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 52 weeks in patients with Type 1 Diabetes Mellitus (EASE-2)

Summary

EudraCT number	2014-001922-14
Trial protocol	GB BE ES SE FI DK DE NL CZ AT PL
Global end of trial date	23 October 2017

Results information

Result version number	v1 (current)
This version publication date	07 November 2018
First version publication date	07 November 2018

Trial information

Trial identification

Sponsor protocol code	1245.69

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02414958
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	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 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	08 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2017
Global end of trial reached?	Yes
Global end of trial date	23 October 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 10 milligram (mg) and 25 mg compared with placebo in patients with type 1 diabetes mellitus (T1DM) as adjunctive to optimised insulin therapy.

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be randomised 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	02 July 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	Austria: 22
Country: Number of subjects enrolled	Australia: 51
Country: Number of subjects enrolled	Belgium: 104
Country: Number of subjects enrolled	Canada: 147
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Denmark: 52
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Germany: 78
Country: Number of subjects enrolled	Netherlands: 41
Country: Number of subjects enrolled	Norway: 28
Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	Spain: 120
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	United Kingdom: 84
Country: Number of subjects enrolled	United States: 402
Country: Number of subjects enrolled	Taiwan: 24
Worldwide total number of subjects	1338
EEA total number of subjects	714

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)	1228
From 65 to 84 years	110
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Randomised, double-blind, placebo-controlled, parallel group, 52-week trial comparing 2 oral once daily doses (10 mg and 25 mg) of empagliflozin with placebo in patients with type 1 diabetes mellitus (T1DM), each as adjunctive to optimised insulin therapy. A total of 1338 screened, 730 randomised/ treated.

Pre-assignment

Screening details:

6-week T1DM therapy (insulin) optimisation period followed by a 2-week placebo run-in period before randomisation. Patients who successfully completed both of the periods were randomised into the 52-week double-blind treatment period. All treatments were administered in addition to optimised 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, Monitor, Data analyst

Blinding implementation details:

This is randomised 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 as adjunctive to optimised insulin therapy for 52 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:

matching Empagliflozin dosage once daily

Arm title	Empagliflozin 10 mg

Arm description:

Patients administered empagliflozin 10 mg film-coated tablet orally once daily as adjunctive to optimised insulin therapy for 52 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:

10 mg once daily

Arm title	Empagliflozin 25 mg

Arm description:

Patients administered empagliflozin 25 mg film-coated tablet orally once daily as adjunctive to optimised

insulin therapy for 52 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:

25 mg once daily

Number of subjects in period 1[1]	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg
Started	243	243	244
Completed	211	223	230
Not completed	32	20	14
Consent withdrawn by subject	5	3	5
Adverse event, non-fatal	6	6	3
Other than specified	4	4	5
Lost to follow-up	7	4	-
Protocol deviation	10	3	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 the patients who were randomised after successfully completing the screening period.
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Baseline characteristics

Reporting groups	
Reporting group title	Placebo matching Empagliflozin
Reporting group description:	
Patients administered placebo matching empagliflozin film-coated tablet orally once daily as adjunctive to optimised insulin therapy for 52 weeks	
Reporting group title	Empagliflozin 10 mg
Reporting group description:	
Patients administered empagliflozin 10 mg film-coated tablet orally once daily as adjunctive to optimised insulin therapy for 52 weeks.	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Patients administered empagliflozin 25 mg film-coated tablet orally once daily as adjunctive to optimised insulin therapy for 52 weeks.	

Reporting group values	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg
Number of subjects	243	243	244
Age categorical			
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			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
RS			
Units: years			
arithmetic mean	44.2	45.7	45.3
standard deviation	± 13.6	± 12.5	± 14.0
Sex: Female, Male			
RS			
Units: Subjects			
Female	133	125	131
Male	110	118	113
Race (NIH/OMB)			
RS			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	7	6	10
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	7	6	4

White	227	230	230
More than one race	2	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
RS			
Units: Subjects			
Hispanic or Latino	7	4	6
Not Hispanic or Latino	236	239	238
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	730		
Age categorical			
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			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
RS			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
RS			
Units: Subjects			
Female	389		
Male	341		
Race (NIH/OMB)			
RS			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	23		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	17		
White	687		
More than one race	2		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
RS			
Units: Subjects			
Hispanic or Latino	17		
Not Hispanic or Latino	713		

Unknown or Not Reported	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 as adjunctive to optimised insulin therapy for 52 weeks	
Reporting group title	Empagliflozin 10 mg
Reporting group description:	
Patients administered empagliflozin 10 mg film-coated tablet orally once daily as adjunctive to optimised insulin therapy for 52 weeks.	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Patients administered empagliflozin 25 mg film-coated tablet orally once daily as adjunctive to optimised insulin therapy for 52 weeks.	

Primary: Change from baseline in glycated haemoglobin (HbA1c) at Week 26

End point title	Change from baseline in glycated haemoglobin (HbA1c) at Week 26
End point description:	
Change from baseline in glycated haemoglobin (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 randomised trial medication. Least squares mean is adjusted mean change from baseline. Restricted maximum likelihood estimation based on mixed-effect model for repeated measures (MMRM) analysis was used to obtain adjusted means for the treatment effects. Full analysis set (FAS) (observed cases [OC]): Patients in the Treated Set (TS) who had a baseline and at least 1 on-treatment HbA1c measurement; the FAS was the basis for the primary efficacy analysis	
End point type	Primary
End point timeframe:	
Baseline to week 26	

End point values	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	239[1]	243[2]	241[3]	
Units: Percentage (%)				
least squares mean (standard error)	0.09 (± 0.04)	-0.44 (± 0.04)	-0.44 (± 0.04)	

Notes:

[1] - Full analysis set (FAS) (observed cases [OC])

[2] - Full analysis set (FAS) (observed cases [OC])

[3] - Full analysis set (FAS) (observed cases [OC])

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Model Mixed effect Model Repeated Measures (MMRM) included the fixed categorical effects of	

treatment, pre-existing insulin therapy, visit , and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline HbA1c, baseline estimated glomerular filtration rate (eGFR), and baseline HbA1c-by- visit interaction. Patient was included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Empagliflozin 10 mg v Placebo matching Empagliflozin
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Mixed effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.54
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.66
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[4] - Mean Difference= Empagliflozin 10 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model MMRM included the fixed categorical effects of treatment, pre-existing insulin therapy, visit, and treatment-by- visit interaction, as well as the continuous, fixed covariates of baseline HbA1c, baseline eGFR, and baseline HbA1c-by- visit interaction. Patient was 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[5]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.66
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[5] - Mean Difference= Empagliflozin 25 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean

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

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

End point description:

Change from baseline in glycated haemoglobin (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 randomised trial medication. Least squares mean is adjusted mean change from baseline. Restricted maximum likelihood estimation based on mixed-effect model for repeated measures (MMRM) analysis was used to obtain adjusted means for the treatment effects.

Modified intention-to-treat set (mITT) (observed case – all data [OC-AD]): Patients in the TS who had a baseline and at least 1 post-baseline HbA1c measurement.

End point type	Primary

End point timeframe:

Baseline to week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	241[6]	243[7]	243[8]	
Units: Percentage (%)				
least squares mean (standard error)	0.09 (± 0.04)	-0.43 (± 0.04)	-0.42 (± 0.04)	

Notes:

[6] - mITT(OC-AD)

[7] - mITT(OC-AD)

[8] - mITT(OC-AD)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Model MMRM 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	484
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.65
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[9] - Mean Difference= Empagliflozin 10 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model MMRM 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[10]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.64
upper limit	-0.39

Notes:

[10] - Mean Difference= Empagliflozin 25 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

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

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

End point description:

This is a key secondary endpoint. Rate per patient-year of investigator-reported symptomatic hypoglycaemia adverse events (AEs) with confirmed plasma glucose (PG) <54 milligram per deciliter (mg/dL) (<3.0 millimoles per litre (mmol/L)) and/or severe hypoglycaemia AEs (i.e. all investigator-reported AEs that had confirmed PG <54 mg/dL [<3.0 mmol/L] with symptoms reported and all severe hypoglycaemia 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.

End point type	Secondary

End point timeframe:

Week 5 to Week 26, Week 1 to Week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243[11]	243[12]	244[13]	
Units: Event Rate per patient year				
least squares mean (confidence interval 95%)				
Week 5 to 26| (N= 238; 243; 239)	8.92 (7.15 to 11.14)	6.64 (5.32 to 8.28)	6.48 (5.18 to 8.12)	
Week 1 to 26| (N= 239; 243; 241)	9.13 (7.36 to 11.34)	7.07 (5.70 to 8.76)	7.15 (5.75 to 8.88)	

Notes:

[11] - FAS (OC)

[12] - FAS (OC)

[13] - FAS (OC)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

For week 5 to 26, negative binomial model includes baseline rate of hypoglycaemia, baseline HbA1c, and baseline 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	486
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.0623
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	0.744
Confidence interval	
level	Other: 97.75 %
sides	2-sided
lower limit	0.518
upper limit	1.069

Notes:

[14] - Empagliflozin 10 milligram (mg) adjusted rate/Placebo matching Empagliflozin adjusted rate. The automatically calculated number of subjects included in analysis (486) does not reflect the actual number of subjects analyzed for week 5 to 26 that was used for this statistical analysis. The actual number of subjects analyzed is 481.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

For week 5 to 26, negative binomial model includes baseline rate of hypoglycaemia, baseline HbA1c, and baseline 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	487
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.048
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	0.726
Confidence interval	
level	Other: 97.75 %
sides	2-sided
lower limit	0.502
upper limit	1.501

Notes:

[15] - Empagliflozin 25 milligram (mg) adjusted rate/Placebo matching Empagliflozin adjusted rate. The automatically calculated number of subjects included in analysis (487) does not reflect the actual number of subjects analyzed for week 5 to 26 that was used for this statistical analysis. The actual

number of subjects analyzed is 477.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

For week 1 to 26, negative binomial model includes baseline rate of hypoglycaemia, baseline HbA1c, and baseline 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	486
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.0972 [17]
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	0.774
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.572
upper limit	1.048

Notes:

[16] - Empagliflozin 10 milligram (mg) adjusted rate/Placebo matching Empagliflozin adjusted rate. The automatically calculated number of subjects included in analysis (486) does not reflect the actual number of subjects analyzed for week 1 to 26 that was used for this statistical analysis. The actual number of subjects analyzed is 482.

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

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

For week 1 to 26, negative binomial model includes baseline rate of hypoglycaemia, baseline HbA1c, and baseline 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	487
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.118 [19]
Method	MMRM
Parameter estimate	Adjusted Rate Ratio (%)
Point estimate	0.782
Confidence interval	
level	Other: 97.75 %
sides	2-sided
lower limit	0.575
upper limit	1.064

Notes:

[18] - Empagliflozin 25 milligram (mg) adjusted rate/Placebo matching Empagliflozin adjusted rate. The automatically calculated number of subjects included in analysis (487) does not reflect the actual number of subjects analyzed for week 1 to 26 that was used for this statistical analysis. The actual number of subjects analyzed is 480.

[19] - Negative binomial model

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 randomised 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 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238[20]	243[21]	240[22]	
Units: Kilogram (kg)				
least squares mean (standard error)	-0.10 (± 0.21)	-2.79 (± 0.20)	-3.37 (± 0.20)	

Notes:

[20] - FAS (OC)

[21] - FAS (OC)

[22] - FAS (OC)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Model MMRM includes baseline weight, baseline 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[23]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.69
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-3.57
upper limit	-1.8
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[23] - Mean Difference= Empagliflozin 10 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model MMRM includes baseline weight, baseline 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[24]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.27
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-4.15
upper limit	-2.39

Notes:

[24] - Mean Difference= Empagliflozin 25 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Secondary: Change from baseline in percentage of time spent in target glucose range from Weeks 23 to 26

End point title	Change from baseline in percentage of time spent in target glucose range from Weeks 23 to 26

End point description:

Change from baseline in the percentage of time spent in target glucose range of >70 to ≤180 mg/dL (>3.9 to ≤10.0 mmol/L) as determined by continuous glucose monitoring (CGM) is presented in week 23 to 26. Least squares mean is actually an adjusted event rate.

FAS observed cases excluding data after use of paracetamol (OC-P)

End point type	Secondary

End point timeframe:

Week 23 to 26

End point values	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179[25]	188[26]	192[27]	
Units: Percentage				
least squares mean (standard error)	-1.13 (± 0.72)	10.73 (± 0.71)	11.74 (± 0.70)	

Notes:

[25] - FAS (OC-P)

[26] - FAS (OC-P)

[27] - FAS (OC-P)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis of covariance (ANCOVA) model includes baseline time in the target range, baseline HbA1c, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.86
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	8.78
upper limit	14.93

Notes:

[28] - Mean Difference= Empagliflozin 10 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis of covariance (ANCOVA) model includes baseline time in the target range, baseline HbA1c, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	12.87
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	9.81
upper limit	15.93
Variability estimate	Standard error of the mean
Dispersion value	1.01

Notes:

[29] - Mean Difference= Empagliflozin 25 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Secondary: Change from baseline in interstitial glucose variability based on the interquartile range (IQR) as determined by CGM in Weeks 23 to 26

End point title	Change from baseline in interstitial glucose variability based on the interquartile range (IQR) as determined by CGM in Weeks 23 to 26

End point description:

Change from baseline in interstitial glucose variability based on the IQR as determined by CGM is presented for week 23 to 26. Least squares mean is actually an adjusted event rate.

End point type	Secondary

End point timeframe:

Week 23 to 26

End point values	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179[30]	188[31]	192[32]	
Units: milligrams (mg)/ deciliter (dL)				
least squares mean (standard error)	1.62 (± 1.21)	-15.30 (± 1.18)	-17.41 (± 1.16)	

Notes:

[30] - FAS (OC-P)

[31] - FAS (OC-P)

[32] - FAS (OC-P)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis of covariance (ANCOVA) model includes model includes baseline IQR of glucose, baseline HbA1c, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 10 mg
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-16.92
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-22.04
upper limit	-11.81
Variability estimate	Standard error of the mean
Dispersion value	1.68

Notes:

[33] - Mean Difference= Empagliflozin 10 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis of covariance (ANCOVA) model includes model includes baseline IQR of glucose, baseline HbA1c, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects.

Comparison groups	Placebo matching Empagliflozin v Empagliflozin 25 mg

Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-19.04
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-24.13
upper limit	-13.95
Variability estimate	Standard error of the mean
Dispersion value	1.68

Notes:

[34] - Mean Difference= Empagliflozin 25 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

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 TDID is presented. With regards to efficacy and safety endpoints, the term 'baseline' referred to the last observed measurement prior to administration of any randomised 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 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223[35]	227[36]	226[37]	
Units: Unit/kilogram (U/kg)				
least squares mean (standard error)	-0.010 (± 0.007)	-0.102 (± 0.007)	-0.100 (± 0.007)	

Notes:

[35] - FAS (OC)

[36] - FAS (OC)

[37] - FAS (OC)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Model MMRM includes baseline total daily insulin dose, baseline estimated 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	450
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.092
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-0.121
upper limit	-0.063
Variability estimate	Standard error of the mean
Dispersion value	0.009

Notes:

[38] - Mean Difference= Empagliflozin 10 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Model MMRM includes baseline total daily insulin dose, baseline estimated 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	449
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-0.119
upper limit	-0.062
Variability estimate	Standard error of the mean
Dispersion value	0.009

Notes:

[39] - Mean Difference= Empagliflozin 25 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean.

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 SBP and DBP is presented. With regards to efficacy and safety endpoints, the term ‘baseline’ referred to the last observed measurement prior to administration of any randomised trial medication. Least squares mean is adjusted mean change from baseline.

FAS observed cases excluding data after change in use of anti-hypertensives (OC-H)

End point type	Secondary

End point timeframe:

Baseline to week 26

End point values	Placebo matching Empagliflozin	Empagliflozin 10 mg	Empagliflozin 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243[40]	243[41]	244[42]	
Units: Millimeters of mercury (mmHg)				
least squares mean (standard error)				
SBP (N= 238; 243; 238)	-0.8 (± 0.7)	-2.9 (± 0.7)	-4.5 (± 0.7)	
DBP (N= 239; 243; 241)	-0.3 (± 0.5)	-1.6 (± 0.5)	-2.6 (± 0.5)	

Notes:

[40] - FAS (OC-H)

[41] - FAS (OC-H)

[42] - FAS (OC-H)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

For SBP, the model MMRM includes baseline SBP seated, baseline estimated 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	486
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.0397
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-5.2
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[43] - Mean Difference= Empagliflozin 10 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean. The automatically calculated number of subjects included in analysis (486) does not reflect the actual number of subjects analyzed for SBP that was used for this statistical analysis. The actual number of subjects analyzed is 481.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

For SBP, the model includes baseline SBP seated, baseline estimated 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	487
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.0003
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.7
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-6.8
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[44] - Mean Difference= Empagliflozin 25 milligram (mg) adjusted mean - Placebo matching Empagliflozin adjusted mean. The automatically calculated number of subjects included in analysis (487) does not reflect the actual number of subjects analyzed for SBP that was used for this statistical analysis. The actual number of subjects analyzed is 476.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

For DBP, the model MMRM includes baseline DBP seated, baseline 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 10 mg
Number of subjects included in analysis	486
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0457 [45]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-2.7
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.7

Notes:

[45] - Nominal p-value

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

For DBP, the model MMRM includes baseline DBP seated, baseline estimated 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 25 mg

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.3
Confidence interval	
level	Other: 99.75 %
sides	2-sided
lower limit	-4.3
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of trial medication until 7 days after last in-take of trial medication, up to 422 days

Adverse event reporting additional description:

Treated set (TS): all patients who were treated with at least one dose of randomised trial medication; the TS was the basis for safety analyses. The total number of participants at risk is based on treated set.

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 optimised insulin therapy for 52 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 optimised insulin therapy for 52 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 optimised insulin therapy for 52 weeks.

Serious adverse events	Placebo matching Empagliflozin	Empagliflozin 25 mg	Empagliflozin 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 243 (11.52%)	26 / 244 (10.66%)	43 / 243 (17.70%)
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)			
Benign breast neoplasm			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Anaphylactic shock			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menstrual disorder			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric decompensation			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Investigations			
Bacterial test positive			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
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 ketone body increased			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium test positive			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Hepatic enzyme increased			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Injury, poisoning and procedural complications			
Carbon monoxide poisoning			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Concussion			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Procedural pain			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Shunt malfunction			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Tendon rupture			

subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Ulna fracture			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Dystonia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Hemiparesis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Hypoglycaemic coma			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Lacunar stroke			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Partial seizures			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular syndrome			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory disturbance			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Syncope			

subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 243 (0.00%)	2 / 244 (0.82%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Macular fibrosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Normal tension glaucoma			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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

Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 243 (0.41%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Spinal osteoarthritis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Pleurisy viral			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 243 (0.00%)	2 / 244 (0.82%)	0 / 243 (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
Pneumonia klebsiella			

subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tinea versicolour			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (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
Viral infection			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
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			
Dehydration			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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
Diabetic ketoacidosis			
subjects affected / exposed	4 / 243 (1.65%)	8 / 244 (3.28%)	12 / 243 (4.94%)
occurrences causally related to treatment / all	1 / 6	8 / 9	8 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			

subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 243 (0.82%)	1 / 244 (0.41%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	6 / 243 (2.47%)	3 / 244 (1.23%)	9 / 243 (3.70%)
occurrences causally related to treatment / all	3 / 9	1 / 3	9 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	2 / 243 (0.82%)	2 / 244 (0.82%)	4 / 243 (1.65%)
occurrences causally related to treatment / all	0 / 2	0 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketosis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (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

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

Non-serious adverse events	Placebo matching Empagliflozin	Empagliflozin 25 mg	Empagliflozin 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 243 (81.07%)	195 / 244 (79.92%)	197 / 243 (81.07%)
Investigations			
Blood ketone body increased			
subjects affected / exposed	10 / 243 (4.12%)	20 / 244 (8.20%)	18 / 243 (7.41%)
occurrences (all)	17	52	21
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 243 (3.70%)	8 / 244 (3.28%)	13 / 243 (5.35%)
occurrences (all)	9	10	14
Nausea			

subjects affected / exposed	14 / 243 (5.76%)	14 / 244 (5.74%)	12 / 243 (4.94%)
occurrences (all)	15	15	13
Vomiting			
subjects affected / exposed	12 / 243 (4.94%)	12 / 244 (4.92%)	19 / 243 (7.82%)
occurrences (all)	14	13	20
Infections and infestations			
Influenza			
subjects affected / exposed	11 / 243 (4.53%)	12 / 244 (4.92%)	20 / 243 (8.23%)
occurrences (all)	13	14	22
Nasopharyngitis			
subjects affected / exposed	41 / 243 (16.87%)	43 / 244 (17.62%)	52 / 243 (21.40%)
occurrences (all)	60	57	68
Sinusitis			
subjects affected / exposed	13 / 243 (5.35%)	9 / 244 (3.69%)	14 / 243 (5.76%)
occurrences (all)	14	10	15
Upper respiratory tract infection			
subjects affected / exposed	25 / 243 (10.29%)	27 / 244 (11.07%)	15 / 243 (6.17%)
occurrences (all)	32	28	19
Urinary tract infection			
subjects affected / exposed	29 / 243 (11.93%)	20 / 244 (8.20%)	37 / 243 (15.23%)
occurrences (all)	49	26	46
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 243 (0.82%)	14 / 244 (5.74%)	9 / 243 (3.70%)
occurrences (all)	4	30	11
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	152 / 243 (62.55%)	147 / 244 (60.25%)	154 / 243 (63.37%)
occurrences (all)	3186	2773	2656

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2016	Amendment 1 was implemented when 385 patients (about half of all randomised) had been randomised. The main effect of this amendment was to clarify the eligibility criteria, which were made consistent with the other pivotal trial 1245.72. The amendment also introduced additional blood ketone measurements for improved safety monitoring. Insulin titration was clarified and optimised: in the original clinical trial protocol (CTP) investigators were advised to reduce the total insulin dose by 10% regardless of HbA1c values. The amendment maintained this advice for patients with glycated haemoglobin (HbA1c) of 7.5 to <8%, and advised investigators to adjust the total insulin dose based on need for patients with HbA1c of ≥8%. Furthermore, the amendment introduced more details on the hierarchical testing procedure, based on regulatory feedback. The inclusion and exclusion criteria were modified for the purpose of safety, clarification, and for alignment with the trial 1245.72.
04 January 2017	Amendment 2 was implemented when all patients had been randomised. The main effect of this amendment was to introduce 2 continuous glucose monitoring (CGM)-related endpoints as key secondary endpoints, given that sodium-glucose co-transporter (SGLT-2)inhibitor treatment in T1DM may improve the burden of glycaemic variability, which remains a fundamental treatment challenge in the management of this disease. Accordingly, the hierarchical testing procedure was revised to accommodate the added confirmatory endpoints based on CGM. Events involving lower-limb amputation were added as an adverse event of special interest (AESI) to meet new regulatory requirements. The inclusion criteria were modified with regard to the definition of women of child-bearing potential. In addition, 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