Clinical trial results:
A randomised, double blind, placebo controlled, parallel group efficacy and safety study of oral administration of empagliflozin twice daily versus once daily in two different daily doses over 16 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with type 2 diabetes mellitus and insufficient glycaemic control

Summary

EudraCT number	2012-000905-53
Trial protocol	EE LV DE LT ES PL IT
Global end of trial date	03 December 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	1276.10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01649297
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasee 173, Ingelheim am Rhein, Germany,
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co KG, +49 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co KG, +49 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	11 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2013
Global end of trial reached?	Yes
Global end of trial date	03 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of different dosage regimens of empagliflozin, 5mg twice daily compared to 10 mg once daily versus placebo and 12.5 mg twice daily compared to 25 mg once daily versus placebo, administered orally as add-on therapy to metformin in patients with T2DM and insufficient glycaemic control.
The study is designed to show non-inferiority of empagliflozin 5 mg bid and 12.5 mg bid treatment versus reference therapy with empagliflozin 10 mg qd and 25 mg qd respectively.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were 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. Rescue medication was allowed for all patients as required.
The safety of the patients was ensured by monitoring the patients for adverse events, both clinically and by laboratory testing. Symptoms that could be attributed to hypo- or hyperglycaemia were to be closely monitored in this trial. Furthermore, due to the expected effect of empagliflozin on blood pressure, symptoms that could be attributed to hypo- or hypertension were to be closely monitored in this trial.

Background therapy:

All patients in this trial were on a metformin background medication and therefore received a medication approved for treatment of their disease.

Evidence for comparator: -

Actual start date of recruitment	26 October 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	Poland: 80
Country: Number of subjects enrolled	Spain: 69
Country: Number of subjects enrolled	Estonia: 68
Country: Number of subjects enrolled	France: 66
Country: Number of subjects enrolled	Germany: 122
Country: Number of subjects enrolled	Italy: 88
Country: Number of subjects enrolled	Latvia: 83
Country: Number of subjects enrolled	Lithuania: 31
Country: Number of subjects enrolled	Canada: 128

Country: Number of subjects enrolled	Georgia: 100
Country: Number of subjects enrolled	Guatemala: 119
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Mexico: 63
Country: Number of subjects enrolled	New Zealand: 17
Country: Number of subjects enrolled	Russian Federation: 62
Country: Number of subjects enrolled	South Africa: 70
Country: Number of subjects enrolled	Ukraine: 54
Country: Number of subjects enrolled	United States: 398
Worldwide total number of subjects	1626
EEA total number of subjects	607

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)	1140
From 65 to 84 years	484
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not randomised to trial treatment if any one of the specific entry criteria were violated.

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	Empa 12.5mg BID

Arm description:

Oral administration of Empagliflozin (Empa) 12.5 mg twice daily (BID)

(Randomised set (RS) are the subjects who were randomised to receive the trial medication; this population is used for the Subject disposition and Baseline characteristics)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin 12.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Empagliflozin (Empa) 12.5 mg twice daily (BID)

Arm title	Empa 25mg QD

Arm description:

Oral administration of Empagliflozin (Empa) 25 mg once daily (QD)

(RS is the population used for Subject disposition and Baseline characteristics)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin 25mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Empagliflozin (Empa) 25 mg once daily (QD)

Arm title	Empa 5mg BID

Arm description:

Oral administration of Empagliflozin (Empa) 5 mg twice daily (BID).

RS is the population used for Subject disposition and Baseline characteristics.

Arm type	Experimental
Investigational medicinal product name	Empagliflozin 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Empagliflozin (Empa) 5 mg twice daily (BID)

Arm title	Empa 10mg QD

Arm description:

Oral administration of Empagliflozin (Empa) 10 mg once daily (QD).

RS is the population used for Subject disposition and Baseline characteristics.

Arm type	Experimental
Investigational medicinal product name	Empagliflozin 10mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Empagliflozin (Empa) 10 mg once daily (QD)

Arm title	Placebo

Arm description:

Oral administration of Placebo tablets matching empagliflozin 25 mg, 10 mg, 5 mg, and 2.5 mg.

RS is the population used for Subject disposition and Baseline characteristics.

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

Dosage and administration details:

Oral administration of Placebo tablets matching empagliflozin 25 mg, 10 mg, 5 mg, and 2.5 mg

Unit strength: Not applicable

Number of subjects in period 1[1]	Empa 12.5mg BID	Empa 25mg QD	Empa 5mg BID
Started	219	218	219
Completed	205	205	202
Not completed	14	13	17
For other reason	4	1	2
Patient withdrawal (not due to AE)	3	6	4
Adverse event, non-fatal	5	5	4
Non compliant with Protocol	1	-	3

Lost to follow-up	1	1	4
Lack of efficacy	-	-	-

Number of subjects in period 1[1]	Empa 10mg QD	Placebo
Started	220	107
Completed	201	103
Not completed	19	4
For other reason	-	-
Patient withdrawal (not due to AE)	1	1
Adverse event, non-fatal	13	1
Non compliant with Protocol	2	1
Lost to follow-up	3	-
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 randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Empa 12.5mg BID
Reporting group description:	
Oral administration of Empagliflozin (Empa) 12.5 mg twice daily (BID) (Randomised set (RS) are the subjects who were randomised to receive the trial medication; this population is used for the Subject disposition and Baseline characteristics)	
Reporting group title	Empa 25mg QD
Reporting group description:	
Oral administration of Empagliflozin (Empa) 25 mg once daily (QD) (RS is the population used for Subject disposition and Baseline characteristics)	
Reporting group title	Empa 5mg BID
Reporting group description:	
Oral administration of Empagliflozin (Empa) 5 mg twice daily (BID). RS is the population used for Subject disposition and Baseline characteristics.	
Reporting group title	Empa 10mg QD
Reporting group description:	
Oral administration of Empagliflozin (Empa) 10 mg once daily (QD). RS is the population used for Subject disposition and Baseline characteristics.	
Reporting group title	Placebo
Reporting group description:	
Oral administration of Placebo tablets matching empagliflozin 25 mg, 10 mg, 5 mg, and 2.5 mg. RS is the population used for Subject disposition and Baseline characteristics.	

Reporting group values	Empa 12.5mg BID	Empa 25mg QD	Empa 5mg BID
Number of subjects	219	218	219
Age categorical Units: Subjects			
Age continuous			
Randomised set (RS) includes subjects who were randomised to receive the trial medication; this population is used for the Subject disposition and Baseline characteristics			
Units: years			
arithmetic mean	57.6	58.1	58.9
standard deviation	± 9.9	± 10.3	± 10.1
Gender categorical Units: Subjects			
Female	93	100	96
Male	126	118	123

Reporting group values	Empa 10mg QD	Placebo	Total
Number of subjects	220	107	983
Age categorical Units: Subjects			

Age continuous			
Randomised set (RS) includes subjects who were randomised to receive the trial medication; this population is used for the Subject disposition and Baseline characteristics			
Units: years			
arithmetic mean	58.4	57.9	
standard deviation	± 10.9	± 11.2	-
Gender categorical			
Units: Subjects			
Female	109	52	450
Male	111	55	533

End points

End points reporting groups

Reporting group title	Empa 12.5mg BID

Reporting group description:

Oral administration of Empagliflozin (Empa) 12.5 mg twice daily (BID)

(Randomised set (RS) are the subjects who were randomised to receive the trial medication; this population is used for the Subject disposition and Baseline characteristics)

Reporting group title	Empa 25mg QD

Reporting group description:

Oral administration of Empagliflozin (Empa) 25 mg once daily (QD)

(RS is the population used for Subject disposition and Baseline characteristics)

Reporting group title	Empa 5mg BID

Reporting group description:

Oral administration of Empagliflozin (Empa) 5 mg twice daily (BID).

RS is the population used for Subject disposition and Baseline characteristics.

Reporting group title	Empa 10mg QD

Reporting group description:

Oral administration of Empagliflozin (Empa) 10 mg once daily (QD).

RS is the population used for Subject disposition and Baseline characteristics.

Reporting group title	Placebo

Reporting group description:

Oral administration of Placebo tablets matching empagliflozin 25 mg, 10 mg, 5 mg, and 2.5 mg.

RS is the population used for Subject disposition and Baseline characteristics.

Primary: HbA1c (Glycosylated Haemoglobin) Change From Baseline at Week 16

End point title	HbA1c (Glycosylated Haemoglobin) Change From Baseline at Week 16

End point description:

Change from baseline in HbA1c (%) after 16 weeks of treatment.
The term 'baseline' refers to the last observation prior to the first intake of any randomised study medication.
Means provided are the adjusted means.

Full Analysis Set (FAS): All randomised patients who were treated with at least 1 dose of the trial medication,had a baseline and at least 1 on treatment HbA1c assessment.
FAS is the basis for the intention-to-treat analysis. FAS with last observation carried forward (LOCF) imputation is used as the primary method of accounting for missing data.
Values after the patient started rescue medication were excluded from analysis (and imputed with an LOCF procedure).

End point type	Primary

End point timeframe:

Baseline and 16 weeks

End point values	Empa 12.5mg BID	Empa 25mg QD	Empa 5mg BID	Empa 10mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	215[1]	214[2]	215[3]	213[4]
Units: percentage of HbA1c				
arithmetic mean (standard error)	-0.83 (± 0.05)	-0.72 (± 0.05)	-0.66 (± 0.05)	-0.64 (± 0.05)

Notes:

[1] - FAS with LOCF has been used for HbA1c analyses

[2] - FAS with LOCF has been used for HbA1c analyses

[3] - FAS with LOCF has been used for HbA1c analyses

[4] - FAS with LOCF has been used for HbA1c analyses

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	107[5]			
Units: percentage of HbA1c				
arithmetic mean (standard error)	-0.22 (± 0.07)			

Notes:

[5] - FAS with LOCF has been used for HbA1c analyses

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The primary objective was to test the non-inferiority of empagliflozin 5 mg BID versus empagliflozin 10 mg QD, and non-inferiority of empagliflozin 12.5 mg BID versus empagliflozin 25 mg QD, assuming a non-inferiority margin of 0.35%

ANCOVA: Treatment, geographical region, renal function (screening eGFR [MDRD] value)- fixed effects and baseline HbA1c- linear covariate.

(Empa 5mg BID - Empa 10mg QD)

Comparison groups	Empa 5mg BID v Empa 10mg QD
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[6] - Null hypotheses for non-inferiority:
H10: Mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 5 mg twice daily ≥ mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 10 mg once daily + 0.35%
H20: Mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 12.5 mg twice daily ≥ mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 25 mg once daily + 0. 35%

[7] - The two non-inferiority hypotheses H10 and H20 were tested using the Hochberg procedure in order to control the family-wise type I error at 0.025 (one-sided).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The primary objective was to test the non-inferiority of empagliflozin 5 mg BID versus empagliflozin 10 mg QD, and non-inferiority of empagliflozin 12.5 mg BID versus empagliflozin 25 mg QD, assuming a non-inferiority margin of 0.35%

ANCOVA: Treatment, geographical region, renal function (screening eGFR [MDRD] value)- fixed effects and baseline HbA1c- linear covariate.

(Empa 12.5 mg BID - Empa 25 mg QD)

Comparison groups	Empa 12.5mg BID v Empa 25mg QD
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	< 0.0001 [9]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[8] - Null hypotheses for non-inferiority:
H10: Mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 5 mg twice daily ≥ mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 10 mg once daily + 0.35%
H20: Mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 12.5 mg twice daily ≥ mean change from baseline in HbA1c (%) after 16 weeks of treatment with empagliflozin 25 mg once daily + 0. 35%
[9] - The two non-inferiority hypotheses H10 and H20 were tested using the Hochberg procedure in order to control the family-wise type I error at 0.025 (one-sided).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing HbA1c after 16 weeks of treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided).
ANCOVA: Treatment, geographical region, renal function (screening eGFR [MDRD] value)- fixed effects and baseline HbA1c- linear covariate.
(Empa 12.5 mg BID - Placebo)

Comparison groups	Empa 12.5mg BID v Placebo
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing HbA1c after 16 weeks of treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided).

ANCOVA: Treatment, geographical region, renal function (screening eGFR [MDRD] value)- fixed effects and baseline HbA1c- linear covariate.
(Empa 25 mg QD - Placebo)

Comparison groups	Placebo v Empa 25mg QD
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.32
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing HbA1c after 16 weeks of treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided).
ANCOVA: Treatment, geographical region, renal function (screening eGFR [MDRD] value)- fixed effects and baseline HbA1c- linear covariate.
(Empa 5mg BID - Placebo)

Comparison groups	Placebo v Empa 5mg BID

Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.27
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing HbA1c after 16 weeks of treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided).
ANCOVA: Treatment, geographical region, renal function (screening eGFR [MDRD] value)- fixed effects and baseline HbA1c- linear covariate.
(Empa 10mg QD - Placebo)

Comparison groups	Placebo v Empa 10mg QD
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Fasting Plasma Glucose (FPG) Change From Baseline at Week 16

End point title	Fasting Plasma Glucose (FPG) Change From Baseline at Week 16

End point description:

Change from baseline in FPG (mg/dL) after 16 weeks of treatment.
The term 'baseline' refers to the last observation prior to the first intake of any randomised study medication.
Means provided are the adjusted means.

End point type	Secondary

End point timeframe:
Baseline and 16 weeks

End point values	Empa 12.5mg BID	Empa 25mg QD	Empa 5mg BID	Empa 10mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	213[10]	214[11]	213[12]	213[13]
Units: mg/dL				
arithmetic mean (standard error)	-27.7 (± 2)	-22.7 (± 2)	-21.2 (± 2)	-17.6 (± 2)

Notes:
[10] - FAS with LOCF has been used for FPG analyses
[11] - FAS with LOCF has been used for FPG analyses
[12] - FAS with LOCF has been used for FPG analyses
[13] - FAS with LOCF has been used for FPG analyses

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	107[14]			
Units: mg/dL				
arithmetic mean (standard error)	-0.2 (± 2.8)			

Notes:
[14] - FAS with LOCF has been used for FPG analyses

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:
ANCOVA: Treatment, geographical region, renal function (screening (eGFR) [MDRD]value)-fixed effects and baseline HbA1c,baseline FPG-linear covariates

Empa 5mg BID - Empa 10 mg QD

Comparison groups	Empa 5mg BID v Empa 10mg QD
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	2.8

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA: Treatment, geographical region, renal function (screening (eGFR) [MDRD]value)-fixed effects and baseline HbA1c and baseline FPG-linear covariates

Empa 12.5mg BID - Empa 25mg QD

Comparison groups	Empa 12.5mg BID v Empa 25mg QD
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	2.8

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing FPG after 16 weeks of treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided)
ANCOVA: Treatment, geographical region, renal function (screening (eGFR) [MDRD]value)-fixed effects and baseline HbA1c,baseline FPG-linear covariates
Empa 12.5mg BID -Placebo

Comparison groups	Placebo v Empa 12.5mg BID
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-27.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.2
upper limit	-20.9
Variability estimate	Standard error of the mean
Dispersion value	3.4

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing FPG after 16 weeks of

treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided)
ANCOVA: Treatment, geographical region, renal function (screening (eGFR) [MDRD]value)-fixed effects and baseline HbA1c,baseline FPG-linear covariates
Empa 25mg QD - Placebo

Comparison groups	Placebo v Empa 25mg QD
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-22.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.2
upper limit	-15.9
Variability estimate	Standard error of the mean
Dispersion value	3.4

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing FPG after 16 weeks of treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided)
ANCOVA: Treatment, geographical region, renal function (screening (eGFR) [MDRD]value)-fixed effects and baseline HbA1c,baseline FPG-linear covariates
Empa 5mg BID - Placebo

Comparison groups	Placebo v Empa 5mg BID
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-21.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.7
upper limit	-14.4
Variability estimate	Standard error of the mean
Dispersion value	3.4

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Superiority of once daily dose of empagliflozin (10 mg and 25 mg) versus placebo and superiority of twice daily dose of empagliflozin (5 mg and 12.5 mg) versus placebo in reducing FPG after 16 weeks of treatment was tested in an exploratory manner, to demonstrate assay sensitivity against placebo at 0.05 level (two-sided)
ANCOVA: Treatment, geographical region, renal function (screening (eGFR) [MDRD]value)-fixed effects and baseline HbA1c,baseline FPG-linear covariates
Empa 10mg QD vs Placebo

Comparison groups	Placebo v Empa 10mg QD
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-17.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.1
upper limit	-10.8
Variability estimate	Standard error of the mean
Dispersion value	3.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 16 weeks + 1 week follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Empa 12.5mg BID
Reporting group description: Oral administration of Empagliflozin (Empa) 12.5 mg twice daily (BID)	
Reporting group title	Empa 25mg QD
Reporting group description: Oral administration of Empagliflozin (Empa) 25 mg once daily (QD)	
Reporting group title	Empa 5mg BID
Reporting group description: Oral administration of Empagliflozin (Empa) 5 mg twice daily (BID)	
Reporting group title	Empa 10mg QD
Reporting group description: Oral administration of Empagliflozin (Empa) 10 mg once daily (QD)	
Reporting group title	Placebo
Reporting group description: Oral administration of Placebo tablets matching empagliflozin 25 mg, 10 mg, 5mg, and 2.5 mg	

Serious adverse events	Empa 12.5mg BID	Empa 25mg QD	Empa 5mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 219 (2.28%)	2 / 218 (0.92%)	7 / 219 (3.20%)
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)			
Biliary adenoma			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	0 / 219 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	0 / 219 (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
Prostate cancer			

subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 219 (0.46%)	0 / 218 (0.00%)	0 / 219 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
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 / 219 (0.00%)	0 / 218 (0.00%)	0 / 219 (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
Ischaemic stroke			
subjects affected / exposed	1 / 219 (0.46%)	0 / 218 (0.00%)	0 / 219 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 219 (0.46%)	0 / 218 (0.00%)	0 / 219 (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
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 219 (0.00%)	1 / 218 (0.46%)	0 / 219 (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
Gastrointestinal disorders			
Inguinal hernia			

subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	0 / 219 (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
Pancreatitis acute			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotid gland enlargement			
subjects affected / exposed	1 / 219 (0.46%)	0 / 218 (0.00%)	0 / 219 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 219 (0.46%)	0 / 218 (0.00%)	0 / 219 (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
Salivary gland pain			
subjects affected / exposed	1 / 219 (0.46%)	0 / 218 (0.00%)	0 / 219 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	0 / 219 (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			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	0 / 219 (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 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
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 and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 218 (0.00%)	0 / 219 (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
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Exostosis of jaw			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	0 / 219 (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
Synovial cyst			
subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 218 (0.46%)	0 / 219 (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
Pharyngotonsillitis			

subjects affected / exposed	0 / 219 (0.00%)	0 / 218 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Empa 10mg QD	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 220 (2.27%)	1 / 107 (0.93%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Biliary adenoma			
subjects affected / exposed	1 / 220 (0.45%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 220 (0.45%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 220 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 220 (0.45%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 220 (0.45%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland pain			

subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 220 (0.45%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 220 (0.45%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Exostosis of jaw			

subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 220 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Empa 12.5mg BID	Empa 25mg QD	Empa 5mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 219 (4.57%)	10 / 218 (4.59%)	8 / 219 (3.65%)
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	10 / 219 (4.57%)	10 / 218 (4.59%)	8 / 219 (3.65%)
occurrences (all)	11	10	8

Non-serious adverse events	Empa 10mg QD	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 220 (6.82%)	4 / 107 (3.74%)	
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	15 / 220 (6.82%) 16	4 / 107 (3.74%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2012	Global amendments involved only logistical or administrative aspects and had no impact on trial conduct. These amendments were therefore implemented without IEC or Competent Authority approval.
11 October 2012	Global amendments involved only logistical or administrative aspects and had no impact on trial conduct. These amendments were therefore implemented without IEC or Competent Authority approval.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported