1). At baseline, 166 participants had CKD stage 3a and 146 had CKD stage 3b. Normal to mildly increased

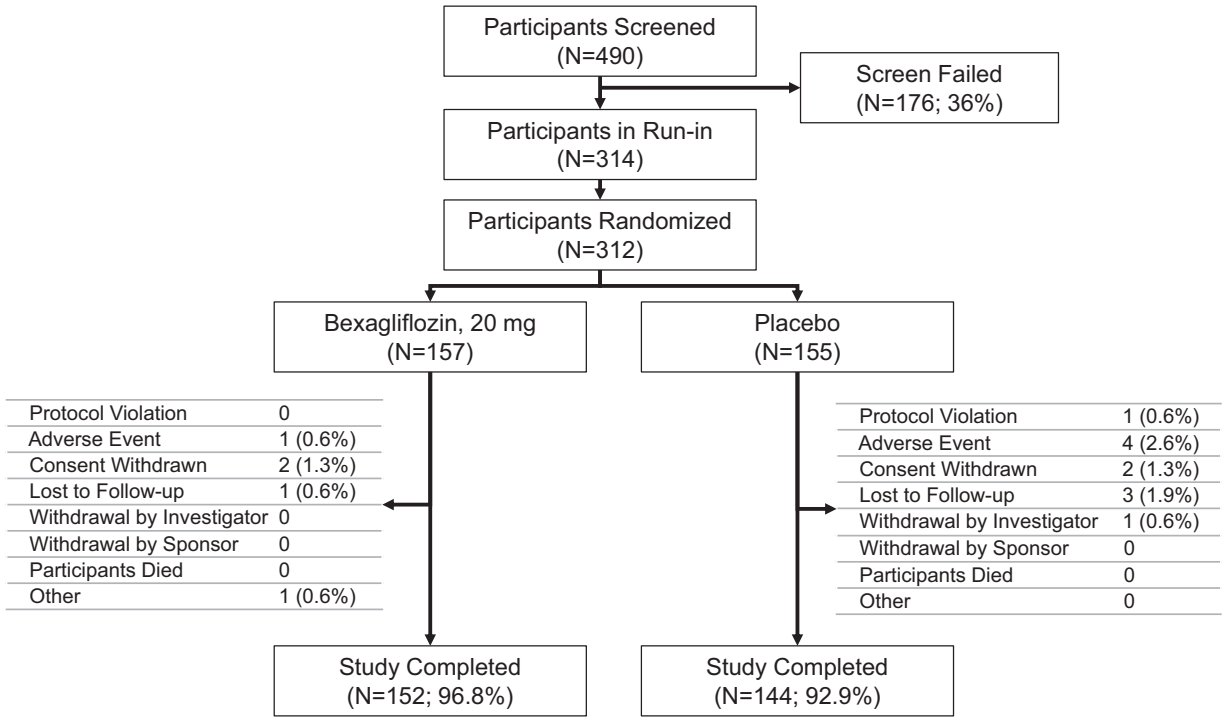

Figure 1. Flow chart of patient disposition.

albuminuria (UACR < 30 mg/g) was observed in 116 of 312 (37%) patients; moderately increased albuminuria (UACR, 30-299 mg/g), in 118 of 312 (38%); and severely increased albuminuria (UACR ≥ 300 mg/g), in 78 of 312 (25%). Mean duration of diabetes as assessed by medical history was nearly 16 years, and mean baseline HbA_{1c} level was 7.98% ± 0.798% (SD). Approximately 56% of patients were prescribed insulin as part of their regimen for glycemic control. Mean age was 69.6 ± 8.32 years, 116 of 312 (37%) were women, and 171 of 312 (55%) were self-described as white or Caucasian. Mean baseline BMI was 30.2 ± 5.87 kg/m^2, and mean systolic blood pressure (SBP) was 137 ± 14.5 mm Hg. Baseline characteristics, including variables used to stratify randomization (Table 1), and early withdrawal rates (Fig S2) were similar between treatment groups. Frequently used concomitant baseline medications are presented in Table 2.

Table 1. Baseline Characteristics by Randomization Status

	Bexagliflozin 20 mg (n = 157)	Placebo (n = 155)	Total (N = 312)
Male sex	92 (58.6%)	104 (67.1%)	196 (62.8%)
Age, y	69.3 ± 8.36	69.9 ± 8.29	69.6 ± 8.32
Race			
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%)
United States	53 (33.8%)	50 (32.3%)	103 (33.0%)
Japan	58 (36.9%)	58 (37.4%)	116 (37.2%)
BMI, kg/m^2	30.29 ± 5.988	30.10 ± 5.774	30.20 ± 5.874
Body weight, kg	82.90 ± 20.509	82.59 ± 21.196	82.75 ± 20.820
SBP, mm Hg	135.9 ± 14.25	137.6 ± 14.75	136.8 ± 14.50
Hemoglobin A_{1c}, %	8.01 ± 0.786	7.95 ± 0.812	7.98 ± 0.798
Hemoglobin A_{1c} group			
7.0%-8.5%	124 (79.0%)	123 (79.4%)	247 (79.2%)
8.6%-10.5%	33 (21.0%)	32 (20.6%)	65 (20.8%)
Fasting plasma glucose, mmol/L	8.61 ± 2.525	8.63 ± 2.246	8.62 ± 2.387
No. in eGFR subgroup at baseline			
Stage 3a CKD: eGFR 45-<60	86 (54.8%)	80 (51.6%)	166 (53.2%)
Stage 3b CKD: eGFR 30-<45	71 (45.2%)	75 (48.4%)	146 (46.8%)
eGFR, mL/min/1.73 m^2	45.44 ± 8.565	44.78 ± 8.085	45.11 ± 8.323
eGFR in subgroups, mL/min/1.73 m^2			
Stage 3a CKD	51.76 ± 5.307	51.27 ± 4.404	51.52 ± 4.884
Stage 3b CKD	37.79 ± 4.572	37.87 ± 4.629	37.83 ± 4.586
UACR group			
UACR < 30 mg/g	61 (38.9%)	55 (35.5%)	116 (37.2%)
UACR 30-<300 mg/g	65 (41.4%)	53 (34.2%)	118 (37.8%)
UACR ≥ 300 mg/g	31 (19.7%)	47 (30.3%)	78 (25.0%)
Duration of diabetes, y	15.54 ± 9.198	16.28 ± 8.977	15.91 ± 9.082
Antidiabetic treatment			
Insulin	86 (54.8%)	88 (56.8%)	174 (55.8%)
α-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%)

Note: Values expressed as mean ± standard deviation or number (percent).
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio.

Table 2. Frequently Used Concomitant Medications

	Bexagliflozin 20 mg (n = 157)	Placebo (n = 155)	Total (N = 312)
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%)
Noninsulin	125 (79.6%)	126 (81.3%)	251 (80.4%)
α-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%)
β-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%)
Anti-inflammatory 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%)

Note: Concomitant medication is any medication that the participant had been taking before 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 the World Health Organization Drug Dictionary, version March 2016. Anatomical Therapeutic Chemical classes and preferred terms are presented.

Change in HbA_{1c} from Baseline to Week 24

Participants treated with bexagliflozin had a mean reduction in HbA_{1c} level 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%; $P < 0.001$; Fig 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, participants treated with bexagliflozin had a mean reduction in HbA_{1c} level of 0.59%, whereas those treated with placebo had a mean reduction of 0.31%, a placebo-corrected reduction in HbA_{1c} level of 0.28% (95% CI, 0.10%-0.46%; $P = 0.003$).

Participants with stage 3a CKD who were treated with bexagliflozin had a mean reduction in HbA_{1c} level 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 who were treated with bexagliflozin had a mean reduction in HbA_{1c} level 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%; $P = 0.002$; Fig 2). The magnitudes of the reduction in HbA_{1c} level 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 End Points at 24 Weeks

Change in HbA_{1c} level over time is reported in Figure 3A. At 24 weeks, bexagliflozin increased the proportion of patients who achieved HbA_{1c} levels < 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 (Fig 3B). Bexagliflozin treatment over 24 weeks resulted in an average 1.61 (95% CI, 1.00-2.22)-kg body weight reduction compared to placebo ($P < 0.001$). The body weight reduction was consistent throughout the 24-week treatment period (Fig 3C). More bexagliflozin-treated patients with baseline BMI ≥ 25 kg/m had a ≥5% decrease in body weight compared to placebo (19% vs 9%, $P = 0.03$). Bexagliflozin decreased SBP by 3.8 [95% CI, 0.6-7.1] mm Hg ($P = 0.02$; Fig 3D) and decreased fasting plasma glucose levels by 0.76 [95% CI, 0.26-1.26] mmol/L ($P = 0.003$; Fig 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

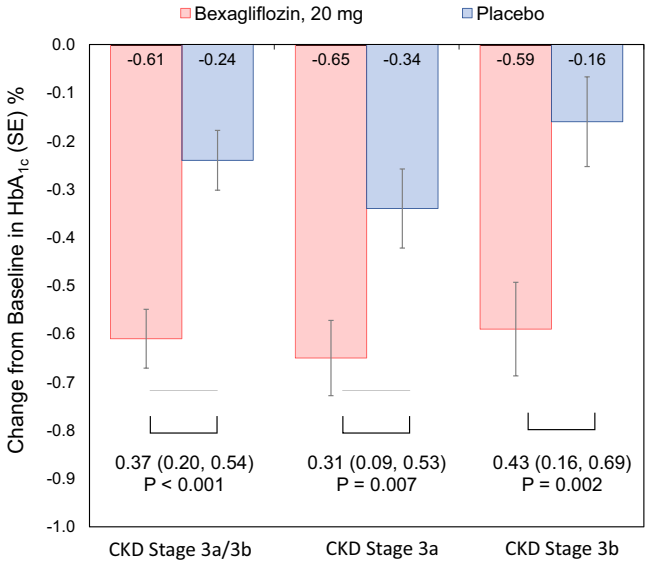

Figure 2. Estimated mean change from baseline in hemoglobin A_{1c} (HbA_{1c}) level by treatment and kidney function group at week 24. The analysis used a mixed-effects repeated-measures model that included region, insulin-treated status, baseline estimated glomerular filtration rate, treatment, visit, treatment-by-visit interaction, and baseline HbA_{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 postbaseline observation before rescue medication was carried forward. Abbreviations: CKD, chronic kidney disease; SE, standard error.

(2.1 mm Hg). At week 24, those treated with bexagliflozin had a geometric mean ratio reduction in UACR of 20.1% (95% CI, 2.52%-34.56%; P = 0.03; Fig 3F).

Safety End Points

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 1 AKI. Stage 2/3 AKI or need for kidney replacement therapy was not reported. AKI events did not lead to withdrawals. New malignancies were uncommon (3 [2%] bexagliflozin vs 4 [3%] placebo). There were 5 genital mycotic infections in the bexagliflozin arm, 1 amputation in the bexagliflozin arm, and 7 falls/fractures in the bexagliflozin arm (compared to 6 in the placebo arm). There were 2 adjudicated MACE, both in the bexagliflozin arm. There were no cases of diabetic ketoacidosis 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 was observed in participants assigned to the bexagliflozin arm throughout the treatment period. An increase in creatinine level of 0.08 mg/dL and a decrease in eGFR of 2.41 mL/min/1.73 m^2 were observed at week 24. Two weeks after the end of the treatment period, eGFR for the bexagliflozin arm had increased to near-baseline values (net increase from baseline, 1.37 mL/min/1.73 m^2).

Discussion

Bexagliflozin is a novel member of the SGLT2 inhibitor class currently in phase 3 development. In earlier studies of patients with eGFRs > 60 mL/min/1.73 m^2, bexagliflozin demonstrated good safety and efficacy, with HbA_{1c} level reductions comparable to those of the already approved members of the class (ClinicalTrials.gov registration numbers NCT02715258, NCT02769481, and NCT02956044).

In the current study, we aimed to examine the impact of bexagliflozin in patients with substantially decreased kidney function and determine whether HbA_{1c}-lowering efficacy was preserved despite this reducted 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 HbA_{1c} levels. The effect was more marked in the subpopulation with eGFR between 30 and <45 mL/min/1.73 m^2 (CKD stage 3b), an outcome that was ascribed to a larger placebo effect on HbA_{1c} in participants with an eGFR between 45 and 60 mL/min/1.73 m^2 (CKD stage 3a). Similar positive short-term effects on body weight, systolic blood pressure, albuminuria, and eGFR have been reported for other drugs in the class.[13,15] However, to our knowledge, no previous study has reported a statistically significant HbA_{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 HbA_{1c} levels observed for participants 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 data of the current study, data from studies of other SGLT2 inhibitors in participants with CKD stages 3a/3b have failed to show HbA_{1c}-lowering

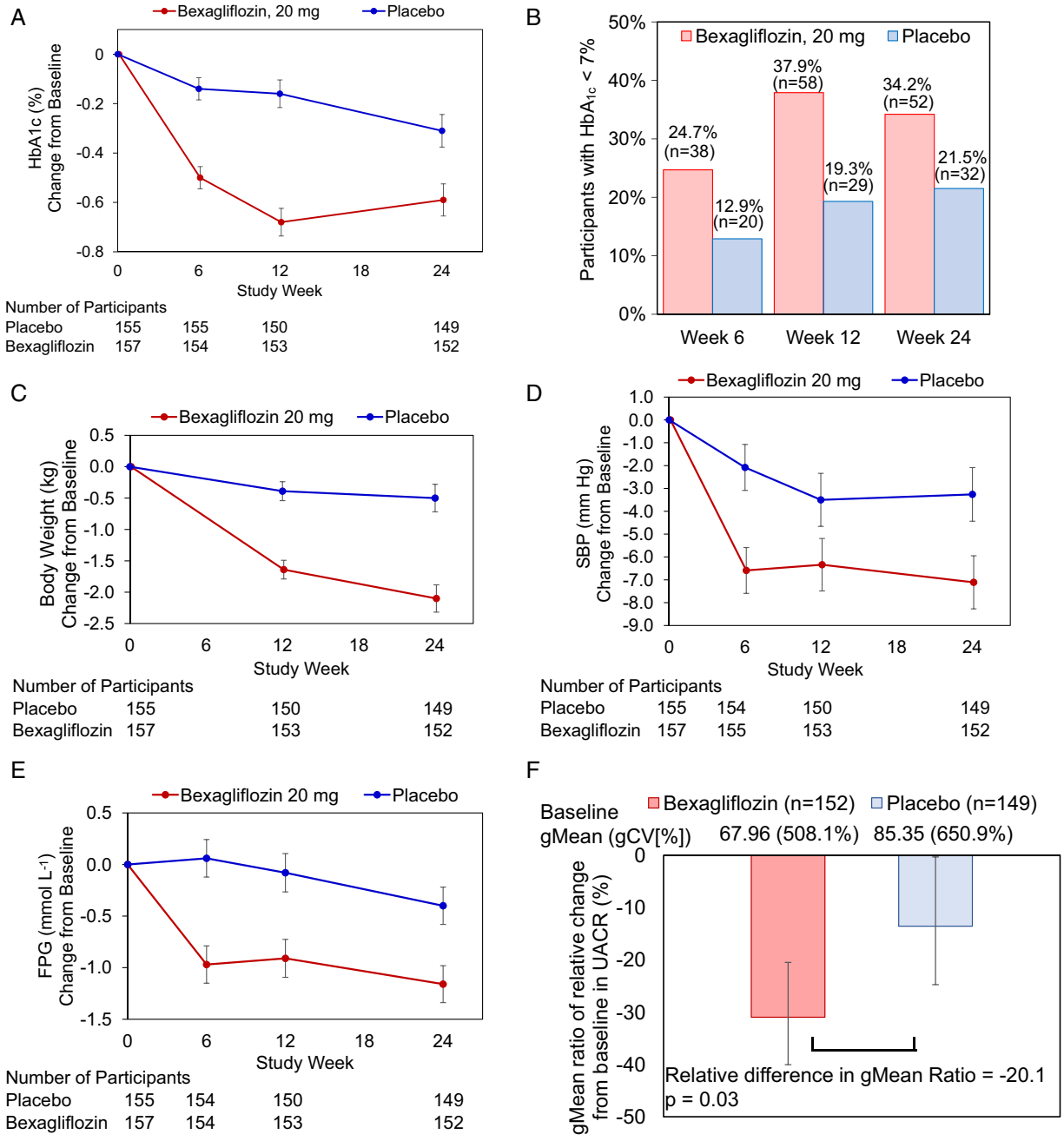

Figure 3. Change over time in clinical outcomes of (A) hemoglobin A_{1c} (HbA_{1c}) level, (B) proportion of patients who achieved HbA_{1c} level < 7%, (C) body weight, (D) systolic blood pressure (SBP), (E) fasting plasma glucose (FPG) level, and (F) albuminuria (urine albumin-creatinine ratio [UACR]) at week 24 by treatment group. (A, C-E) Estimated mean (± standard error) change from baseline in HbA_{1c} level (%), body weight (kg), SBP (mm Hg), and FPG level (mmol/L) for all participants. The full model is a mixed-effects repeated measures analysis. (B) Proportion of participants with HbA_{1c} level < 7% over time summarized using mixed-effects logistic regression for repeated-measures analysis. An unstructured covariance matrix is assumed. (F) Adjusted geometric mean (gMean) ratios of relative change from baseline in UACR was calculated as gMean of week 24 divided by gMean of baseline and their 95% confidence intervals (CIs) calculated as the antilog of the least squares mean values and 95% CI of change from baseline in log-transformed, are values minus 1, converted to percentage. Abbreviation: gCV, geometric coefficient of variation.

effects.[19,20] Further study is needed to determine the properties of SGLT2 inhibitors that allow for persistent effectiveness in lowering HbA_{1c} levels 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]

Table 3. Adverse Events by Randomization Status

	Bexagliflozin (n = 157)	Placebo (n = 155)	Total (N = 312)
Participants with any TEAE	109 (69.4%)	105 (67.7%)	214 (68.6%)
Total no. of reports of TEAEs	562	533	1,095
Participants with any treatment-related AE[a]	60 (38.2%)	42 (27.1%)	102 (32.7%)
Participants with any serious AE	11 (7.0%)	9 (5.8%)	20 (6.4%)
Participants with any serious treatment-related AE[a]	1 (0.6%)	0 (0%)	1 (0.3%)
Participants with AEs leading to dosing discontinuation[b]	4 (2.5%)	7 (4.5%)	11 (3.5%)
Participants with AEs leading to participant discontinuation[c]	1 (0.6%)	4 (2.6%)	5 (1.6%)
Participants with AE leading to death	0 (0%)	0 (0%)	0 (0%)
Participants 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 (0%)	5 (1.6%)
Rash	0 (0%)	3 (1.9%)	3 (1.0%)
Acid-base disorder	1 (0.6%)	0 (0%)	1 (0.3%)
Syncope	1 (0.6%)	0 (0%)	1 (0.3%)
Amputation	1 (0.6%)	0 (0%)	1 (0.3%)
MACE (adjudicated)	2 (1.3%)	0 (0%)	2 (0.6%)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; MACE, major adverse cardiac event; UTI, urinary tract infection.
[a]AEs are considered treatment-related if the causality is definite, probable, possible, or missing.
[b]Permanent discontinuation of study drug due to AE.
[c]Participant withdrew due to AE.

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.

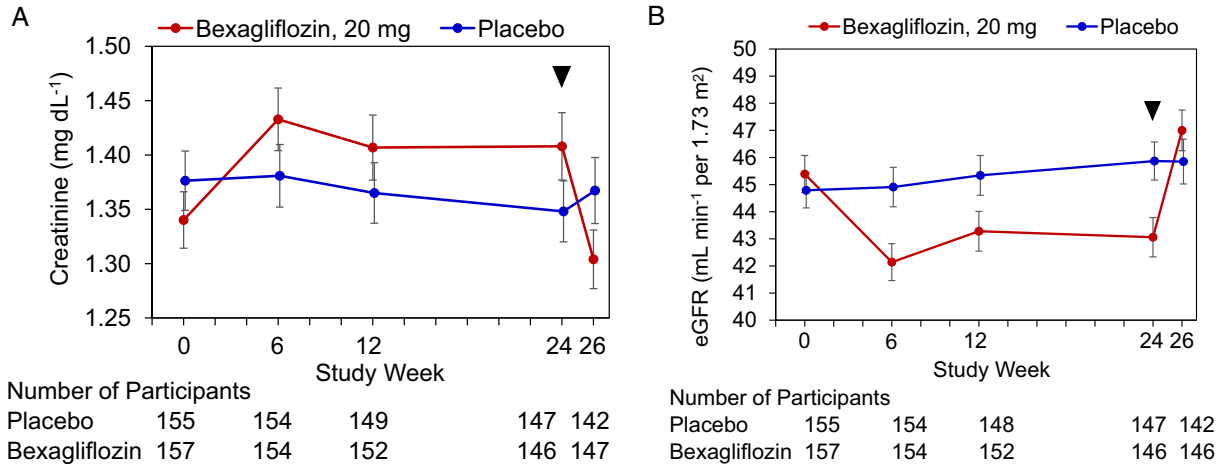

Figure 4. Change in kidney function by treatment group for (A) creatinine level and (B) estimated glomerular filtration rate (eGFR). Bexagliflozin/placebo was dosed through week 24, with arrow denoting last dose.

A plausible mechanism for eGFR reduction invokes tubuloglomerular feedback mediated by 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 in eGFR has been documented in studies of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers that have since been incorporated into 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.

Reductions 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] Although outside the direct scope of this trial, long-term studies 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 that SGLT2 inhibitors have demonstrated toward 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 SGLT2 inhibition. The findings of mild volume depletion, weight loss, and reduction in SBP reported here are consistent with the expected osmotic diuresis and caloric wasting induced by SGLT2 inhibition. Similarly, the elevation in serum creatinine concentration, described as AKI, is consistent with the pharmacology of the SGLT2 inhibitor class and the expected effect of natriuresis on GFR. Other serious adverse events were rare and included 2 MACE in the bexagliflozin arm, 1 amputation in the bexagliflozin arm, and 7 falls/fractures in the bexagliflozin arm (compared to 6 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 vasoprotective effects. Larger trials evaluating cardiovascular outcomes of bexagliflozin are ongoing.

Patients with diabetes and mild to moderate kidney failure have fewer treatment options compared with those with preserved kidney function. Bexagliflozin appears to be beneficial for the intensification of glycemic control for patients in this vulnerable condition. Additional therapeutic advantages of bexagliflozin include reductions in body weight, SBP, 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

Supplementary File (PDF)

Figure S1: AKI staging and flow chart of kidney function monitoring plan.

Figure S2: Time to study drug discontinuation by treatment assignment.

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