Clinical trial results:
A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of Empagliflozin as Adjunctive to inSulin thErapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3)

Summary

EudraCT number	2014-005256-26
Trial protocol	DE SE GB FI IE LV NL HU PT GR FR CZ IT
Global end of trial date	20 September 2017

Results information

Result version number	v2 (current)
This version publication date	13 December 2021
First version publication date	06 October 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1245.72

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02580591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, 011 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, 011 8002430127, clintriage.rdg@boehringer-ingelheim.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	23 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2017
Global end of trial reached?	Yes
Global end of trial date	20 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess the efficacy, safety, tolerability and pharmacokinetics (PK) of once daily oral doses of Empagliflozin 2.5 milligram (mg), 10 mg and 25 mg compared with placebo in patients with type 1 diabetes mellitus (T1DM) as adjunctive to optimized insulin therapy.

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be randomized in the study. All patients were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all patients was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2015
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	Australia: 39
Country: Number of subjects enrolled	Canada: 111
Country: Number of subjects enrolled	Czechia: 78
Country: Number of subjects enrolled	Finland: 30
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 159
Country: Number of subjects enrolled	Greece: 25
Country: Number of subjects enrolled	Hungary: 112
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Latvia: 56
Country: Number of subjects enrolled	Mexico: 90
Country: Number of subjects enrolled	Netherlands: 50
Country: Number of subjects enrolled	New Zealand: 27
Country: Number of subjects enrolled	Norway: 39
Country: Number of subjects enrolled	Poland: 108
Country: Number of subjects enrolled	Portugal: 49
Country: Number of subjects enrolled	Romania: 57
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	South Africa: 59

Country: Number of subjects enrolled	Spain: 59
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	United Kingdom: 72
Country: Number of subjects enrolled	United States: 370
Worldwide total number of subjects	1751
EEA total number of subjects	923

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)	1642
From 65 to 84 years	109
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A randomized, placebo-controlled, double-blind, parallel-group study compared 3 doses of Empagliflozin (2.5 milligram (mg), 10 mg, and 25 mg) with placebo in patients with type 1 diabetes mellitus (T1DM) as adjunctive to optimized insulin therapy. A total of 1751 subjects were screened, 977 were entered/randomized and 975 were treated.

Pre-assignment

Screening details:

6-Week T1DM therapy (insulin) optimisation period followed by a 2-Week placebo run-in period before randomization. Patients who successfully completed both of the periods were randomized into the 26-Week double-blind treatment period. All treatments were administered in addition to optimized insulin therapy.

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

Blinding implementation details:

This was a Double-blind trial. This is Randomized and controlled trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo matching Empagliflozin

Arm description:

Patients administered Placebo matching Empagliflozin film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo matching Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients administered Placebo matching Empagliflozin film-coated tablet orally once daily in addition to optimized insulin therapy for 26 weeks.

Arm title	Empagliflozin 2.5 milligram (mg)

Arm description:

Patients administered Empagliflozin 2.5 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients administered Empagliflozin 2.5 mg film-coated tablet orally once daily in addition to optimized insulin therapy for 26 weeks.

Arm title	Empagliflozin 10 mg

Arm description:	
Patients administered Empagliflozin 10 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Patients administered Empagliflozin 10 mg film-coated tablet orally once daily in addition to optimized insulin therapy for 26 weeks.	
Arm title	Empagliflozin 25 mg
Arm description:	
Patients administered Empagliflozin 25 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Patients administered Empagliflozin 25 mg film-coated tablet orally once daily in addition to optimized insulin therapy for 26 weeks.	

Number of subjects in period 1[1]	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg
Started	242	242	248
Completed	224	232	235
Not completed	18	10	13
Protocol deviation	3	2	1
Other than specified	3	2	5
Adverse event, serious fatal	-	-	-
Adverse event, non-fatal	-	1	2
Consent withdrawn by subject	6	1	2
Not treated	1	1	-
Lost to follow-up	5	3	3

Number of subjects in period 1[1]	Empagliflozin 25 mg
Started	245
Completed	233
Not completed	12
Protocol deviation	1
Other than specified	2

Adverse event, serious fatal	1
Adverse event, non-fatal	4
Consent withdrawn by subject	3
Not treated	-
Lost to follow-up	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo matching Empagliflozin
Reporting group description:	
Patients administered Placebo matching Empagliflozin film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 2.5 milligram (mg)
Reporting group description:	
Patients administered Empagliflozin 2.5 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 10 mg
Reporting group description:	
Patients administered Empagliflozin 10 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Patients administered Empagliflozin 25 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	

Reporting group values	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg
Number of subjects	242	242	248
Age categorical Units: Subjects			
Age Continuous			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: years			
arithmetic mean	42.3	43.4	42.3
standard deviation	± 13.2	± 14.3	± 13.2
Sex: Female, Male			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: Subjects			
Female	126	120	132
Male	116	122	116
Race (NIH/OMB)			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: Subjects			
American Indian or Alaska Native	7	0	1
Asian	2	2	2
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	5	3	10
White	227	234	234
More than one race	0	3	1
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial			

medication, regardless of whether any trial medication was taken.			
Units: Subjects			
Hispanic or Latino	215	220	233
Not Hispanic or Latino	27	22	15
Unknown or Not Reported	0	0	0

Reporting group values	Empagliflozin 25 mg	Total	
Number of subjects	245	977	
Age categorical Units: Subjects			

Age Continuous			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: years			
arithmetic mean	44.4		
standard deviation	± 13.6	-	
Sex: Female, Male			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: Subjects			
Female	121	499	
Male	124	478	
Race (NIH/OMB)			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: Subjects			
American Indian or Alaska Native	5	13	
Asian	5	11	
Native Hawaiian or Other Pacific Islander	0	1	
Black or African American	4	22	
White	231	926	
More than one race	0	4	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Randomised set (RS): All patients from the Screened set (SCR) who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: Subjects			
Hispanic or Latino	224	892	
Not Hispanic or Latino	21	85	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Placebo matching Empagliflozin
Reporting group description:	
Patients administered Placebo matching Empagliflozin film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 2.5 milligram (mg)
Reporting group description:	
Patients administered Empagliflozin 2.5 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 10 mg
Reporting group description:	
Patients administered Empagliflozin 10 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Patients administered Empagliflozin 25 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	

Primary: Change from baseline in Glycated hemoglobin (HbA1c) at Week 26 for full analysis set (FAS) (observed cases [OC])

End point title	Change from baseline in Glycated hemoglobin (HbA1c) at Week 26 for full analysis set (FAS) (observed cases [OC])
End point description:	
Change from baseline in Glycated hemoglobin (HbA1c) for full analysis set (FAS) (observed cases [OC]) is presented. With regards to efficacy and safety endpoints, the term 'baseline' referred to the last observed measurement prior to administration of any randomized trial medication. Least squares mean is adjusted mean change from baseline.	
End point type	Primary
End point timeframe:	
Baseline to week 26	

End point values	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg	Empagliflozin 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	238	237	244	242
Units: Percentage (%)				
least squares mean (standard error)	0.20 (± 0.05)	-0.09 (± 0.05)	-0.25 (± 0.05)	-0.33 (± 0.05)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Model includes baseline HbA1c, baseline Estimated glomerular filtration rate (eGFR) as linear covariates and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline	

HbA1c by visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Empagliflozin 2.5 milligram (mg) v Placebo matching Empagliflozin
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.28
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.46
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model includes baseline HbA1c, baseline eGFR as linear covariates and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline HbA1c by visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.6
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Model includes baseline HbA1c, baseline eGFR as linear covariates and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline HbA1c by visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	480

Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.52
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.68
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	0.07

Primary: Change from baseline in Glycated hemoglobin (HbA1c) at Week 26 for modified intention-to-treat population set (mITT) (observed case – all data [OC-AD])

End point title	Change from baseline in Glycated hemoglobin (HbA1c) at Week 26 for modified intention-to-treat population set (mITT) (observed case – all data [OC-AD])

End point description:

Change from baseline in Glycated hemoglobin (HbA1c) for modified intention-to-treat population set (mITT) (observed case – all data [OC-AD]) is presented. With regards to efficacy and safety endpoints, the term 'baseline' referred to the last observed measurement prior to administration of any randomized trial medication. Least squares mean is adjusted mean change from baseline.

End point type	Primary

End point timeframe:

Baseline to week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg	Empagliflozin 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	239	239	246	245
Units: Percentage (%)				
least squares mean (standard error)	0.21 (± 0.05)	-0.06 (± 0.05)	-0.23 (± 0.05)	-0.30 (± 0.05)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Model includes baseline HbA1c, baseline eGFR as linear covariates and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline HbA1c by visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 2.5 milligram (mg)

Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model includes baseline HbA1c, baseline eGFR as linear covariates and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline HbA1c by visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Median difference (final values)
Point estimate	-0.44
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.59
upper limit	-0.28
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Model includes baseline HbA1c, baseline eGFR as linear covariates and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline HbA1c by visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement

Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.66
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	0.07

Secondary: Rate per patient-year of investigator-reported symptomatic hypoglycemic adverse events (AEs) with confirmed plasma glucose (PG)

End point title	Rate per patient-year of investigator-reported symptomatic hypoglycemic adverse events (AEs) with confirmed plasma glucose (PG)

End point description:

Rate per patient-year of investigator-reported symptomatic hypoglycemic adverse events (AEs) with confirmed plasma glucose (PG) <54 milligram per deciliter (mg/dL) (<3.0 millimoles per litre (mmol/L)) and/or severe hypoglycemic AEs (i.e. all investigator-reported AEs that had confirmed PG <54 mg/dL [<3.0 mmol/L] with symptoms reported and all severe hypoglycemic events that were confirmed by adjudication) is presented for (i) From week 5 to 26 and (ii) From week 1 to 26. Least squares mean is actually an adjusted event rate. This is key secondary endpoints.

End point type	Secondary

End point timeframe:

Week 5 to Week 26, Week 1 to Week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg	Empagliflozin 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	235	237	241	237
Units: Per patient year				
least squares mean (confidence interval 95%)				
Week 5 to 26|	6.13 (4.83 to 7.78)	5.77 (4.53 to 7.34)	7.37 (5.83 to 9.31)	6.25 (4.94 to 7.91)
Week 1 to 26|	6.62 (5.30 to 8.27)	6.17 (4.93 to 7.73)	8.33 (6.70 to 10.37)	6.96 (5.58 to 8.67)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

For Week 5 to 26, negative binomial model includes baseline rate of hypoglycemia, baseline HbA1c, and baseline Estimated glomerular filtration rate (eGFR) as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects. Log (time at risk [days]) was used as offset.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 2.5 milligram (mg)
Number of subjects included in analysis	472

Analysis specification	Pre-specified
Analysis type	superiority
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.673
upper limit	1.314

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

For Week 5 to 26, negative binomial model includes baseline rate of hypoglycemia, baseline HbA1c, and baseline Estimated glomerular filtration rate (eGFR) as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects. Log (time at risk [days]) was used as offset.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2752
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	1.202
Confidence interval	
level	Other: 97.75 %
sides	2-sided
lower limit	0.818
upper limit	1.766

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

For Week 5 to 26, negative binomial model includes baseline rate of hypoglycemia, baseline HbA1c, and baseline Estimated glomerular filtration rate (eGFR) as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects. Log (time at risk [days]) was used as offset.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9077
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	1.02
Confidence interval	
level	Other: 97.75 %
sides	2-sided
lower limit	0.693
upper limit	1.501

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
For Week 1 to 26, negative binomial model includes baseline rate of hypoglycemia, baseline HbA1c, and baseline Estimated glomerular filtration rate (eGFR) as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects. Log (time at risk [days]) was used as offset.	
Comparison groups	Placebo matching Empagliflozin v Empagliflozin 2.5 milligram (mg)
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	0.932
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.682
upper limit	1.274

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
For Week 1 to 26, negative binomial model includes baseline rate of hypoglycemia, baseline HbA1c, and baseline Estimated glomerular filtration rate (eGFR) as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects. Log (time at risk [days]) was used as offset.	
Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1438 [1]
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	1.258
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.925
upper limit	1.713

Notes:

[1] - This is a nominal p-value.

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
For Week 1 to 26, negative binomial model includes baseline rate of hypoglycemia, baseline HbA1c, and baseline Estimated glomerular filtration rate (eGFR) as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects. Log (time at risk [days]) was used as offset.	
Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	472

Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7543 [2]
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	1.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.771
upper limit	1.433

Notes:

[2] - This is a nominal p-value.

Secondary: Change from baseline in body weight at Week 26

End point title	Change from baseline in body weight at Week 26

End point description:

Change from baseline in body weight is presented With regards to efficacy and safety endpoints, the term 'baseline' referred to the last observed measurement prior to administration of any randomized trial medication. Least squares mean is adjusted mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline to week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg	Empagliflozin 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	238	237	243	240
Units: Kilogram (kg)				
least squares mean (standard error)	0.21 (± 0.20)	-1.55 (± 0.20)	-2.83 (± 0.20)	-3.22 (± 0.20)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Model includes baseline weight, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline weight by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 2.5 milligram (mg)
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)

Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	-1.2

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model includes baseline weight, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline weight by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-3.04
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-3.91
upper limit	-2.18

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Model includes baseline weight, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline weight by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-3.43
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-4.3
upper limit	-2.57

Secondary: Change from baseline in Total daily insulin dose (TDID) at Week 26

End point title	Change from baseline in Total daily insulin dose (TDID) at Week 26

End point description:

Change from baseline in Total daily insulin dose (TDID) is presented. With regards to efficacy and safety endpoints, the term 'baseline' referred to the last observed measurement prior to administration of any randomized trial medication. Least squares mean is adjusted mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline to week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg	Empagliflozin 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	217	223	217	220
Units: Unit/kilogram (U/kg)				
least squares mean (standard error)	-0.011 (± 0.007)	-0.060 (± 0.007)	-0.080 (± 0.007)	-0.102 (± 0.007)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Model includes baseline total daily insulin dose, baseline estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline total daily insulin dose by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 2.5 milligram (mg)
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	-0.03

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model includes baseline total daily insulin dose, baseline estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline total daily insulin dose by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-0.101
upper limit	-0.039

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Model includes baseline total daily insulin dose, baseline estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, visit by treatment interaction, baseline total daily insulin dose by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.091
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-0.122
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.01

Secondary: Change from baseline in Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) at Week 26

End point title	Change from baseline in Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) at Week 26

End point description:

Change from baseline in Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) is presented. With regards to efficacy and safety endpoints, the term ‘baseline’ referred to the last observed measurement prior to administration of any randomized trial medication. Least squares mean is

adjusted mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline to week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg	Empagliflozin 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	237	236	240	238
Units: Millimeters of mercury (mmHg)				
least squares mean (standard error)				
SBP|	0.4 (± 0.7)	-1.7 (± 0.7)	-3.5 (± 0.7)	-3.4 (± 0.7)
DBP|	0.0 (± 0.4)	-0.4 (± 0.4)	-1.8 (± 0.4)	-1.5 (± 0.4)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

For SBP, the model includes baseline SBP seated, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, treatment by visit interaction, baseline SBP seated by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 2.5 milligram (mg)
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed effect Model Repeat MeasurementMix
Parameter estimate	Median difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	-0.2

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

For SBP, the model includes baseline SBP seated, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, , treatment by visit interaction, baseline SBP seated by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified

Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-3.9
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-6.8
upper limit	-1.1

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

For SBP, the model includes baseline SBP seated, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, treatment by visit interaction, baseline SBP seated by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-3.7
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-6.6
upper limit	-0.9

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

For DBP, the model includes baseline DBP seated, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, treatment by visit interaction, baseline DBP seated by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 2.5 milligram (mg)
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided

lower limit	-1.5
upper limit	0.9

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

For DBP, the model includes baseline DBP seated, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, ß, treatment by visit interaction, baseline DBP seated by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-3.6
upper limit	0.1

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

For DBP, the model includes baseline DBP seated, baseline Estimated glomerular filtration rate (eGFR), baseline HbA1c as linear covariate and baseline pre−existing insulin therapy, treatment, visit, ß, treatment by visit interaction, baseline DBP seated by visit interaction as fixed effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0202
Method	Mixed effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-3.3
upper limit	0.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first drug administration until 7 days after the last drug administration.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Placebo matching Empagliflozin
Reporting group description: Patients administered Placebo matching Empagliflozin film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 2.5 milligram (mg)
Reporting group description: Patients administered Empagliflozin 2.5 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 10 mg
Reporting group description: Patients administered Empagliflozin 10 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	
Reporting group title	Empagliflozin 25 mg
Reporting group description: Patients administered Empagliflozin 25 mg film-coated tablet orally once daily in addition as adjunctive to optimized insulin therapy for 26 weeks.	

Serious adverse events	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 241 (6.64%)	13 / 241 (5.39%)	21 / 248 (8.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	2 / 241 (0.83%)	1 / 241 (0.41%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal cancer stage 0			

subjects affected / exposed	0 / 241 (0.00%)	1 / 241 (0.41%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 241 (0.00%)	1 / 241 (0.41%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to	0 / 0	0 / 0	0 / 1

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Anion gap increased			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bicarbonate increased			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood gases abnormal			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose decreased			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood ketone body increased			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium increased			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine ketone body present			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 241 (0.00%)	2 / 241 (0.83%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Demyelination			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disturbance in attention			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye haemorrhage			

subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy haemorrhagic			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	2 / 248 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatolithiasis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	2 / 248 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acetonaemia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 241 (0.41%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	2 / 241 (0.83%)	2 / 241 (0.83%)	6 / 248 (2.42%)
occurrences causally related to treatment / all	0 / 2	1 / 3	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diabetic ketosis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Euglycaemic diabetic ketoacidosis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	4 / 241 (1.66%)	3 / 241 (1.24%)	3 / 248 (1.21%)
occurrences causally related to treatment / all	1 / 4	2 / 3	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	1 / 241 (0.41%)	1 / 241 (0.41%)	3 / 248 (1.21%)
occurrences causally related to treatment / all	0 / 1	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketosis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 241 (0.41%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic disorder			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			

subjects affected / exposed	0 / 241 (0.00%)	1 / 241 (0.41%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	1 / 248 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	1 / 241 (0.41%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 241 (0.00%)	0 / 248 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Empagliflozin 25 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 245 (6.53%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 245 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Basal cell carcinoma			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vaginal cancer stage 0			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 245 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 245 (0.00%)		

occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Anion gap increased				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bicarbonate increased				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood gases abnormal				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood glucose decreased				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood glucose increased				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood ketone body increased				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood potassium increased				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to	0 / 0			

treatment / all				
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urine ketone body present				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Respiratory arrest				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Demyelination				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disturbance in attention				

subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinopathy haemorrhagic			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vestibular disorder			
subjects affected / exposed	1 / 245 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 245 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastritis				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatolithiasis				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral disc degeneration				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acetonaemia				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			

deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	5 / 245 (2.04%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Diabetic ketosis				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Euglycaemic diabetic ketoacidosis				
subjects affected / exposed	1 / 245 (0.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ketoacidosis				
subjects affected / exposed	2 / 245 (0.82%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ketosis				
subjects affected / exposed	3 / 245 (1.22%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolic disorder				
subjects affected / exposed	0 / 245 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
H1N1 influenza			
subjects affected / exposed	1 / 245 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis viral			
subjects affected / exposed	0 / 245 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 245 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 245 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo matching Empagliflozin	Empagliflozin 2.5 milligram (mg)	Empagliflozin 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	153 / 241 (63.49%)	146 / 241 (60.58%)	172 / 248 (69.35%)
Investigations			
Blood ketone body increased			
subjects affected / exposed	3 / 241 (1.24%)	4 / 241 (1.66%)	15 / 248 (6.05%)
occurrences (all)	3	5	24
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	144 / 241 (59.75%)	137 / 241 (56.85%)	162 / 248 (65.32%)
occurrences (all)	2047	1610	2232
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 241 (9.96%)	23 / 241 (9.54%)	22 / 248 (8.87%)
occurrences (all)	29	27	24
Urinary tract infection			
subjects affected / exposed	12 / 241 (4.98%)	12 / 241 (4.98%)	9 / 248 (3.63%)
occurrences (all)	14	15	10

Non-serious adverse events	Empagliflozin 25 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	162 / 245 (66.12%)		
Investigations			
Blood ketone body increased			
subjects affected / exposed	10 / 245 (4.08%)		
occurrences (all)	20		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	151 / 245 (61.63%)		
occurrences (all)	1956		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 245 (10.61%)		
occurrences (all)	31		
Urinary tract infection			
subjects affected / exposed	16 / 245 (6.53%)		
occurrences (all)	17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2016	Added confirmatory testing step for the effectiveness for the primary endpoint, based on regulatory feedback and moved the exploratory efficacy endpoints based on Continuous glucose monitoring (CGM) from 'secondary endpoints' to 'further exploratory efficacy endpoints', to align with project standards. Events involving lower-limb amputation were added as an Adverse event of special interest (protocol-defined) (AESI) to meet new regulatory requirements. Insulin titration was clarified and optimized: in the original Clinical Trial Protocol investigators were advised to reduce the total insulin dose by 10% regardless of HbA1c values. In the amended protocol this advice was upheld for patients with HbA1c of 7.5 to <8%, whereas for patients with HbA1c of ≥8% investigators were advised to adjust the total insulin dose based on need. Changes to the inclusion and exclusion criteria for the purpose of safety and for clarification introduced. The removal of patients from the trial was modified with regard to concomitant medications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported