Clinical trial results:
A Phase 3, Randomized, Double-blind, Active-controlled Study to Evaluate the Effects of Bexagliflozin versus Glimepiride in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control by Metformin

Summary

EudraCT number	2016-002013-21
Trial protocol	ES PL
Global end of trial date	19 June 2019

Results information

Result version number	v1 (current)
This version publication date	09 September 2021
First version publication date	09 September 2021

Trial information

Trial identification

Sponsor protocol code	THR-1442-C-480

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02769481
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Theracos Sub, LLC
Sponsor organisation address	225 Cedar Hill Road, Suite 200, Marlborough, United States, 01752
Public contact	Geoffrey Walford, M.D., Theracos Sub, LLC, 001 6176434986, gwalford@partners.org
Scientific contact	Geoffrey Walford, M.D., Theracos Sub, LLC, 001 6176434986, gwalford@partners.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2018
Global end of trial reached?	Yes
Global end of trial date	19 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective is to demonstrate that bexagliflozin is non-inferior to glimepiride by evaluating the treatment effect on hemoglobin A1c (HbA1c) reduction at week 60 in subjects whose type 2 diabetes mellitus (T2DM) is inadequately controlled by metformin.

Protection of trial subjects:

Subjects were advised to continue daily, fasting SMBG measurements and contact the clinic if any fasting SMBG is >= 270 mg/dL from baseline to Week 6, >= 240 mg/dL after Week 6 to Week 12, or >=200 mg/dL after Week 12. Hyperglycemia were monitored by FPG at scheduled visits. Hyperglycemia was managed first with diet and exercise counseling. If this failed, medical therapy was intesified at the investigator's discretion for the well-being of the subject, including up-titration of glimepiride dose and addition of rescue medication. The investigator had the ability to provide rescue treatment with any approved medication for diabetes that is not otherwise contraindicated, with the exception of SGLT2 inhibitor, sulfonylurea and metformin. The study drug could be discontinued at the discretion of the investigator if symptomatic hypoglycemia occurs in subjects not prescribed rescue medication. Other safety monitoring activities included assessments of vital signs, 12-lead ECG, physical examinations, urinalysis, blood chemistry, hematology, adverse events and concomitant medication use. An independent Data and Safety Monitoring Board (DSMB) will monitor overall safety information during the bexagliflozin development program. An independent adjudication committee was established to review all potential cardiovascular events and all potential diabetic ketoacidosis events.

Background therapy:

The study will enroll T2DM patients who are treated with only metformin or who are treated with metformin and one additional oral hypoglycemic agent. All subjects must have taken metformin at a stable dose of >= 1500 mg/day for >= 8 weeks prior to screening. Study subjects will continue receiving open-labeled metformin background medication during the entire study at a stable dose and frequency.

Evidence for comparator:

Metformin is the most commonly prescribed oral hypoglycemic agent and is recommended as the first-line therapy for the treatment for T2DM. Subjects with T2DM often require multiple anti-diabetic medications for glycemic control. Sulfonylureas are often prescribed with metformin as a combination therapy for treating T2DM. Sulfonylureas can reduce the risk of long-term microvascular complications via effective glycemic control. Common side effects of sulfonylureas include weight gain and increased risk of hypoglycemia. Glimepiride is one of the most commonly prescribed second-generation sulfonylureas. Therefore, it is an appropriate active comparator in the subject population studied during the treatment period (96 weeks).

Actual start date of recruitment	10 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 153

Country: Number of subjects enrolled	Spain: 88
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	United States: 128
Worldwide total number of subjects	426
EEA total number of subjects	298

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	296
From 65 to 84 years	128
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study population included ~420 subjects whose T2DM was inadequately controlled by metformin and who met all of the inclusion criteria and none of the exclusion criteria. Clinical sites in the North America and Europe participated and recruited subjects. Clinical sites in other continents were also allowed to participate in the trial.

Pre-assignment

Screening details:

Subjects who were treated with metformin + OHA will undergo a 6-week wash-out of the non-metformin OHA to exclude the potential influence of other OHAs on the study outcomes. Subjects continued to take metformin at the same dose and frequency. Subjects in the glimepiride arm started at 2 mg daily and underwent dose up-titration.

Pre-assignment period milestones

Number of subjects started	812[1]
Intermediate milestone: Number of subjects	Entered Run-In: 539
Intermediate milestone: Number of subjects	Randomized: 427
Number of subjects completed	426

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen fails prior to Run-In: 273
Reason: Number of subjects	Screen fails prior to randomization: 112
Reason: Number of subjects	Excluded due to duplicate enrollment: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects (812) who started the pre-assignment period included those who signed the informed consent form. However, only 426 subjects were included in the intention-to-treat analysis set. Others were excluded due to screen fails prior to Run-in and screen fails prior to randomization. The worldwide number enrolled in the trial (426) included all those who were successfully randomized, except for one randomized subject who was excluded due to duplicate enrollment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Bexagliflozin

Arm description:

Subjects will receive a bexagliflozin tablet, 20 mg, once daily for the duration of the study. Subjects will continue taking metformin and receive placebo for glimepiride for the duration of the study. Glimepiride capsules are inactive and their appearance are made to match the active comparator.

Arm type	Experimental

Investigational medicinal product name	Bexagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bexagliflozin tablet, 20 mg, is to be administered once daily to subjects in the active arm.

Arm title	Glimepiride

Arm description:

Subjects received a glimepiride capsule at different dose of 2, 4 or 6 mg, once daily for the duration of the study. Subjects continued to take metformin and receive placebo for bexagliflozin for the duration of the study. The placebo tablets are inactive and their appearances are made to match the active comparator.

Arm type	Active comparator
Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Glimepiride capsules, 2, 4, or 6 mg or placebo, were taken once daily with the first meal. Subjects will receive the starting dose of glimepiride at 2 mg or placebo at week 0 (V6). At weeks 2, 4, and 6, subjects will return to the clinic for the assessment of glimepiride dose up-titration and safety evaluation. If a subject had >= 50% of documented fasting SMBG measurements > 110 mg/dL and no severe or documented symptomatic hypoglycemia events in the preceding 2 weeks, glimepiride dose was increased to the next level. During weeks 0 to 6, each up-titration visit was conducted no more than 2 weeks after the prior visit. If subjects did not meet up-titration glycemic criteria, subjects continued glimepiride at the same dose prescribed to them at the previous visit. Subjects assigned to receive placebo glimepiride received mock titrations at Week 2, 4, and 6. No dose changes in glimepiride occurred after 6 weeks of treatment.

Number of subjects in period 1	Bexagliflozin	Glimepiride
Started	213	213
Study complete at Week 60	193	192
Completed	180	177
Not completed	33	36
Consent withdrawn by subject	14	16
Physician decision	-	1
Adverse event, non-fatal	3	6
Death	-	1
Terminated by sponsor	1	-
Undefined	4	1
Lost to follow-up	9	9
Entry criteria not met	1	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Bexagliflozin
Reporting group description:	
Subjects will receive a bexagliflozin tablet, 20 mg, once daily for the duration of the study. Subjects will continue taking metformin and receive placebo for glimepiride for the duration of the study. Glimepiride capsules are inactive and their appearance are made to match the active comparator.	
Reporting group title	Glimepiride
Reporting group description:	
Subjects received a glimepiride capsule at different dose of 2, 4 or 6 mg, once daily for the duration of the study. Subjects continued to take metformin and receive placebo for bexagliflozin for the duration of the study. The placebo tablets are inactive and their appearances are made to match the active comparator.	

Reporting group values	Bexagliflozin	Glimepiride	Total
Number of subjects	213	213	426
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	59.5	59.7	
standard deviation	± 9.06	± 10.35	-
Gender categorical			
Units: Subjects			
Female	95	83	178
Male	118	130	248
Ethnicity			
Units: Subjects			
Hispanic or Latino	46	47	93
Not Hispanic or Latino	167	166	333
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	9	4	13
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	5	4	9
White	198	204	402

More than one race	0	0	0
Unknown or Not Reported	0	1	1
Region of Enrollment Units: Subjects			
United States	65	63	128
Poland	74	79	153
Germany	28	29	57
Spain	46	42	88
Systolic Blood Pressure Categories Units: Subjects			
< 140 mm Hg	135	138	273
> 140 mm Hg	78	75	153
Height Units: cm			
arithmetic mean	166.7	167.1	
standard deviation	± 11.13	± 9.53	-
Body Weight at Baseline Units: kg			
arithmetic mean	87.95	90.23	
standard deviation	± 19.122	± 17.616	-
BMI Units: kg/m^2			
arithmetic mean	31.45	32.22	
standard deviation	± 4.861	± 5.155	-
Systolic Blood Pressure at Baseline Units: mm Hg			
arithmetic mean	133.3	134.2	
standard deviation	± 14.88	± 14.37	-

End points

End points reporting groups

Reporting group title	Bexagliflozin

Reporting group description:

Subjects will receive a bexagliflozin tablet, 20 mg, once daily for the duration of the study. Subjects will continue taking metformin and receive placebo for glimepiride for the duration of the study. Glimepiride capsules are inactive and their appearance are made to match the active comparator.

Reporting group title	Glimepiride

Reporting group description:

Subjects received a glimepiride capsule at different dose of 2, 4 or 6 mg, once daily for the duration of the study. Subjects continued to take metformin and receive placebo for bexagliflozin for the duration of the study. The placebo tablets are inactive and their appearances are made to match the active comparator.

Primary: Change from Baseline in HbA1c at Week 60

End point title	Change from Baseline in HbA1c at Week 60

End point description:

The primary objective is to demonstrate that bexagliflozin is non-inferior to glimepiride by evaluating the treatment effect on HbA1c reduction at week 60 in subjects whose T2DM is inadequately controlled by metformin. The least square mean (LSM) change from baseline to Week 60 was analyzed using a mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA).

End point type	Primary

End point timeframe:

Baseline to Week 60

End point values	Bexagliflozin	Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	191		
Units: Percentage of glycated hemoglobin				
least squares mean (standard error)	-0.70 (± 0.058)	-0.66 (± 0.058)		

Statistical analyses

Statistical analysis title	Comparing bexagliflozin to glimepiride

Statistical analysis description:

The primary objective is to demonstrate that bexagliflozin is non-inferior to glimepiride by evaluating the treatment effect on HbA1c reduction at week 60 in subjects whose T2DM is inadequately controlled by metformin. The least square mean (LSM) change from baseline to Week 60 was analyzed using a mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA).

Comparison groups	Bexagliflozin v Glimepiride

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.11

Notes:

[1] - The null hypothesis for the primary endpoint was that the change in HbA1c from baseline to week 60 in the bexagliflozin arm would be greater than change in the glimepiride arm by greater than 0.35%. A 95% CI was calculated to estimate the range of values in which the treatment difference was likely to lie. If the 95% CI fell below the specified non inferiority margin of 0.35%, the non inferiority of bexagliflozin to glimepiride would be demonstrated and the null hypothesis would be rejected.

Secondary: Change from Baseline in Body Weight at Week 60 for Subjects with Baseline BMI ≥ 25 kg/m2

End point title	Change from Baseline in Body Weight at Week 60 for Subjects with Baseline BMI ≥ 25 kg/m2

End point description:

Least squares (LS) mean treatment difference between the bexagliflozin group and placebo group in the change of body weight in subjects with baseline BMI ≥ 25 kg/m2 at week 60 is analyzed using ANCOVA.

End point type	Secondary

End point timeframe:

Baseline to Week 60

End point values	Bexagliflozin	Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	182		
Units: kg				
least squares mean (standard error)	-3.71 (± 0.285)	0.59 (± 0.284)		

Statistical analyses

Statistical analysis title	Comparing bexagliflozin to glimepiride

Statistical analysis description:

Least squares (LS) mean treatment difference between the bexagliflozin group and placebo group in the change of body weight in subjects with baseline BMI ≥ 25 kg/m^2 at week 60 is analyzed using ANCOVA.

Comparison groups	Bexagliflozin v Glimepiride

Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed-effects repeated measures
Parameter estimate	Difference of LS Means
Point estimate	-4.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	-3.52

Notes:

[2] - P-value is based on one sided statistical tests using a 0.025 level of significance.

Secondary: Change From Baseline in Systolic Blood Pressure (SBP) at Week 60 for Subjects With Baseline SBP ≥ 140 mmHg

End point title	Change From Baseline in Systolic Blood Pressure (SBP) at Week 60 for Subjects With Baseline SBP ≥ 140 mmHg

End point description:

Least squares (LS) mean treatment difference between the bexagliflozin group and placebo group in the change of SBP in subjects with baseline SBP ≥ 140 mmHg at week 60 is analyzed using ANCOVA.

End point type	Secondary

End point timeframe:

Baseline to Week 60

End point values	Bexagliflozin	Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	68		
Units: mm Hg				
least squares mean (standard error)	-13.48 (± 1.404)	-6.95 (± 1.460)		

Statistical analyses

Statistical analysis title	Comparing bexagliflozin to glimepiride

Statistical analysis description:

Least squares (LS) mean treatment difference between the bexagliflozin group and placebo group in the change of SBP in subjects with baseline SBP ≥ 140 mmHg at week 60 is analyzed using ANCOVA.

Comparison groups	Bexagliflozin v Glimepiride
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [3]
Method	Mixed-effects repeated measures
Parameter estimate	Difference of LS Means
Point estimate	-6.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.56
upper limit	-2.51

Notes:

[3] - P-value is based on one sided statistical tests using a 0.025 level of significance.

Secondary: Difference in Proportion of Subjects With ≥ 1 Severe or Documented Symptomatic Hypoglycemia Events Over 96 Weeks

End point title	Difference in Proportion of Subjects With ≥ 1 Severe or Documented Symptomatic Hypoglycemia Events Over 96 Weeks

End point description:

The difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events in the bexagliflozin group compared with glimepiride group over 96 weeks is analyzed using a logistic regression model. The full model included region, baseline HbA1c value, background treatment status (metformin or metformin + OHA), eGFR at baseline ≥ 90 or < 90 mL min 1 per 1.73 m^2), treatment as a fixed effect covariate.

End point type	Secondary

End point timeframe:

During the 96 week treatment period

End point values	Bexagliflozin	Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	212		
Units: Proportion of participants				
number (confidence interval 95%)	0.02 (0.01 to 0.05)	0.15 (0.10 to 0.22)		

Statistical analyses

Statistical analysis title	Comparing bexagliflozin to glimepiride

Statistical analysis description:

The difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events in the bexagliflozin group compared with glimepiride group over 96 weeks is analyzed using a logistic regression model. The full model included region, baseline HbA1c value, background treatment status (metformin or metformin + OHA), eGFR at baseline ≥ 90 or < 90 mL min 1 per 1.73 m^2), treatment as a fixed effect covariate.

Comparison groups	Bexagliflozin v Glimepiride
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.28

Notes:

[4] - P-value is based on one sided statistical tests using a 0.025 level of significance.

Secondary: Superiority of Bexagliflozin Over Glimepiride in HbA1c Reduction at Week 60

End point title	Superiority of Bexagliflozin Over Glimepiride in HbA1c Reduction at Week 60

End point description:

Superiority of bexagliflozin over glimepiride in HbA1c reduction from baseline to week 60 will be declared if the upper bound of 95% CI is less than 0.

End point type	Secondary

End point timeframe:

Baseline to Week 60

End point values	Bexagliflozin	Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	191		
Units: Percentage of glycated hemoglobin				
least squares mean (standard error)	-0.70 (± 0.058)	-0.66 (± 0.058)		

Statistical analyses

Statistical analysis title	Comparing bexagliflozin to glimepiride

Statistical analysis description:

Superiority of bexagliflozin over glimepiride in HbA1c reduction from baseline to week 60 will be declared if the upper bound of 95% CI is less than 0.

Comparison groups	Bexagliflozin v Glimepiride
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of LS Means
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.11

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data was collected from Week -8 (V2, wash-out) to Week 98 (V18, follow-up).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Bexagliflozin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Bexagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 213 (11.74%)	26 / 213 (12.21%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal adenocarcinoma			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Genital hemorrhage			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 213 (0.94%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischemia			
subjects affected / exposed	1 / 213 (0.47%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 213 (0.47%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitation			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischemic attack			
subjects affected / exposed	1 / 213 (0.47%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic stroke			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ectropion			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Entropion			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Faecaloma			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 213 (0.47%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecchymosis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 213 (0.00%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder disorder			

subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 213 (0.47%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 213 (0.94%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Bexagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 213 (46.01%)	112 / 213 (52.58%)	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	6 / 213 (2.82%)	16 / 213 (7.51%)	
occurrences (all)	6	16	
Arthralgia			
subjects affected / exposed	13 / 213 (6.10%)	4 / 213 (1.88%)	
occurrences (all)	13	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	29 / 213 (13.62%)	29 / 213 (13.62%)	
occurrences (all)	29	29	
Urinary Tract Infection			
subjects affected / exposed	25 / 213 (11.74%)	10 / 213 (4.69%)	
occurrences (all)	25	10	
Bronchitis			
subjects affected / exposed	14 / 213 (6.57%)	16 / 213 (7.51%)	
occurrences (all)	14	16	
Metabolism and nutrition disorders			
Hypoglycemia			
subjects affected / exposed	36 / 213 (16.90%)	71 / 213 (33.33%)	
occurrences (all)	36	71	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 213 (0.47%)	17 / 213 (7.98%)	
occurrences (all)	1	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2016	1. The Sponsor Contact and Medical Monitor were changed. 2. Language regarding persistent hyperglycemia and up-titration visits was updated to include all scheduled visits instead of only V8 and V9. 3. Amputation was added to the list of AESI following a potential safety issue of amputation identified from another SGLT2 inhibitor canagliflozin in 2016. 4. Language regarding OHAs was revised to prevent confusion regarding the number of oral medications that were allowed to be taken. 5. Metformin was included in the safe use of OHAs to ensure subject safety as subjects were required to be on a stable background of metformin to participate in the study. 6. Correction of error in protocol to maintain consistency with synopsis inclusion criteria: adhere to the investigational product administration requirements evidenced by missing no more than 2 doses of run-in medications. 7. Modification to exclusion criteria to include metformin to ensure subject safety as subjects are required to be on a stable background of metformin to participate in the study. 8. Modification to include any increase in LFTs >= 3 times the ULN be automatically considered as a laboratory AE unless diagnosed otherwise by the investigator. Any increase in LFTs that are < 3 times could also be considered as an AE if the change was determined to be clinically significant by investigators. 9. Languages regarding any amputation and related adverse events and procedures were added in Section 6.14.14. Investigators were reminded to counsel appropriate foot care to avoid cuts or sores and to treat even minor cuts/sores to prevent infection and ulceration. Special attention to be paid for patients who were also receiving thiazide diuretics as these have been shown to increase the risk of amputation in diabetes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported