Clinical trial results:
A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug naïve patients with type 2 diabetes mellitus.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-021375-92
Trial protocol	GB DE ES CZ
Global end of trial date	01 December 2014

Results information

Result version number	v1 (current)
This version publication date	01 July 2016
First version publication date	01 July 2016

Trial information

Trial identification

Sponsor protocol code	1276.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01719003
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	18 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2014
Global end of trial reached?	Yes
Global end of trial date	01 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to investigate the efficacy, safety, and tolerability of the combinations of empagliflozin (12.5 mg bid or 5 mg bid) and metformin (1000 mg bid or 500 mg bid) compared with the corresponding individual components (empagliflozin 25 mg qd, empagliflozin 10 mg qd, metformin 1000 mg bid, and metformin 500 mg bid) after 24 weeks of treatment in patients with type 2 diabetes mellitus and insufficient glycaemic control, despite diet and exercise.

An additional objective of the study was to investigate the non-inferiority and subsequent superiority of the efficacy of empagliflozin 25 mg qd and empagliflozin 10 mg qd vs. metformin 1000 mg bid, measured by the change from baseline in HbA1c (Glycosylated Haemoglobin) after 24 weeks of treatment in this population.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 252
Country: Number of subjects enrolled	Canada: 106
Country: Number of subjects enrolled	Czech Republic: 63
Country: Number of subjects enrolled	Egypt: 52
Country: Number of subjects enrolled	France: 63
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Guatemala: 191
Country: Number of subjects enrolled	Korea, Republic of: 88
Country: Number of subjects enrolled	Lebanon: 68
Country: Number of subjects enrolled	Malaysia: 52
Country: Number of subjects enrolled	Mexico: 134
Country: Number of subjects enrolled	Peru: 90

Country: Number of subjects enrolled	Philippines: 190
Country: Number of subjects enrolled	Russian Federation: 140
Country: Number of subjects enrolled	Serbia: 101
Country: Number of subjects enrolled	Spain: 82
Country: Number of subjects enrolled	Taiwan: 49
Country: Number of subjects enrolled	Thailand: 35
Country: Number of subjects enrolled	Turkey: 51
Country: Number of subjects enrolled	United Kingdom: 96
Country: Number of subjects enrolled	United States: 520
Worldwide total number of subjects	2482
EEA total number of subjects	363

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)	2070
From 65 to 84 years	403
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

With the first global protocol amendment (13-Dec-2012), the HbA1c inclusion criterion changed and further enrolment in the open label (OL) group was stopped, but the patients already entered in the OL group could continue until their scheduled end of the study.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects were not to be randomised to trial treatment if any one of the trial specific entry criteria were violated. Patients with HbA1c >10.0% at screening and meeting all other inclusion criteria were initially directly included in an OL treatment group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid

Arm description:

Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg twice daily (bid)

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:

12.5 mg (two tables: 10mg + 2.5 mg) of Empagliflozin administered orally twice daily

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg of Metformin administered orally twice daily

Arm title	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid

Arm description:

Oral administration of Empagliflozin 12.5 mg and Metformin 500 mg bid

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

Dosage and administration details:

500 mg of Metformin administered orally twice daily

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:

12.5 mg (two tables: 10mg + 2.5 mg) of Empagliflozin administered orally twice daily

Arm title	Empagliflozin 5 mg bid + Metformin 1000 mg bid

Arm description:

Oral administration of Empagliflozin 5 mg and Metformin 1000 mg bid. Patient that was randomised to the Empagliflozin 5 mg bid + Metformin 1000 mg bid arm was not treated. Consequently, number of subjects that started is 172 but only 171 treated, thus reported.

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

Dosage and administration details:

1000 mg of Metformin administered orally twice daily

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:

5 mg of Empagliflozin administered orally twice daily

Arm title	Empagliflozin 5 mg bid + Metformin 500 mg bid

Arm description:

Oral administration of Empagliflozin 5 mg and Metformin 500 mg bid. Patient that was randomised to the Empagliflozin 5 mg bid + Metformin 500 mg bid arm was not treated. Consequently, number of subjects that started is 170 but only 169 treated, thus reported.

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:

5 mg of Empagliflozin administered orally twice daily

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg of Metformin administered orally twice daily

Arm title	Empagliflozin 25 mg qd

Arm description:

Oral administration of Empagliflozin 25 mg once daily (qd). Patient that was randomised to the Empagliflozin 25 mg qd arm was not treated. Consequently, number of subjects that started is 168 but only 167 treated, thus reported.

Arm type	Active comparator
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 of Empagliflozin administered orally once daily

Arm title	Empagliflozin 10 mg qd

Arm description:

Oral administration of Empagliflozin 10 mg qd

Arm type	Active comparator
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 of Empagliflozin administered orally once daily

Arm title	Metformin 1000 mg bid

Arm description:

Oral administration of Metformin 1000 mg bid. Patient that was randomised to the Metformin 1000 mg bid arm was not treated. Consequently, number of subjects that started is 171 but only 170 treated, thus reported.

Arm type	Active comparator
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg of Metformin administered orally twice daily

Arm title	Metformin 500 mg bid

Arm description:

Oral administration of Metformin 500 mg bid

Arm type	Active comparator
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg of Metformin administered orally twice daily

Arm title	Empagliflozin 12.5 mg bid + Metformin 1000 mg bid OL

Arm description:

Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg bid in an open label (OL)

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:

12.5 mg (two tables: 10mg + 2.5 mg) of Empagliflozin administered orally twice daily

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg of Metformin administered orally twice daily

Number of subjects in period 1[1]	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid	Empagliflozin 5 mg bid + Metformin 1000 mg bid
Started	170	170	171
Completed	161	153	154
Not completed	9	17	17
Non compliant with protocol	1	1	-
Adverse event, non-fatal	6	5	4
Refusal to continue, not due to AE	2	5	4
Lost to follow-up	-	6	7
Reason other than those specified	-	-	2
Lack of efficacy	-	-	-

Number of subjects in period 1[1]	Empagliflozin 5 mg bid + Metformin 500 mg bid	Empagliflozin 25 mg qd	Empagliflozin 10 mg qd
Started	169	167	172
Completed	156	150	160
Not completed	13	17	12
Non compliant with protocol	1	2	1
Adverse event, non-fatal	3	4	3
Refusal to continue, not due to AE	4	4	3
Lost to follow-up	2	3	4
Reason other than those specified	3	4	1
Lack of efficacy	-	-	-

Number of subjects in period 1[1]	Metformin 1000 mg bid	Metformin 500 mg bid	Empagliflozin 12.5 mg bid + Metformin 1000 mg bid OL
Started	170	171	53
Completed	150	151	49
Not completed	20	20	4

Non compliant with protocol	2	3	-
Adverse event, non-fatal	6	5	-
Refusal to continue, not due to AE	8	7	1
Lost to follow-up	3	2	2
Reason other than those specified	-	3	1
Lack of efficacy	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 randomized after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid
Reporting group description:	
Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg twice daily (bid)	
Reporting group title	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid
Reporting group description:	
Oral administration of Empagliflozin 12.5 mg and Metformin 500 mg bid	
Reporting group title	Empagliflozin 5 mg bid + Metformin 1000 mg bid
Reporting group description:	
Oral administration of Empagliflozin 5 mg and Metformin 1000 mg bid. Patient that was randomised to the Empagliflozin 5 mg bid + Metformin 1000 mg bid arm was not treated. Consequently, number of subjects that started is 172 but only 171 treated, thus reported.	
Reporting group title	Empagliflozin 5 mg bid + Metformin 500 mg bid
Reporting group description:	
Oral administration of Empagliflozin 5 mg and Metformin 500 mg bid. Patient that was randomised to the Empagliflozin 5 mg bid + Metformin 500 mg bid arm was not treated. Consequently, number of subjects that started is 170 but only 169 treated, thus reported.	
Reporting group title	Empagliflozin 25 mg qd
Reporting group description:	
Oral administration of Empagliflozin 25 mg once daily (qd). Patient that was randomised to the Empagliflozin 25 mg qd arm was not treated. Consequently, number of subjects that started is 168 but only 167 treated, thus reported.	
Reporting group title	Empagliflozin 10 mg qd
Reporting group description:	
Oral administration of Empagliflozin 10 mg qd	
Reporting group title	Metformin 1000 mg bid
Reporting group description:	
Oral administration of Metformin 1000 mg bid. Patient that was randomised to the Metformin 1000 mg bid arm was not treated. Consequently, number of subjects that started is 171 but only 170 treated, thus reported.	
Reporting group title	Metformin 500 mg bid
Reporting group description:	
Oral administration of Metformin 500 mg bid	
Reporting group title	Empagliflozin 12.5 mg bid + Metformin 1000 mg bid OL
Reporting group description:	
Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg bid in an open label (OL)	

Reporting group values	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid	Empagliflozin 5 mg bid + Metformin 1000 mg bid
Number of subjects	170	170	171
Age categorical Units: Subjects			

Age Continuous |			
Treated set (TS): TS included all patients treated with at least 1 dose of randomised trial medication. Open label set (OL): included all patients that were not eligible to be randomised to double blind treatment due to HbA1c >10.0%			
Units: years			
arithmetic mean	53.6	50.8	52.4
standard deviation	± 10.7	± 10.6	± 11.3

Gender, Male/Female Units: participants			
Female	81	61	70
Male	89	109	101

Reporting group values	Empagliflozin 5 mg bid + Metformin 500 mg bid	Empagliflozin 25 mg qd	Empagliflozin 10 mg qd
Number of subjects	169	167	172
Age categorical Units: Subjects			

Age Continuous |			
Treated set (TS): TS included all patients treated with at least 1 dose of randomised trial medication. Open label set (OL): included all patients that were not eligible to be randomised to double blind treatment due to HbA1c >10.0%			
Units: years			
arithmetic mean	52.3	53.3	53.2
standard deviation	± 11.5	± 10.9	± 10.6
Gender, Male/Female Units: participants			
Female	67	83	72
Male	102	84	100

Reporting group values	Metformin 1000 mg bid	Metformin 500 mg bid	Empagliflozin 12.5 mg bid + Metformin 1000 mg bid OL
Number of subjects	170	171	53
Age categorical Units: Subjects			

Age Continuous |			
Treated set (TS): TS included all patients treated with at least 1 dose of randomised trial medication. Open label set (OL): included all patients that were not eligible to be randomised to double blind treatment due to HbA1c >10.0%			
Units: years			
arithmetic mean	52	53.4	50.3
standard deviation	± 10.9	± 10.8	± 10
Gender, Male/Female Units: participants			
Female	76	83	12
Male	94	88	41

Reporting group values	Total		
Number of subjects	1413		
Age categorical Units: Subjects			

Age Continuous |			
Treated set (TS): TS included all patients treated with at least 1 dose of randomised trial medication. Open label set (OL): included all patients that were not eligible to be randomised to double blind treatment due to HbA1c >10.0%			
Units: years			
arithmetic mean			

standard deviation	-		

Gender, Male/Female Units: participants			
Female	605		
Male	808		

End points

End points reporting groups

Reporting group title	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid
Reporting group description:	
Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg twice daily (bid)	
Reporting group title	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid
Reporting group description:	
Oral administration of Empagliflozin 12.5 mg and Metformin 500 mg bid	
Reporting group title	Empagliflozin 5 mg bid + Metformin 1000 mg bid
Reporting group description:	
Oral administration of Empagliflozin 5 mg and Metformin 1000 mg bid. Patient that was randomised to the Empagliflozin 5 mg bid + Metformin 1000 mg bid arm was not treated. Consequently, number of subjects that started is 172 but only 171 treated, thus reported.	
Reporting group title	Empagliflozin 5 mg bid + Metformin 500 mg bid
Reporting group description:	
Oral administration of Empagliflozin 5 mg and Metformin 500 mg bid. Patient that was randomised to the Empagliflozin 5 mg bid + Metformin 500 mg bid arm was not treated. Consequently, number of subjects that started is 170 but only 169 treated, thus reported.	
Reporting group title	Empagliflozin 25 mg qd
Reporting group description:	
Oral administration of Empagliflozin 25 mg once daily (qd). Patient that was randomised to the Empagliflozin 25 mg qd arm was not treated. Consequently, number of subjects that started is 168 but only 167 treated, thus reported.	
Reporting group title	Empagliflozin 10 mg qd
Reporting group description:	
Oral administration of Empagliflozin 10 mg qd	
Reporting group title	Metformin 1000 mg bid
Reporting group description:	
Oral administration of Metformin 1000 mg bid. Patient that was randomised to the Metformin 1000 mg bid arm was not treated. Consequently, number of subjects that started is 171 but only 170 treated, thus reported.	
Reporting group title	Metformin 500 mg bid
Reporting group description:	
Oral administration of Metformin 500 mg bid	
Reporting group title	Empagliflozin 12.5 mg bid + Metformin 1000 mg bid OL
Reporting group description:	
Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg bid in an open label (OL)	

Primary: HbA1c (Glycosylated Haemoglobin) Change From Baseline at Week 24

End point title	HbA1c (Glycosylated Haemoglobin) Change From Baseline at Week 24[1]

End point description:

Change from baseline in HbA1c (%) after 24 weeks of treatment. "Baseline" refers to the last observation before the start of any randomised trial treatment medication. Means presented are the adjusted means.

Full analysis set (FAS): FAS comprised all randomised patients treated with at least 1 dose of trial medication, with a baseline and at least 1 on-treatment HbA1c assessment. The FAS observed cases (OC) was used to evaluate primary endpoint, where only patients with available data were analysed.

End point type	Primary

End point timeframe:

baseline and 24 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the small number of patients entered to open label arm, the results for this arm were not included in primary analysis.

End point values	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid	Empagliflozin 5 mg bid + Metformin 1000 mg bid	Empagliflozin 5 mg bid + Metformin 500 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159[2]	149[3]	151[4]	153[5]
Units: percentage of HbA1c				
arithmetic mean (standard error)	-2.08 (± 0.08)	-1.93 (± 0.08)	-2.07 (± 0.08)	-1.98 (± 0.08)

Notes:

[2] - FAS observed cases (OC). Only patients with available data were analysed.

[3] - FAS observed cases (OC). Only patients with available data were analysed.

[4] - FAS observed cases (OC). Only patients with available data were analysed.

[5] - FAS observed cases (OC). Only patients with available data were analysed.

End point values	Empagliflozin 25 mg qd	Empagliflozin 10 mg qd	Metformin 1000 mg bid	Metformin 500 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	143[6]	156[7]	146[8]	142[9]
Units: percentage of HbA1c				
arithmetic mean (standard error)	-1.36 (± 0.08)	-1.35 (± 0.08)	-1.75 (± 0.09)	-1.18 (± 0.08)

Notes:

[6] - FAS observed cases (OC). Only patients with available data were analysed.

[7] - FAS observed cases (OC). Only patients with available data were analysed.

[8] - FAS observed cases (OC). Only patients with available data were analysed.

[9] - FAS observed cases (OC). Only patients with available data were analysed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid v Metformin 1000 mg bid
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056 [10]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[10] - Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid minus Metformin 1000 mg bid

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid v Empagliflozin 25 mg qd
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[11] - Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid minus Empagliflozin 25 mg qd

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid v Metformin 500 mg bid
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-0.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	-0.51
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[12] - Empagliflozin 12.5 mg bid+ Metformin 500 mg bid minus Metformin 500 mg bid

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid v Empagliflozin 25 mg qd
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[13] - Empagliflozin 12.5 mg bid+ Metformin 500 mg bid minus Empagliflozin 25 mg qd

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 1000 mg bid v Metformin 1000 mg bid
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0062 [14]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[14] - Empagliflozin 5 mg bid + Metformin 1000 mg bid minus Metformin 1000 mg bid

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 1000 mg bid v Empagliflozin 10 mg qd
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	-0.49
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[15] - Empagliflozin 5 mg bid + Metformin 1000 mg bid minus Empagliflozin 10 mg qd

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 500 mg bid v Metformin 500 mg bid
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-0.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	-0.56
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[16] - Empagliflozin 5 mg bid + Metformin 500 mg bid minus Metformin 500 mg bid

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 500 mg bid v Empagliflozin 10 mg qd
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[17] - Empagliflozin 5 mg bid + Metformin 500 mg bid minus Empagliflozin 10 mg qd

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 25 mg qd v Metformin 1000 mg bid
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
P-value	= 0.6246 [19]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	0.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.62
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[18] - The noninferiority of empagliflozin 10 mg qd against metformin 1000 mg bid were to be tested for HbA1c change from baseline to Week 24 at the level of α=0.025 (one-sided), through application of a non-inferiority margin of 0.35%.
[19] - Empagliflozin 25 mg qd minus Metformin 1000 mg bid

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of HbA1c (in units of %) after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 10 mg qd v Metformin 1000 mg bid
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
P-value	= 0.6558 [21]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.63
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[20] - The noninferiority of empagliflozin 10 mg qd against metformin 1000 mg bid were to be tested for HbA1c change from baseline to Week 24 at the level of α=0.025 (one-sided), through application of a non-inferiority margin of 0.35%.
[21] - Empagliflozin 10 mg qd minus Metformin 1000 mg bid

Secondary: FPG (Fasting Plasma Glucose) Change From Baseline at Week 24

End point title	FPG (Fasting Plasma Glucose) Change From Baseline at Week 24[22]

End point description:

Change from baseline in FPG (mg/dL) after 24 weeks of treatment. "Baseline" refers to the last observation before the start of any randomised trial treatment medication. Means presented are the adjusted means.

End point type	Secondary

End point timeframe:

baseline and 24 weeks

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the small number of patients entered to open label arm, the results for this arm were not included in primary analysis.

End point values	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid	Empagliflozin 5 mg bid + Metformin 1000 mg bid	Empagliflozin 5 mg bid + Metformin 500 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158[23]	146[24]	146[25]	153[26]
Units: mg/dL				
arithmetic mean (standard error)	-51 (± 2.4)	-44 (± 2.4)	-47.8 (± 2.4)	-45.5 (± 2.4)

Notes:

[23] - FAS observed cases (OC). Only patients with available data were analysed.

[24] - FAS observed cases (OC). Only patients with available data were analysed.

[25] - FAS observed cases (OC). Only patients with available data were analysed.

[26] - FAS observed cases (OC). Only patients with available data were analysed.

End point values	Empagliflozin 25 mg qd	Empagliflozin 10 mg qd	Metformin 1000 mg bid	Metformin 500 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	139[27]	154[28]	145[29]	139[30]
Units: mg/dL				
arithmetic mean (standard error)	-28 (± 2.5)	-32.9 (± 2.4)	-32.1 (± 2.4)	-17.2 (± 2.5)

Notes:

[27] - FAS observed cases (OC). Only patients with available data were analysed.

[28] - FAS observed cases (OC). Only patients with available data were analysed.

[29] - FAS observed cases (OC). Only patients with available data were analysed.

[30] - FAS observed cases (OC). Only patients with available data were analysed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose', 'region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid v Metformin 1000 mg bid
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	< 0.0001 [32]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-18.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.5
upper limit	-12.2
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[31] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG andbody weight are considered exploratory and not confirmatory

[32] - Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid minus Metformin 1000 mg bid

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose','region','visit' & 'visit by treatment interaction':fixed effects.	
Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid v Empagliflozin 25 mg qd
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.0001 [34]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.7
upper limit	-16.3
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[33] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG andbody weight are considered exploratory and not confirmatory
[34] - Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid minus Empagliflozin 25 mg qd

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose','region','visit' & 'visit by treatment interaction':fixed effects.	
Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid v Metformin 500 mg bid
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	< 0.0001 [36]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-26.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.5
upper limit	-20
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[35] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory

[36] - Empagliflozin 12.5 mg bid+ Metformin 500 mg bid minus Metformin 500 mg bid

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid v Empagliflozin 25 mg qd
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.0001 [38]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	-9.2
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[37] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory

[38] - Empagliflozin 12.5 mg bid+ Metformin 500 mg bid minus Empagliflozin 25 mg qd

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 1000 mg bid v Metformin 1000 mg bid
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	< 0.0001 [40]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-15.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.3
upper limit	-8.9
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[39] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory.
[40] - Empagliflozin 5 mg bid + Metformin 1000 mg bid minus Metformin 1000 mg bid

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 1000 mg bid v Empagliflozin 10 mg qd
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	< 0.0001 [42]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.4
upper limit	-8.2
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[41] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory
[42] - Empagliflozin 5 mg bid + Metformin 1000 mg bid minus Empagliflozin 10 mg qd

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 500 mg bid v Metformin 500 mg bid
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	< 0.0001 [44]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-28.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35
upper limit	-21.5
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[43] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory

[44] - Empagliflozin 5 mg bid + Metformin 500 mg bid minus Metformin 500 mg bid

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of FPG after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function', 'baseline fasting plasma glucose','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 500 mg bid v Empagliflozin 10 mg qd
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.0002 [46]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-12.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.1
upper limit	-6
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[45] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory

[46] - Empagliflozin 5 mg bid + Metformin 500 mg bid minus Empagliflozin 10 mg qd

Secondary: Body weight Change From Baseline at Week 24

End point title	Body weight Change From Baseline at Week 24[47]

End point description:

Change from baseline in body weight (kg) after 24 weeks of treatment. "Baseline" refers to the last observation before the start of any randomised trial treatment. medication. Means presented are the adjusted means.

End point type	Secondary

End point timeframe:

baseline and 24 weeks

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the small number of patients entered to open label arm, the results for this arm were not included in primary analysis.

End point values	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid	Empagliflozin 5 mg bid + Metformin 1000 mg bid	Empagliflozin 5 mg bid + Metformin 500 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	160[48]	149[49]	150[50]	155[51]
Units: kg				
arithmetic mean (standard error)	-3.78 (± 0.29)	-3.04 (± 0.3)	-3.48 (± 0.3)	-2.77 (± 0.3)

Notes:

[48] - FAS observed cases (OC). Only patients with available data were analysed.

[49] - FAS observed cases (OC). Only patients with available data were analysed.

[50] - FAS observed cases (OC). Only patients with available data were analysed.

[51] - FAS observed cases (OC). Only patients with available data were analysed.

End point values	Empagliflozin 25 mg qd	Empagliflozin 10 mg qd	Metformin 1000 mg bid	Metformin 500 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	143[52]	155[53]	148[54]	140[55]
Units: kg				
arithmetic mean (standard error)	-2.38 (± 0.3)	-2.39 (± 0.29)	-1.27 (± 0.3)	-0.52 (± 0.3)

Notes:

[52] - FAS observed cases (OC). Only patients with available data were analysed.

[53] - FAS observed cases (OC). Only patients with available data were analysed.

[54] - FAS observed cases (OC). Only patients with available data were analysed.

[55] - FAS observed cases (OC). Only patients with available data were analysed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of body weight after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid v Metformin 1000 mg bid
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	< 0.0001 [57]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	-1.68
Variability estimate	Standard error of the mean
Dispersion value	0.42

Notes:

[56] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory

[57] - Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid minus Metformin 1000 mg bid

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of body weight after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid v Metformin 500 mg bid
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	< 0.0001 [59]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.35
upper limit	-1.69
Variability estimate	Standard error of the mean
Dispersion value	0.42

Notes:

[58] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory
[59] - Empagliflozin 12.5 mg bid+ Metformin 500 mg bid minus Metformin 500 mg bid

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of body weight after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 1000 mg bid v Metformin 1000 mg bid
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other[60]
P-value	< 0.0001 [61]
Method	Mixed models analysis
Parameter estimate	Adjusted mean
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.03
upper limit	-1.37
Variability estimate	Standard error of the mean
Dispersion value	0.42

Notes:

[60] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory

[61] - Empagliflozin 5 mg bid + Metformin 1000 mg bid minus Metformin 1000 mg bid

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline of body weight after 24 weeks of double-blind treatment. 'Baseline HbA1c':linear covariate;'treatment','baseline renal function','region','visit' & 'visit by treatment interaction':fixed effects.

Comparison groups	Empagliflozin 5 mg bid + Metformin 500 mg bid v Metformin 500 mg bid
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other[62]
P-value	< 0.0001 [63]
Method	Mixed models analysis
Parameter estimate	Adjusted Mean
Point estimate	-2.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	-1.43
Variability estimate	Standard error of the mean
Dispersion value	0.42

Notes:

[62] - Since previous step in the hierarchical testing failed (primary measure analyses 9 and 10), the analyses for secondary measures of FPG and body weight are considered exploratory and not confirmatory

[63] - Empagliflozin 5 mg bid + Metformin 500 mg bid minus Metformin 500 mg bid

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events with an onset after the first dose of randomised trial medication up to a period of 7 days after the last dose (Up to 237 days)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Empagliflozin 10 mg qd
Reporting group description: Oral administration of Empagliflozin 10 mg qd	
Reporting group title	Empagliflozin 25 mg qd
Reporting group description: Oral administration of Empagliflozin 25 mg once daily (qd)	
Reporting group title	Empagliflozin 5 mg bid + Metformin 500 mg bid
Reporting group description: Oral administration of Empagliflozin 5 mg and Metformin 500 mg bid	
Reporting group title	Empagliflozin 5 mg bid + Metformin 1000 mg bid
Reporting group description: Oral administration of Empagliflozin 5 mg and Metformin 1000 mg bid	
Reporting group title	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid
Reporting group description: Oral administration of Empagliflozin 12.5 mg and Metformin 500 mg bid	
Reporting group title	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid
Reporting group description: Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg twice daily (bid)	
Reporting group title	Metformin 500 mg bid
Reporting group description: Oral administration of Metformin 500 mg bid	
Reporting group title	Metformin 1000 mg bid
Reporting group description: Oral administration of Metformin 1000 mg bid	
Reporting group title	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid OL
Reporting group description: Oral administration of Empagliflozin 12.5 mg and Metformin 1000 mg twice daily (bid) in an open label (OL)	

Serious adverse events	Empagliflozin 10 mg qd	Empagliflozin 25 mg qd	Empagliflozin 5 mg bid + Metformin 500 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 172 (0.58%)	3 / 167 (1.80%)	2 / 169 (1.18%)
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)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 169 (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 / 172 (0.00%)	0 / 167 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Rib fracture			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 169 (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
Angina unstable			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Tachycardia paroxysmal			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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			
Cerebral infarction			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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 and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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			
Pancreatitis acute			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 169 (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
Cholangitis acute			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 169 (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
Cholelithiasis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 169 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 169 (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
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Dengue fever			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Herpes simplex encephalitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Nasal abscess			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 169 (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 5 mg bid + Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 171 (1.75%)	6 / 170 (3.53%)	2 / 170 (1.18%)
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)			
Chronic lymphocytic leukaemia			

subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 170 (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
Rib fracture			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 170 (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	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Tachycardia paroxysmal			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 170 (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			
Pancreatitis acute			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Cholangitis acute			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Cholelithiasis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Dengue fever			

subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Herpes simplex encephalitis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Nasal abscess			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 170 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 170 (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	Metformin 500 mg bid	Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid OL
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 171 (1.75%)	3 / 170 (1.76%)	2 / 53 (3.77%)
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)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Uterine leiomyoma			

subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 53 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Rib fracture			

subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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			
Cerebral infarction			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 53 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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			
Pancreatitis acute			

subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Cholangitis acute			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Cholelithiasis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Dengue fever			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 53 (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

Herpes simplex encephalitis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 53 (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
Nasal abscess			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	0 / 53 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 53 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Empagliflozin 10 mg qd	Empagliflozin 25 mg qd	Empagliflozin 5 mg bid + Metformin 500 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 172 (20.93%)	41 / 167 (24.55%)	42 / 169 (24.85%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 172 (2.33%)	3 / 167 (1.80%)	5 / 169 (2.96%)
occurrences (all)	4	4	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 172 (1.16%)	6 / 167 (3.59%)	9 / 169 (5.33%)
occurrences (all)	2	7	12
Gastritis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	1 / 169 (0.59%)
occurrences (all)	0	2	1
Nausea			

subjects affected / exposed	1 / 172 (0.58%)	1 / 167 (0.60%)	5 / 169 (2.96%)
occurrences (all)	1	1	5
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 172 (2.91%)	7 / 167 (4.19%)	4 / 169 (2.37%)
occurrences (all)	5	8	4
Urinary tract infection			
subjects affected / exposed	12 / 172 (6.98%)	13 / 167 (7.78%)	9 / 169 (5.33%)
occurrences (all)	16	15	11
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	15 / 172 (8.72%)	11 / 167 (6.59%)	15 / 169 (8.88%)
occurrences (all)	15	11	15
Hypoglycaemia			
subjects affected / exposed	2 / 172 (1.16%)	1 / 167 (0.60%)	0 / 169 (0.00%)
occurrences (all)	2	1	0

Non-serious adverse events	Empagliflozin 5 mg bid + Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 500 mg bid	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 171 (20.47%)	40 / 170 (23.53%)	48 / 170 (28.24%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 171 (2.34%)	9 / 170 (5.29%)	6 / 170 (3.53%)
occurrences (all)	4	9	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 171 (2.92%)	6 / 170 (3.53%)	12 / 170 (7.06%)
occurrences (all)	6	14	13
Gastritis			
subjects affected / exposed	2 / 171 (1.17%)	1 / 170 (0.59%)	0 / 170 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	5 / 171 (2.92%)	4 / 170 (2.35%)	6 / 170 (3.53%)
occurrences (all)	5	4	6
Infections and infestations			
Upper respiratory tract infection			

subjects affected / exposed	8 / 171 (4.68%)	5 / 170 (2.94%)	4 / 170 (2.35%)
occurrences (all)	11	8	4
Urinary tract infection			
subjects affected / exposed	12 / 171 (7.02%)	17 / 170 (10.00%)	18 / 170 (10.59%)
occurrences (all)	14	19	20
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	8 / 171 (4.68%)	6 / 170 (3.53%)	8 / 170 (4.71%)
occurrences (all)	8	6	8
Hypoglycaemia			
subjects affected / exposed	1 / 171 (0.58%)	4 / 170 (2.35%)	4 / 170 (2.35%)
occurrences (all)	1	5	6

Non-serious adverse events	Metformin 500 mg bid	Metformin 1000 mg bid	Empagliflozin 12.5 mg bid+ Metformin 1000 mg bid OL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 171 (22.22%)	53 / 170 (31.18%)	16 / 53 (30.19%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 171 (4.09%)	4 / 170 (2.35%)	3 / 53 (5.66%)
occurrences (all)	7	7	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 171 (3.51%)	24 / 170 (14.12%)	4 / 53 (7.55%)
occurrences (all)	6	29	6
Gastritis			
subjects affected / exposed	2 / 171 (1.17%)	4 / 170 (2.35%)	3 / 53 (5.66%)
occurrences (all)	2	4	3
Nausea			
subjects affected / exposed	1 / 171 (0.58%)	3 / 170 (1.76%)	3 / 53 (5.66%)
occurrences (all)	1	4	3
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 171 (5.85%)	5 / 170 (2.94%)	3 / 53 (5.66%)
occurrences (all)	11	7	3
Urinary tract infection			

subjects affected / exposed	12 / 171 (7.02%)	14 / 170 (8.24%)	0 / 53 (0.00%)
occurrences (all)	13	16	0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	7 / 171 (4.09%)	8 / 170 (4.71%)	2 / 53 (3.77%)
occurrences (all)	8	8	2
Hypoglycaemia			
subjects affected / exposed	0 / 171 (0.00%)	2 / 170 (1.18%)	3 / 53 (5.66%)
occurrences (all)	0	2	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2012	The first amendment introduced a change in inclusion criterion no. 3. In the original version of the CTP, patients were to have an HbA1c value of ≥ 7.0% and ≤ 10% (≥53.0 mmol/mol and ≤85.8 mmol/mol) at Visit 1 (screening) to be eligible for randomised treatment and patients with HbA1dc >12% were eligible for OL arm. The values were changed to HbA1c ≥ 7.5% and ≤ 12.0% (≥ 58.5 mmol/mol and ≤ 107.7 mmol/mol) at Visit 1 (screening). This change was introduced to investigate the potential of empagliflozin treatment for reducing higher HbA1c values in a randomised set-up rather than in an open label group. As a consequence, patients were no longer to be recruited in the open-label group after the introduction of this amendment. Subsequently, the planned total number of patients was changed from from 1424 to 1344. However, patients who had already entered the open-label treatment group based on the original inclusion criteria had the option to continue in the trial and complete their assigned treatment. The ANCOVA (LOCF) analysis used for the main analysis of the primary and key secondary endpoints was replaced by an MMRM (OC) model following an FDA request (also see Section 9.7.1.1). The last paragraph in Section 5.4.2 of the CTP (Physical examiniation and ECG) was deleted, because after the finalisation of the CTP it was decided that ECGs will not be stored by the vendor. A clarification was added that pulse rate (PR) should be measured during second blood pressure (BP) measurement when automated BP devices were used.
06 March 2014	An additional study objective was added, namely to investigate the efficacy of empagliflozin 10 mg qd and 25 mg qd compared with metformin 1000 mg bid. The following tests were added in the null and alternative hypotheses section: non-inferiority testing of empagliflozin 25mg qd vs. metformin 1000 mg bid followed by non-inferiority testing of empagliflozin 10mg qd vs. metformin 1000 mg bid, superiority testing of empagliflozin 25mg qd vs. metformin 1000 mg bid followed by superiority testing of empagliflozin 10mg qd vs. metformin 1000 mg bid: The power calculation for non-inferiority tests was also added. A new process was implemented for the further evaluation and assessment of hepatic events and cases of cancer. The timing for submitting SAE forms was changed from 'within 24 hours or the next business day whichever is shorter' to 'within 24 hours of awareness' to comply with new company standards for AE reporting. The Cockcroft-Gault formula for calculating creatinine clearance was corrected. The description of the open-label set (OLS) was added, as it was previously missing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported