Clinical trial results:
A double blind placebo controlled study to evaluate the effect of bexagliflozin tablets on hemoglobin A1c in patients with type 2 diabetes mellitus and moderate renal impairment

Summary

EudraCT number	2016-002580-34
Trial protocol	ES
Global end of trial date	11 January 2018

Results information

Result version number	v1 (current)
This version publication date	23 August 2019
First version publication date	23 August 2019
Summary attachment (see zip file)	THR-1442-C-448 Synopsis (thr-1442-c-448-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	THR-1442-C-448

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02836873
WHO universal trial number (UTN)	-
Other trial identifiers	EMA: UPI number 498543

Notes:

Sponsors

Sponsor organisation name	Theracos Sub, LLC
Sponsor organisation address	225 Cedar Hill St, Marlborough, MA, United States, 01752
Public contact	Clinical Trial Project Management, Translational Medicine Group, 001 5086884221, info@theracos.com
Scientific contact	Clinical Trial Project Management, Translational Medicine Group, 001 6176430699, info@theracos.com

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	20 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2018
Global end of trial reached?	Yes
Global end of trial date	11 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the efficacy of bexagliflozin on lowering HbA1c in patients with type 2 diabetes mellitus and moderate renal impairment.

Protection of trial subjects:

During the run-in period, subjects received diet and exercise counseling and instructions on contacting the clinic in the event of hypoglycemia, hyperglycemia, or symptoms that may suggest ketoacidosis. Subjects were trained to use the glucometer and record any events in the glycemic control diary. Health status of subjects were reviewed regularly by review of adverse events (AEs), concomitant medications use, vital signs, electrocardiograms (ECGs), and results from physical examinations and blood and urine specimen collections. At every visit, including the phone interviews, participants were queried regarding AEs and information on all events that potentially represent diabetic ketoacidosis (DKA) or major adverse cardiovascular events. Following the exit visit, subjects were advised to see their primary physician to
undergo treatment to control their diabetes and cardiovascular conditions.
Subjects with hyperglycemia based on blood glucose levels during the treatment period received, at the Investigator's discretion, approved anti-diabetic medication. In addition, adjustment by the investigator to the pre-screening anti-diabetic therapies were recommended if hypoglycemia occurred.
Evaluation and management of subjects with and at risk for acute kidney injury (AKI) were performed during the study period based on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline in 2012.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Japan: 116
Country: Number of subjects enrolled	United States: 103
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	France: 28
Worldwide total number of subjects	312
EEA total number of subjects	93

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)	77
From 65 to 84 years	232
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Recruitment occurred between 23 Sep 2016 and 14 Jun 2017. Subjects were recruited from France, Spain, Japan and the United States.

Pre-assignment

Screening details:

Screening criteria include male or non-pregnant female ≥ 20 years of age with diagnosis of T2DM with HbA1c between 7.0% and 10.5% and stage 3 CKD (eGFR ≥ 30 and< 60 mL min^-1 per 1.73 m^2. All eligible subjects entered a one week run-in period. Subjects compliant in taking run-in medication and had stable eGFR were eligible for randomization.

Period 1

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

Blinding implementation details:

Placebo tablets were produced to match bexagliflozin tablets, 20 mg. Laboratory test urine glucose values were blinded to study team.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bexagliflozin

Arm description:

Each subject will receive a bexagliflozin tablet, 20 mg, once daily for the duration of the study.

Arm type	Experimental
Investigational medicinal product name	Bexagliflozin tablets, 20 mg
Investigational medicinal product code	
Other name	EGT0001442, EGT0001474
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet for once daily oral administration

Arm title	Placebo

Arm description:

Each subject will receive a placebo (inactive) tablet once daily for the duration of the study.

Arm type	Placebo
Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Inactive tablet to match the active bexagliflozin tablet, 20 mg, for once daily oral administration

Number of subjects in period 1	Bexagliflozin	Placebo
Started	157	155
Completed	152	144
Not completed	5	11
Consent withdrawn by subject	2	2
Physician decision	-	1
Adverse event, non-fatal	1	4
Subject moved	1	-
Lost to follow-up	1	3
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Bexagliflozin
Reporting group description:	
Each subject will receive a bexagliflozin tablet, 20 mg, once daily for the duration of the study.	
Reporting group title	Placebo
Reporting group description:	
Each subject will receive a placebo (inactive) tablet once daily for the duration of the study.	

Reporting group values	Bexagliflozin	Placebo	Total
Number of subjects	157	155	312
Age categorical Units: Subjects			
Adults (18-64 years)			0
Age continuous Units: years			
arithmetic mean	69.3	69.9	
standard deviation	± 8.36	± 8.29	-
Gender categorical Units: Subjects			
Female	65	51	116
Male	92	104	196
Race Units: Subjects			
White	83	88	171
Black or African-American	9	6	15
Asian	61	59	120
American Indian/Alaskan Native	0	0	0
Native Hawaiian/Other Pacific Islander	2	0	2
Other	2	2	4
Ethnicity Units: Subjects			
Hispanic or Latino	7	17	24
Not Hispanic or Latino	149	138	287
Not Reported	1	0	1
Country of Investigational Site Units: Subjects			
France	12	16	28
Spain	34	31	65
Japan	58	58	116
USA	53	50	103
SBP Units: mm Hg			
arithmetic mean	135.9	137.6	
standard deviation	± 14.25	± 14.75	-
HbA1c Units: Percent			

arithmetic mean	8.01	7.95	
standard deviation	± 0.786	± 0.812	-
FPG			
Units: mmol/L			
arithmetic mean	8.61	8.63	
standard deviation	± 2.525	± 2.246	-
eGFR			
Units: mL min-1 per 1.73 m2			
arithmetic mean	45.44	44.78	
standard deviation	± 8.565	± 8.085	-
UACR			
Units: mg/g			
arithmetic mean	355.3	510.0	
standard deviation	± 776.77	± 1094.46	-
Duration of Diabetes			
Units: Years			
arithmetic mean	15.54	16.28	
standard deviation	± 9.198	± 8.977	-
Duration of CKD			
Units: years			
arithmetic mean	4.92	5.02	
standard deviation	± 3.926	± 4.99	-
Body Weight			
Units: kg			
arithmetic mean	82.90	82.59	
standard deviation	± 20.509	± 21.196	-

End points

End points reporting groups

Reporting group title	Bexagliflozin
Reporting group description:	
Each subject will receive a bexagliflozin tablet, 20 mg, once daily for the duration of the study.	
Reporting group title	Placebo
Reporting group description:	
Each subject will receive a placebo (inactive) tablet once daily for the duration of the study.	

Primary: Change from Baseline in HbA1c at Week 24

End point title	Change from Baseline in HbA1c at Week 24
End point description:	
End point type	Primary
End point timeframe:	
24 weeks	

End point values	Bexagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	155		
Units: Percent				
least squares mean (confidence interval 95%)	-0.59 (-0.72 to -0.46)	-0.31 (-0.44 to -0.18)		

Statistical analyses

Statistical analysis title	Difference of LS Means from Placebo
Statistical analysis description:	
Model-adjusted using mixed effects repeated measures analysis	
Comparison groups	Bexagliflozin v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0026
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.1

Secondary: Change in Body Weight from Baseline to Week 24 in Subjects with BMI >= 25 kg/m2

End point title	Change in Body Weight from Baseline to Week 24 in Subjects with BMI >= 25 kg/m2

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Bexagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[1]	122[2]		
Units: kg				
least squares mean (confidence interval 95%)	-2.31 (-2.84 to -1.79)	-0.55 (-1.08 to -0.02)		

Notes:

[1] - Subject with BMI >= 25 kg/m2

[2] - Subject with BMI >= 25 kg/m2

Statistical analyses

Statistical analysis title	Difference of LS Means from Placebo
Comparison groups	Bexagliflozin v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-1.03

Secondary: Change in SBP from Baseline to Week 24 in Subject with Baseline SBP >= 130 mm Hg

End point title	Change in SBP from Baseline to Week 24 in Subject with Baseline SBP >= 130 mm Hg

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Bexagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107[3]	113[4]		
Units: mm Hg				
least squares mean (confidence interval 95%)	-10.14 (-13.05 to -7.23)	-7.51 (-10.39 to -4.63)		

Notes:

[3] - Subject with baseline SBP >= 130 mm Hg

[4] - Subjects with baseline SBP >= 130 mm Hg

Statistical analyses

Statistical analysis title	Difference of LS Means from Placebo
Comparison groups	Bexagliflozin v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2035
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	1.44

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 weeks	
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	11 / 157 (7.01%)	9 / 155 (5.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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			
Carotid artery disease			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
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			
Arthralgia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (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			
Hypoglycaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Bexagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 157 (69.43%)	105 / 155 (67.74%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	6 / 157 (3.82%)	3 / 155 (1.94%)	
occurrences (all)	7	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 157 (3.18%)	3 / 155 (1.94%)	
occurrences (all)	5	3	
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 157 (3.18%)	3 / 155 (1.94%)	
occurrences (all)	5	3	
Hypertension			
subjects affected / exposed	5 / 157 (3.18%)	0 / 155 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 157 (4.46%)	11 / 155 (7.10%)	
occurrences (all)	7	12	
Constipation			
subjects affected / exposed	3 / 157 (1.91%)	6 / 155 (3.87%)	
occurrences (all)	3	6	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	11 / 157 (7.01%)	4 / 155 (2.58%)	
occurrences (all)	14	4	
Acute kidney injury			
subjects affected / exposed	8 / 157 (5.10%)	6 / 155 (3.87%)	
occurrences (all)	9	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 157 (5.10%)	5 / 155 (3.23%)	
occurrences (all)	11	5	
Back pain			

subjects affected / exposed	5 / 157 (3.18%)	3 / 155 (1.94%)	
occurrences (all)	5	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 157 (7.01%)	12 / 155 (7.74%)	
occurrences (all)	12	18	
Urinary tract infection			
subjects affected / exposed	9 / 157 (5.73%)	5 / 155 (3.23%)	
occurrences (all)	10	5	
Bronchitis			
subjects affected / exposed	7 / 157 (4.46%)	2 / 155 (1.29%)	
occurrences (all)	7	2	
Sinusitis			
subjects affected / exposed	5 / 157 (3.18%)	0 / 155 (0.00%)	
occurrences (all)	5	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	39 / 157 (24.84%)	38 / 155 (24.52%)	
occurrences (all)	239	249	
Polydipsia			
subjects affected / exposed	7 / 157 (4.46%)	2 / 155 (1.29%)	
occurrences (all)	10	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31101403