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

Summary

EudraCT number	2017-000420-95
Trial protocol	HU CZ ES
Global end of trial date	18 July 2018

Results information

Result version number	v1 (current)
This version publication date	05 September 2021
First version publication date	05 September 2021
Summary attachment (see zip file)	THR-1442-C-423 Synopsis (thr-1442-c-423-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	THR-1442-C-423

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03115112
WHO universal trial number (UTN)	-
Other trial identifiers	EMA: UPI number 498543

Notes:

Sponsors

Sponsor organisation name	Theracos
Sponsor organisation address	225 Cedar Hill St., Marlborough, MA, United States, 01752
Public contact	Clinical Trial Project Management, Translational Medicine Group - MGH, 001 6177264236, info@theracos.com
Scientific contact	Clinical Trial Project Management, Translational Medicine Group - MGH, 001 6177264236, 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	Interim
Date of interim/final analysis	31 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2018
Global end of trial reached?	Yes
Global end of trial date	18 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this trial is to demonstrate that bexagliflozin is non-inferior to sitagliptin by evaluating the treatment effect on HbA1c reduction at week 24 in subjects with inadequately controlled T2DM on metformin.

Protection of trial subjects:

General safety assessments included treatment emergent AE (TEAE), 12-lead electrocardiograms parameters, physical examinations, vital signs including orthostatic blood pressure, urinalysis, blood chemistry, hematology, estimated glomerular filtration rate (eGFR) and use of concomitant medications. During placebo run-in period, subjects were instructed to measure self-monitored blood glucose (SMBG) in fasted state. During the treatment period, study subjects were instructed to measure the fasting SMBG daily. Any approved medication for diabetes that was not contraindicated was permissible to be used as a rescue medication for hyperglycemia, if it continued after diet and exercise counseling. If hypoglycemia occurred in any subjects, either metformin or rescue medication was to be reduced. If recurrent symptomatic hypoglycemia continued, the study drug was to be discontinued and the subject to be withdrawn from the study.

Background therapy:

At the time of screening, all subjects were on metformin at a stable dose of ≥ 1500 mg per day for ≥ 8 weeks and have received diet and exercise counseling. Study subjects continued to receive open-labeled metformin during the entire study at a stable dose and frequency.

Evidence for comparator:

The comparator, sitagliptin, is a DPP-4 inhibitor, which prevents the degradation of incretin. Incretin increases insulin production and reduces hepatic glucose production, leading to better glucose metabolism. DDP-4 inhibitors are considered second-line therapy for T2DM in clinical practice and are often prescribed with metformin as a combination therapy for treating T2DM. DDP-4 inhibitors can reduce the risk of long-term microvascular complications via effective glycemic control and do not have weight gain or increased hypoglycemic risk compared with placebo.

Actual start date of recruitment	12 October 2017
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: 114
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Hungary: 56
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Japan: 62

Worldwide total number of subjects	384
EEA total number of subjects	286

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)	259
From 65 to 84 years	125
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 384 eligible subjects were enrolled in the study. Subjects were recruited from Czech Republic, Hungary, Poland, Spain, USA and Japan.

Pre-assignment

Screening details:

Subjects with inadequately controlled T2DM with HbA1c between 7.0% and 11%, while taking metformin at ≥ 1500 mg per day were enrolled. All eligible subjects had 1 week run-in period. A change in treatment for hypertension or dyslipidemia during the run-in period was considered as screen failure.

Pre-assignment period milestones

Number of subjects started	563[1]
Intermediate milestone: Number of subjects	Entered Run-in: 395
Intermediate milestone: Number of subjects	Randomized: 386
Number of subjects completed	384

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Failure at screening: 168
Reason: Number of subjects	Failure during run-in: 9
Reason: Number of subjects	Excluded due to site closure for GCP violation: 2

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 who started the pre-assignment period included those who signed the informed consent form. The worldwide number enrolled in the trial included all those who were successfully randomized, except for two subjects where the clinical sites were closed due to GCP violation.

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:

Bexagliflozin tablets, 20 mg, and placebo were blue caplet-shaped, film-coated tablets. Sitagliptin tablets, 100 mg, and placebo were beige, round, film-coated tablets with "277" on one side. The results of urinary glucose testing were not available to any study personnel or subjects.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bexagliflozin

Arm description:

The subjects received Bexagliflozin tablets, 20 mg, once daily and Sitagliptin placebo tablets, once daily, for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Bexagliflozin tablets, 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The subjects received Bexagliflozin tablets, 20 mg, once daily orally.

Investigational medicinal product name	Sitagliptin tablets, placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The subjects received Sitagliptin tablets, placebo, once daily orally.

Arm title	Sitagliptin

Arm description:

The subjects received Sitagliptin tablets, 100 mg, once daily and Bexagliflozin placebo tablets, once daily, for 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	Sitagliptin tablets, 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin 100 mg, orally, once daily

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

Dosage and administration details:

The subjects received Bexagliflozin tablets, placebo, once daily orally.

Number of subjects in period 1	Bexagliflozin	Sitagliptin
Started	191	193
Completed	180	189
Not completed	11	4
Adverse event, serious fatal	1	-
Consent withdrawn by subject	4	2
Adverse event, non-fatal	5	1
Pregnancy	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Bexagliflozin
Reporting group description:	
The subjects received Bexagliflozin tablets, 20 mg, once daily and Sitagliptin placebo tablets, once daily, for 24 weeks.	
Reporting group title	Sitagliptin
Reporting group description:	
The subjects received Sitagliptin tablets, 100 mg, once daily and Bexagliflozin placebo tablets, once daily, for 24 weeks.	

Reporting group values	Bexagliflozin	Sitagliptin	Total
Number of subjects	191	193	384
Age categorical Units: Subjects			
Adults (18-64 years)	130	129	259
From 65-84 years	61	64	125
Age continuous			
Age is the age at informed consent, automatically computed in case report form.			
Units: years			
arithmetic mean	59.3	59.6	
standard deviation	± 9.69	± 9.76	-
Gender categorical Units: Subjects			
Female	71	67	138
Male	120	126	246
Race Units: Subjects			
White	158	156	314
Black or African-American	6	2	8
Asian	27	35	62
Ethnicity Units: Subjects			
Hispanic or Latino	3	7	10
Not Hispanic or Latino	188	186	374
Country of Investigational Site Units: Subjects			
Czech Republic	16	25	41
Hungary	33	23	56
Poland	70	44	114
Spain	30	45	75
USA	15	21	36
Japan	27	35	62
Region of Investigational Site Units: Subjects			
North America	15	21	36
Europe	149	137	286
Asia	27	35	62

BMI Categories Units: Subjects			
BMI < 25	22	19	41
BMI ≥ 25	169	174	343
Body Weight Units: kg			
arithmetic mean	90.27	89.44	
standard deviation	± 20.736	± 19.235	-
HbA1c at Baseline Units: Percentage			
arithmetic mean	7.94	8.03	
standard deviation	± 0.808	± 0.921	-
FPG at Baseline Units: mmol/L			
arithmetic mean	9.77	10.02	
standard deviation	± 2.323	± 2.578	-
SBP at Baseline Units: mm Hg			
arithmetic mean	135	135.7	
standard deviation	± 12.17	± 14.32	-
eGFR at Baseline			
For Japanese subjects, eGFR = 194 × (Scr)^(-1.094) × (Age)^(-0.287) × (0.739 if female). For other non-Japanese subjects, eGFR = 175 × (Scr)^(-1.154) × (Age)^(-0.203) × (0.742 if female) × (1.212 if African American). Scr = Serum creatinine, ^ denotes raised to the indicated power.			
Units: mL min-1 per 1.73 m2			
arithmetic mean	88.7	87.15	
standard deviation	± 17.349	± 18.332	-
Duration of Diabetes Units: years			
arithmetic mean	8.22	9.36	
standard deviation	± 5.702	± 5.657	-
BMI Units: kg m-2			
arithmetic mean	32.06	31.39	
standard deviation	± 6.052	± 5.294	-

Subject analysis sets

Subject analysis set title	Bexagliflozin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The subjects received Bexagliflozin tablets, 20 mg, once daily and Sitagliptin placebo tablets, once daily, for 24 weeks.

Subject analysis set title	Sitagliptin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The subjects received Sitagliptin tablets, 100 mg, once daily and Bexagliflozin placebo tablets, once daily, for 24 weeks.

Reporting group values	Bexagliflozin	Sitagliptin	
Number of subjects	191	193	

Age categorical Units: Subjects			
Adults (18-64 years)	130	129	
From 65-84 years	61	64	
Age continuous			
Age is the age at informed consent, automatically computed in case report form.			
Units: years			
arithmetic mean	59.3	59.6	
standard deviation	± 9.69	± 9.76	
Gender categorical Units: Subjects			
Female	71	67	
Male	120	126	
Race Units: Subjects			
White	158	156	
Black or African-American	6	2	
Asian	27	35	
Ethnicity Units: Subjects			
Hispanic or Latino	3	7	
Not Hispanic or Latino	188	186	
Country of Investigational Site Units: Subjects			
Czech Republic	16	25	
Hungary	33	23	
Poland	70	44	
Spain	30	45	
USA	15	21	
Japan	27	35	
Region of Investigational Site Units: Subjects			
North America	15	21	
Europe	149	137	
Asia	27	35	
BMI Categories Units: Subjects			
BMI < 25	22	19	
BMI ≥ 25	169	174	
Body Weight Units: kg			
arithmetic mean	90.27	89.44	
standard deviation	± 20.736	± 19.235	
HbA1c at Baseline Units: Percentage			
arithmetic mean	7.94	8.03	
standard deviation	± 0.808	± 0.921	
FPG at Baseline Units: mmol/L			
arithmetic mean	9.77	10.02	
standard deviation	± 2.323	± 2.578	

SBP at Baseline			
Units: mm Hg			
arithmetic mean	135	135.7	
standard deviation	± 12.17	± 14.32	
eGFR at Baseline			
For Japanese subjects, eGFR = 194 × (Scr)^(-1.094) × (Age)^(-0.287) × (0.739 if female). For other non-Japanese subjects, eGFR = 175 × (Scr)^(-1.154) × (Age)^(-0.203) × (0.742 if female) × (1.212 if African American). Scr = Serum creatinine, ^ denotes raised to the indicated power.			
Units: mL min-1 per 1.73 m2			
arithmetic mean	88.7	87.15	
standard deviation	± 17.349	± 18.332	
Duration of Diabetes			
Units: years			
arithmetic mean	8.22	9.36	
standard deviation	± 5.702	± 5.657	
BMI			
Units: kg m-2			
arithmetic mean	32.06	31.39	
standard deviation	± 6.052	± 5.294	

End points

End points reporting groups

Reporting group title	Bexagliflozin
Reporting group description:	
The subjects received Bexagliflozin tablets, 20 mg, once daily and Sitagliptin placebo tablets, once daily, for 24 weeks.	
Reporting group title	Sitagliptin
Reporting group description:	
The subjects received Sitagliptin tablets, 100 mg, once daily and Bexagliflozin placebo tablets, once daily, for 24 weeks.	
Subject analysis set title	Bexagliflozin
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The subjects received Bexagliflozin tablets, 20 mg, once daily and Sitagliptin placebo tablets, once daily, for 24 weeks.	
Subject analysis set title	Sitagliptin
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The subjects received Sitagliptin tablets, 100 mg, once daily and Bexagliflozin placebo tablets, once daily, for 24 weeks.	

Primary: Change in HbA1c from Baseline at Week 24

End point title	Change in HbA1c from Baseline at Week 24
End point description:	
The primary effectiveness objective was to demonstrate that bexagliflozin was non-inferior to sitagliptin by evaluating the treatment effect on HbA1c reduction at week 24 in subjects with T2DM inadequately controlled by metformin.	
End point type	Primary
End point timeframe:	
HbA1c was measured at weeks -3, 0, 6, 12, 18, 24 and 26 (Follow up).	

End point values	Bexagliflozin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	180[1]	190[2]		
Units: Percentage				
least squares mean (confidence interval 95%)	-0.74 (-0.86 to -0.62)	-0.82 (-0.93 to -0.71)		

Notes:

[1] - 11 subjects in the bexagliflozin arm had missing values for the primary endpoint.

[2] - 3 subjects in the sitagliptin arm had missing values for the primary endpoint.

Statistical analyses

Statistical analysis title	Difference of LS Means from Sitaglitpin 100 mg

Statistical analysis description:

The statistical method to estimate the treatment effect was based on the ITT analysis set using all the observed data and a mixed model repeated measures (MMRM) approach. The full model is a mixed-effects repeated measures analysis that includes region, treatment, visit, treatment-by-visit interaction and the baseline HbA1c value as fixed effect covariates. As unstructured covariance matrix was assumed.

Comparison groups	Bexagliflozin v Sitagliptin
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference of LS Means
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.22

Notes:

[3] - If the 95% confidence interval was below the specified non-inferiority margin 0.35%, the results would have led to a conclusion of non-inferiority of bexagliflozin treatment compared to sitagliptin treatment. The non-inferiority margin of 0.35% was determined based on a reference clinical trial that demonstrated the effectiveness of sitagliptin, 100 mg, compared to placebo on HbA1c reduction in subjects with T2DM.

Secondary: Change in FPG from Baseline at Week 24

End point title	Change in FPG from Baseline at Week 24

End point description:

To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in FPG at week 24.

End point type	Secondary

End point timeframe:

Fasting plasma glucose (FPG) was measured at weeks -3, 0, 6, 12, 18, 24 and 26 (follow-up).

End point values	Bexagliflozin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	180[4]	190[5]		
Units: mmol/L				
least squares mean (confidence interval 95%)	-1.82 (-2.09 to -1.55)	-1.45 (-1.70 to -1.19)		

Notes:

[4] - 11 subjects in the bexagliflozin arm with missing values were excluded.

[5] - 3 subjects in the sitagliptin arm with missing values were excluded.

Statistical analyses

Statistical analysis title	Difference of LS Means from Sitaglitpin 100 mg

Statistical analysis description:

The statistical method to estimate the treatment effect was based on the ITT analysis set using all the observed data and a mixed model repeated measures (MMRM) approach. The full model is a mixed-effects repeated measures analysis that includes region, treatment, visit, treatment-by-visit interaction and the baseline HbA1c value as fixed effect covariates. As unstructured covariance matrix was assumed.

Comparison groups	Bexagliflozin v Sitagliptin

Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123 [6]
Method	Mixed-model repeated measures
Parameter estimate	Difference of LS Means
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.05

Notes:

[6] - P-value was presented based on one sided statistical tests using a 0.025 level of significance.

Secondary: Change in Body Weight from Baseline in Subjects with a BMI ≥ 25 kg m2 at Week 24

End point title	Change in Body Weight from Baseline in Subjects with a BMI ≥ 25 kg m2 at Week 24

End point description:

To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg m2 at Week 24.

End point type	Secondary

End point timeframe:

Body weight was measured at weeks -3, 0, 6, 12, 18, 24 and 26 (follow up).

End point values	Bexagliflozin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158[7]	171[8]		
Units: kg				
least squares mean (confidence interval 95%)	-3.35 (-3.85 to -2.84)	-0.81 (-1.29 to -0.32)		

Notes:

[7] - Only included subjects with a value at baseline and at the specific visit.

[8] - Only included subjects with a value at baseline and at the specific visit.

Statistical analyses

Statistical analysis title	Difference of LS Means from Sitaglitpin 100 mg

Statistical analysis description:

The full model was a mixed-effects repeated measures analysis that included region, treatment, visit, treatment-by-visit interaction and the baseline body weight value as a fixed effect covariate. An unstructured covariance matrix was assumed. Data from Weeks 6, 12, 18 and 24 were used in the model.

Comparison groups	Bexagliflozin v Sitagliptin

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed-model repeated measures
Parameter estimate	Difference of LS Means
Point estimate	-2.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	-1.92

Notes:

[9] - P-value was presented based on one sided statistical tests using a 0.025 level of significance.

Secondary: Change in SBP from Baseline to Week 24

End point title	Change in SBP from Baseline to Week 24

End point description:

To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in systolic blood pressure (SBP) in subjects at week 24.

End point type	Secondary

End point timeframe:

SBP was measured at weeks -3, 0, 6, 12, 18, 24 and 26 (follow up)

End point values	Bexagliflozin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	180[10]	190[11]		
Units: mm Hg				
least squares mean (confidence interval 95%)	-4.23 (-6.18 to -2.28)	-1.90 (-3.75 to -0.06)		

Notes:

[10] - 11 subjects in the bexagliflozin arm with missing values were excluded.

[11] - 3 subjects in the sitagliptin arm with missing values were excluded.

Statistical analyses

Statistical analysis title	Difference of LS Means from Sitaglitpin 100 mg

Statistical analysis description:

The full model was a mixed-effects repeated measures analysis that included region, treatment, visit, treatment-by-visit interaction and the baseline SBP value as a fixed effect covariate. An unstructured covariance matrix was assumed. Data from Weeks 6, 12, 18 and 24 were used in the model.

Comparison groups	Sitagliptin v Bexagliflozin
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0276 [12]
Method	Mixed-model repeated measures
Parameter estimate	Difference of LS Means
Point estimate	-2.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	0.05

Notes:

[12] - P-value was presented based on one sided statistical tests using a 0.025 level of significance.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from Week -1 (run-in period) to Week 26 (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	Sitagliptin
Reporting group description: -	

Serious adverse events	Bexagliflozin	Sitagliptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 191 (3.66%)	4 / 193 (2.07%)	
number of deaths (all causes)	1	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 / 191 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 191 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 191 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microvascular coronary artery disease			

subjects affected / exposed	1 / 191 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial aneurysm			
subjects affected / exposed	0 / 191 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gallstone ileus			
subjects affected / exposed	0 / 191 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 191 (0.00%)	1 / 193 (0.52%)	
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 191 (0.00%)	1 / 193 (0.52%)	
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	2 / 191 (1.05%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Anal abscess			
subjects affected / exposed	1 / 191 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 191 (0.52%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Sitagliptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 191 (14.66%)	47 / 193 (24.35%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 191 (7.85%)	25 / 193 (12.95%)	
occurrences (all)	15	29	
influenza			
subjects affected / exposed	3 / 191 (1.57%)	10 / 193 (5.18%)	
occurrences (all)	3	10	
Urinary tract infection			
subjects affected / exposed	7 / 191 (3.66%)	4 / 193 (2.07%)	
occurrences (all)	9	4	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	6 / 191 (3.14%)	10 / 193 (5.18%)	
occurrences (all)	12	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2017	Sponsor contact changed. Storage guideline for bexagliflozin and sitagliptin tablets was changed. Study procedure modified to include body weight measurement at every visit except Visit 2. Drug accountability added to ensure adequate adherence and record keeping. Study activities modified to include body weight measurement at every visit except Visit 2. Drug accountability check is added to V3, V4, V5, V6 and V7. The investigators and study administrative structure is amended to include guidelines which ensure all qualified persons involved with trial-related duties to have proof of qualification and proof of adequate training on the protocol and assigned tasks. Appendix 1 is amended to match the changes in study activities.
26 October 2017	The current sponsor study contact was updated. The current Theracos Medical Monitor was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported