

**Clinical trial results:**

A phase III, randomised, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy.

Summary

EudraCT number	2012-002270-31
Trial protocol	ES NO IT BG
Global end of trial date	23 March 2015

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	08 April 2016

Trial information**Trial identification**

Sponsor protocol code	1275.9
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01734785
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, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintrriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001184-PIP01-11
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	16 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2015
Global end of trial reached?	Yes
Global end of trial date	23 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin 25 mg (empa 25) and empagliflozin 10 mg (empa 10) versus placebo, each administered on a background of linagliptin 5 mg (lina 5) and metformin, over 24 weeks in patients with type 2 diabetes (T2DM), who had not achieved glycaemic control after 16 weeks of treatment with lina 5 on a background of metformin.

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.

Background therapy:

Metformin was administered as background treatment to all the patients.

Evidence for comparator: -

Actual start date of recruitment	01 March 2013
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	New Zealand: 78
Country: Number of subjects enrolled	Norway: 43
Country: Number of subjects enrolled	Spain: 176
Country: Number of subjects enrolled	Taiwan: 60
Country: Number of subjects enrolled	United States: 442
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Brazil: 152
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Korea, Republic of: 122
Worldwide total number of subjects	1134
EEA total number of subjects	233

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)	910
From 65 to 84 years	219
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

16-week open-label (OL) lina 5 period followed by a 1-week OL period with additional placebo administration preceded randomisation to double-blind treatment. Patients were randomised to double blind treatment only when they had not met glycaemic control criteria after the 16-week OL period. All treatments were administered in addition to metformin.

Period 1

Period 1 title	Open-Label Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The open label treatment period was non randomised and not controlled. Trial medications during the first 16 week treatment period and the placebo add-on period were open-label.

Arms

Arm title	Linagliptin 5 mg
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Arm description:

Patients received 5mg dose of Linagliptin (lina 5), administered orally, once daily for 16 weeks during the OL treatment period, thereafter patients received 1 matching placebo tablet to Fixed dose combination (FDC) empa 25/lina 5, and 1 matching placebo tablet to FDC empa 10/lina 5 per day in addition to lina 5 OL, for 1 week during the open-label placebo add-on treatment period.

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

Dosage and administration details:

Patients received 5mg dose of Linagliptin (lina 5), administered orally, once daily for 16 weeks during the OL treatment period and for 1 week during the placebo add-on treatment period.

Investigational medicinal product name	Placebo to Empagliflozin 25 mg / Linagliptin 5mg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

After 16 weeks of open label treatment period, subjects were orally administered once daily one placebo tablet matching to empa 25 mg in combination with lina 5 mg_FDC tablet for 1 week in addition to lina 5 mg.

Investigational medicinal product name	Placebo to Empagliflozin 10 mg / Linagliptin 5mg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

After 16 weeks of open label treatment period, subjects were orally administered once daily one placebo tablet matching to empa 10 mg in combination with lina 5 mg_FDC tablet for 1 week in addition to lina 5 mg.

Number of subjects in period 1	Linagliptin 5 mg
Started	606
Completed	333
Not completed	273
Consent withdrawn by subject	12
Adverse event, non-fatal	9
Other Reasons	224
Lost to follow-up	14
Lack of efficacy	1
Protocol deviation	13

Period 2

Period 2 title	Double-Blind Period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Medications during the 24 week treatment period were administered double-blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin 25 mg

Arm description:

Patients received 1 fixed dose combination (FDC) Empagliflozin (empa) 25/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period. One subject randomised to Empagliflozin 25 mg was not treated. Although 111 patients were randomised to this treatment arm, 110 patients were therefore treated and included in summaries of baseline characteristics on the treated set.

Arm type	Experimental
Investigational medicinal product name	Empagliflozin 25mg / Linagliptin 5mg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered once daily Empagliflozin 25 mg in combination with lina 5 mg, 1 FDC tablet for 24 weeks during the double-blind treatment period.

Investigational medicinal product name	Placebo matching FDC Empagliflozin 10mg/ Linagliptin 5mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects were orally administered once daily one placebo tablet matching to Empagliflozin 10 mg in combination with Lina 5 mg_FDC tablet for 24 weeks during the double blind treatment period.	
Investigational medicinal product name	Placebo matching Linagliptin 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects were orally administered once daily one placebo tablet matching to Linagliptin 5 mg for 24 weeks during the double blind treatment period.	
Arm title	Empagliflozin 10 mg
Arm description:	
Patients received 1 FDC empa 10/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 25/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.	
Arm type	Experimental
Investigational medicinal product name	Empagliflozin 10mg / Linagliptin 5mg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects were orally administered once daily Empagliflozin 10 mg in combination with lina 5 mg, 1 FDC tablet for 24 weeks during the double-blind treatment period.	
Investigational medicinal product name	Placebo matching FDC Empagliflozin 25mg/ Linagliptin 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects were orally administered once daily one placebo tablet matching to Empagliflozin 25 mg in combination with Lina 5 mg_FDC tablet for 24 weeks during the double blind treatment period.	
Investigational medicinal product name	Placebo matching Linagliptin 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects were orally administered once daily one placebo tablet matching to Linagliptin 5 mg for 24 weeks during the double blind treatment period.	
Arm title	Placebo
Arm description:	
Patients received 1 lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to FDC empa 25/lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.	
Arm type	Comparator
Investigational medicinal product name	Placebo matching FDC Empagliflozin 10mg/ Linagliptin 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered once daily one placebo tablet matching to Empagliflozin 10 mg in combination with Lina 5 mg_FDC tablet for 24 weeks during the double blind treatment period.

Investigational medicinal product name	Placebo matching FDC Empagliflozin 25mg/ Linagliptin 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered once daily one placebo tablet matching to Empagliflozin 25 mg in combination with Lina 5 mg_FDC tablet for 24 weeks during the double blind treatment period.

Investigational medicinal product name	Linagliptin 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered once daily 5mg dose of Linagliptin (lina 5) for 24 weeks during the double blind treatment period.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 is used to report the baseline values due to study design.

Number of subjects in period 2^[2][3]	Empagliflozin 25 mg	Empagliflozin 10 mg	Placebo
Started	110	112	110
Completed	106	103	105
Not completed	4	9	5
Consent withdrawn by subject	2	-	-
Adverse event, non-fatal	-	3	2
Lost to follow-up	2	4	2
Lack of efficacy	-	1	-
Protocol deviation	-	1	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on the patients who were randomized after successfully completing the period 1 and received at least one dose of the period 2 trial medication.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 333 patients completed preceding OL treatment (Period 1). 333 patients were randomised to DB treatment (Period 2). 332 patients received DB treatment (Period 2). One patient (Empa 25mg) was randomised and did not receive treatment.

Baseline characteristics

Reporting groups

Reporting group title	Empagliflozin 25 mg
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Reporting group description:

Patients received 1 fixed dose combination (FDC) Empagliflozin (empa) 25/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period. One subject randomised to Empagliflozin 25 mg was not treated. Although 111 patients were randomised to this treatment arm, 110 patients were therefore treated and included in summaries of baseline characteristics on the treated set.

Reporting group title	Empagliflozin 10 mg
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Reporting group description:

Patients received 1 FDC empa 10/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 25/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group title	Placebo
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Reporting group description:

Patients received 1 lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to FDC empa 25/lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group values	Empagliflozin 25 mg	Empagliflozin 10 mg	Placebo
Number of subjects	110	112	110
Age categorical Units: Subjects			

Age Continuous			
The treated set (TS) consisted of all patients who were randomised and treated with at least 1 dose of study drug during the double-blind part of the trial.			
Units: Years			
arithmetic mean	55.4	54.3	55.9
standard deviation	± 9.9	± 9.5	± 9.6
Gender, Male/Female Units: Participants			
Female	39	46	49
Male	71	66	61

Reporting group values	Total		
Number of subjects	332		
Age categorical Units: Subjects			

Age Continuous			
The treated set (TS) consisted of all patients who were randomised and treated with at least 1 dose of study drug during the double-blind part of the trial.			
Units: Years			
arithmetic mean			
standard deviation	-		

Gender, Male/Female			
Units: Participants			
Female	134		
Male	198		

End points

End points reporting groups

Reporting group title	Linagliptin 5 mg
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Reporting group description:

Patients received 5mg dose of Linagliptin (lina 5), administered orally, once daily for 16 weeks during the OL treatment period, thereafter patients received 1 matching placebo tablet to Fixed dose combination (FDC) empa 25/lina 5, and 1 matching placebo tablet to FDC empa 10/lina 5 per day in addition to lina 5 OL, for 1 week during the open-label placebo add-on treatment period.

Reporting group title	Empagliflozin 25 mg
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Reporting group description:

Patients received 1 fixed dose combination (FDC) Empagliflozin (empa) 25/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period. One subject randomised to Empagliflozin 25 mg was not treated. Although 111 patients were randomised to this treatment arm, 110 patients were therefore treated and included in summaries of baseline characteristics on the treated set.

Reporting group title	Empagliflozin 10 mg
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Reporting group description:

Patients received 1 FDC empa 10/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 25/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group title	Placebo
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Reporting group description:

Patients received 1 lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to FDC empa 25/lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.

Primary: HbA1c change from baseline after 24 weeks double-blind randomised treatment

End point title	HbA1c change from baseline after 24 weeks double-blind randomised treatment
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End point description:

Change from baseline in Glycated haemoglobin (HbA1c) [%] after 24 weeks of treatment with double-blind trial medication. Baseline was defined as the last observation before the first intake of any double-blind randomised trial medication. The term 'baseline' was not used to refer to measurements before the administration of open-label medication. The full analysis set (FAS) consisted of all patients in the TS who had a baseline HbA1c assessment and at least 1 on-treatment HbA1c assessment during the double-blind part of the trial. Observed Case (OC): In the OC analysis, values after the use of rescue medication were set to missing.

End point type	Primary
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End point timeframe:

Baseline and 24 weeks

End point values	Empagliflozin 25 mg	Empagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110 ^[1]	109 ^[2]	106 ^[3]	
Units: Percentage of HbA1c				
least squares mean (standard error)	-0.56 (± 0.08)	-0.65 (± 0.08)	0.14 (± 0.09)	

Notes:

[1] - Patients in the FAS (OC) who were analysed in the MMRM.

[2] - Patients in the FAS (OC) who were analysed in the MMRM.

[3] - Patients in the FAS (OC) who were analysed in the MMRM.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Superiority of Empagliflozin 25 mg vs. placebo: change in HbA1c using a restricted maximum likelihood (REML)- based mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c as linear covariate(s) & baseline Estimated glomerula filtration rate (eGFR), geographical region, treatment, visit, visit by treatment interaction as fixed effect(s).	
Comparison groups	Empagliflozin 25 mg v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[4] - The unstructured co-variance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Empagliflozin 25 mg minus Placebo at week 24.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Superiority of Empagliflozin 10 mg vs. placebo: change in HbA1c using a restricted maximum likelihood (REML)- based mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c as linear covariate(s) & baseline Estimated glomerula filtration rate (eGFR), geographical region, treatment, visit, visit by treatment interaction as fixed effect(s).	
Comparison groups	Empagliflozin 10 mg v Placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	-0.55

Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[5] - The unstructured co-variance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Empagliflozin 10 mg minus Placebo at week 24.

Secondary: Fasting plasma glucose (FPG) change from baseline after 24 weeks of double-blind treatment.

End point title	Fasting plasma glucose (FPG) change from baseline after 24 weeks of double-blind treatment.
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End point description:

Change from baseline FPG (mmol/L) after 24 weeks of treatment with double-blind trial medication.

End point type	Secondary
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End point timeframe:

Baseline and 24 weeks

End point values	Empagliflozin 25 mg	Empagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109 ^[6]	109 ^[7]	106 ^[8]	
Units: mmol/L				
least squares mean (standard error)	-1.75 (± 0.18)	-1.46 (± 0.18)	0.34 (± 0.19)	

Notes:

[6] - Patients in the FAS (OC) who were analysed in the MMRM.

[7] - Patients in the FAS (OC) who were analysed in the MMRM.

[8] - Patients in the FAS (OC) who were analysed in the MMRM.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Superiority of Empagliflozin 25 mg vs. placebo: change in FPG using a restricted maximum likelihood (REML)- based mixed model repeated measures (MMRM) approach. Model includes baseline FPG, baseline HbA1c as linear covariate(s) & baseline eGFR, geographical region, treatment, visit, visit by treatment interaction as fixed effect(s).

Comparison groups	Empagliflozin 25 mg v Placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	-1.57
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[9] - The unstructured co-variance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Empagliflozin 25 mg minus Placebo at week 24.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Superiority of Empagliflozin 10 mg vs. placebo: change in FPG using a restricted maximum likelihood (REML)- based mixed model repeated measures (MMRM) approach. Model includes baseline FPG, baseline HbA1c as linear covariate(s) & baseline eGFR, geographical region, treatment, visit, visit by treatment interaction as fixed effect(s).	
Comparison groups	Empagliflozin 10 mg v Placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.31
upper limit	-1.28
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[10] - The unstructured co-variance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Empagliflozin 10 mg minus Placebo at week 24.

Secondary: Body weight change from baseline after 24 weeks of double-blind treatment.

End point title	Body weight change from baseline after 24 weeks of double-blind treatment.
End point description:	
Change from baseline Body weight after 24 weeks of treatment with double-blind trial medication.	
End point type	Secondary
End point timeframe:	
Baseline and 24 weeks	

End point values	Empagliflozin 25 mg	Empagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110 ^[11]	109 ^[12]	106 ^[13]	
Units: kg				
least squares mean (standard error)	-2.52 (± 0.25)	-3.06 (± 0.25)	-0.3 (± 0.26)	

Notes:

[11] - Patients in the FAS (OC) who were analysed in the MMRM.

[12] - Patients in the FAS (OC) who were analysed in the MMRM.

[13] - Patients in the FAS (OC) who were analysed in the MMRM.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Superiority of Empagliflozin 25 mg vs. placebo: change in body weight using a restricted maximum likelihood (REML)- based mixed model repeated measures (MMRM) approach. Model includes baseline weight, baseline HbA1c as linear covariate(s) & baseline eGFR, geographical region, treatment, visit, visit by treatment interaction as fixed effect(s).	
Comparison groups	Empagliflozin 25 mg v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	-1.52
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[14] - The unstructured co-variance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Empagliflozin 25 mg minus Placebo at week 24.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Superiority of Empagliflozin 10 mg vs. placebo: change in body weight using a restricted maximum likelihood (REML)- based mixed model repeated measures (MMRM) approach. Model includes baseline weight, baseline HbA1c as linear covariate(s) & baseline eGFR, geographical region, treatment, visit, visit by treatment interaction as fixed effect(s).	
Comparison groups	Empagliflozin 10 mg v Placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	-2.07
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[15] - The unstructured co-variance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Empagliflozin 10 mg minus Placebo at week 24.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 7 days after the last drug administration, up to 126 days (open label treatment period) and 176 days (double blind treatment period).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Empagliflozin 25 mg
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Reporting group description:

Patients received 1 FDC Empagliflozin (empa) 25/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group title	Empagliflozin 10 mg
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Reporting group description:

Patients received 1 FDC empa 10/lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to lina 5 and 1 matching placebo tablet to FDC empa 25/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group title	Placebo
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Reporting group description:

Patients received 1 lina 5 mg tablet and two placebo tablets (1 matching placebo tablet to FDC empa 25/lina 5 and 1 matching placebo tablet to FDC empa 10/lina 5), administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group title	Linagliptin 5 mg
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Reporting group description:

Patients received 5mg dose of Linagliptin (lina 5), administered orally, once daily for 16 weeks during the OL treatment period, thereafter patients received 1 matching placebo tablet to FDC empa 25/lina 5, and 1 matching placebo tablet to FDC empa 10/lina 5 per day in addition to lina 5 OL, for 1 week during the open-label placebo add-on treatment period.

Serious adverse events	Empagliflozin 25 mg	Empagliflozin 10 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 110 (3.64%)	5 / 112 (4.46%)	10 / 110 (9.09%)
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)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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 neoplasm			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 110 (0.00%)	1 / 112 (0.89%)	0 / 110 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 110 (0.00%)	1 / 112 (0.89%)	0 / 110 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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			
Oedema			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
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			
Pneumothorax			
subjects affected / exposed	0 / 110 (0.00%)	1 / 112 (0.89%)	0 / 110 (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
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Mania			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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			
Atrial fibrillation			

subjects affected / exposed	1 / 110 (0.91%)	0 / 112 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Coronary artery disease			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
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			
Cervical radiculopathy			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 112 (0.00%)	0 / 110 (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
Colitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 112 (0.89%)	0 / 110 (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
Gastritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Intestinal obstruction			

subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Umbilical hernia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Hypertransaminasaemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 110 (0.91%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 112 (0.00%)	0 / 110 (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
Nephrolithiasis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 112 (0.00%)	0 / 110 (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
Renal failure acute			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
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			
Arthralgia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 112 (0.89%)	0 / 110 (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
Intervertebral disc disorder			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 112 (0.00%)	0 / 110 (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
Osteoarthritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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			
Abscess			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Diarrhoea infectious			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Erysipelas			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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

Pharyngitis bacterial			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Pneumonia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Urosepsis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 112 (0.00%)	0 / 110 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	0 / 110 (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
Metabolic acidosis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 112 (0.00%)	1 / 110 (0.91%)
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	Linagliptin 5 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 606 (2.97%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder neoplasm			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			

subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastritis			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertransaminasaemia			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal failure acute			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc disorder			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastroenteritis			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis bacterial			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	0 / 606 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 606 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Empagliflozin 25 mg	Empagliflozin 10 mg	Placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	11 / 110 (10.00%)	19 / 112 (16.96%)	34 / 110 (30.91%)
Investigations Lipase increased subjects affected / exposed occurrences (all)	3 / 110 (2.73%) 3	4 / 112 (3.57%) 6	6 / 110 (5.45%) 6
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2	3 / 112 (2.68%) 5	8 / 110 (7.27%) 9
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 6 3 / 110 (2.73%) 3	5 / 112 (4.46%) 5 8 / 112 (7.14%) 8	8 / 110 (7.27%) 11 7 / 110 (6.36%) 7
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1	1 / 112 (0.89%) 1	7 / 110 (6.36%) 7

Non-serious adverse events	Linagliptin 5 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	78 / 606 (12.87%)		
Investigations Lipase increased subjects affected / exposed occurrences (all)	10 / 606 (1.65%) 11		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	14 / 606 (2.31%) 21		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection	25 / 606 (4.13%) 27		

subjects affected / exposed occurrences (all)	28 / 606 (4.62%) 28		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 606 (0.99%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2013	Stopping of trial treatment in case of changes in metformin background treatment or with suspected pancreatitis (included in the linagliptin labelling) were added as discontinuation criteria. Minor corrections and clarifications for consistency within the CTP and within the development program were introduced.
17 December 2013	Based upon comments in an advice letter received from health authority on 24 Apr 2013 the primary analysis model was changed from ANCOVA (LOCF) to MMRM (OC). Subsequent changes to the sensitivity analyses of the primary endpoint included the analysis of the primary endpoint using an ANCOVA (LOCF) model. The analysis of key secondary endpoints and the subgroup analyses were updated accordingly. For consistency with the TSAP, the planned analyses were updated by adding definitions of the different analysis sets (SCR, OLS, and OLFAS). The description of the trial objective and the trial design was amended to clarify the use of FDCs of empagliflozin and linagliptin. External independent committees were set-up for the adjudication of safety relevant events (pancreatic events, hepatic events, cancer assessments). To match new requirement for public disclosure AEs, hypoglycaemic events, AESIs and cardiovascular events were part of the safety assessment without being classified as further endpoints. Processes for expedited AE reporting were updated and clarified. Administration of herbal/nutritional supplements/medication that interfered with the investigational products was included as a reason for patient withdrawal. Administrative changes including updates and clarifications on AE reporting requirements including the definition of the REP, minor corrections and further clarifications were introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported