

**Clinical trial results:**

A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of linagliptin 5 mg/empagliflozin 25 mg and linagliptin 5 mg/empagliflozin 10 mg Fixed Dose Combination tablets compared with the individual components (linagliptin 5 mg, empagliflozin 25 mg, and empagliflozin 10 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-000383-10
Trial protocol	EE ES HU SE DK IT BG
Global end of trial date	10 September 2013

Results information

Result version number	v2 (current)
This version publication date	23 July 2016
First version publication date	17 April 2015
Version creation reason	• Correction of full data set Data correction due to system error in EudraCT- Results

Trial information**Trial identification**

Sponsor protocol code	1275.1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01422876
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 , +1 800-243-0127, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 800-243-0127, clintrriage.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	No

1901/2006 apply to this trial?	
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	07 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2013
Global end of trial reached?	Yes
Global end of trial date	10 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to investigate the efficacy, safety and tolerability of empagliflozin 25 mg/linagliptin 5 mg FDC qd and of empagliflozin 10 mg/linagliptin 5 mg FDC qd compared to the individual components (empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg) given for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control.

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: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2011
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: 26
Country: Number of subjects enrolled	Romania: 154
Country: Number of subjects enrolled	Spain: 107
Country: Number of subjects enrolled	Sweden: 95
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Denmark: 40
Country: Number of subjects enrolled	Estonia: 55
Country: Number of subjects enrolled	Hungary: 48
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Argentina: 110
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Brazil: 38

Country: Number of subjects enrolled	Canada: 130
Country: Number of subjects enrolled	Colombia: 68
Country: Number of subjects enrolled	Lebanon: 82
Country: Number of subjects enrolled	Malaysia: 23
Country: Number of subjects enrolled	Mexico: 79
Country: Number of subjects enrolled	Peru: 75
Country: Number of subjects enrolled	Philippines: 109
Country: Number of subjects enrolled	Russian Federation: 69
Country: Number of subjects enrolled	Taiwan: 56
Country: Number of subjects enrolled	United States: 1073
Worldwide total number of subjects	2505
EEA total number of subjects	566

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)	1957
From 65 to 84 years	543
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Of the 1405 patients enrolled and randomized the data for 42 randomized patients were excluded from all analyses due to serious non-compliance. Therefore, 1363 patients were included in the analyses.

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 trial) (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?	No
Arm title	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg

Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral

Arm type	Experimental
Investigational medicinal product name	Empagliflozin + Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin/linagliptin Fixed Dose Combination (FDC) tablets, dose: 25 mg/5 mg q.d.

Arm title	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
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Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral

Arm type	Experimental
Investigational medicinal product name	Empagliflozin + Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin/linagliptin Fixed Dose Combination (FDC) tablets, dose: 10 mg/5 mg q.d

Arm title	Metformin Background: Empagliflozin 25 mg
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Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged

for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral

Arm type	Active comparator
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin tablets 25 mg q.d.

Arm title	Metformin Background: Empagliflozin 10 mg
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Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral

Arm type	Active comparator
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin tablets 10 mg q.d.

Arm title	Metformin Background: Linagliptin 5 mg
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Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral

Arm type	Active comparator
Investigational medicinal product name	Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Linagliptin tablets 5 mg q.d.

Arm title	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
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Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral

Arm type	Experimental
Investigational medicinal product name	Empagliflozin + Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin/linagliptin FDC tablets, 25 mg/5 mg q.d.

Arm title	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
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Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral

Arm type	Experimental
Investigational medicinal product name	Empagliflozin + Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin/linagliptin FDC tablets 10 mg/5 mg q.d.

Arm title	Treatment Naive: Empagliflozin 25 mg
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Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral

Arm type	Active comparator
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin tablets 25 mg q.d.

Arm title	Treatment Naive: Empagliflozin 10 mg
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Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral

Arm type	Active comparator
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin tablets 10 mg q.d.

Arm title	Treatment Naive: Linagliptin 5 mg
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Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral

Arm type	Active comparator
Investigational medicinal product name	Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Linagliptin tablets 5 mg q.d.

Number of subjects in period 1	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 25 mg
Started	137	136	141
Week 24 (continuing trial medication)	126	129	131
Week 52 (completed trial medication)	121 ^[1]	124 ^[2]	125 ^[3]
Week 24 (remaining in the trial)	131	133	136
Week 52 (completed trial)	125	126	128
Completed	125	126	128
Not completed	12	10	13
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	9	4	6
Lost to follow-up	3	5	7

Number of subjects in period 1	Metformin Background: Empagliflozin 10 mg	Metformin Background: Linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Started	140	132	137
Week 24 (continuing trial medication)	124	118	125
Week 52 (completed trial medication)	118 ^[4]	113 ^[5]	114 ^[6]
Week 24 (remaining in the trial)	132	125	131
Week 52 (completed trial)	122	117	120
Completed	122	117	120
Not completed	18	15	17
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	12	7	12
Lost to follow-up	5	8	5

Number of subjects in period 1	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg	Treatment Naive: Empagliflozin 10 mg
Started	136	135	134
Week 24 (continuing trial medication)	124	121	121
Week 52 (completed trial medication)	116 ^[7]	114	110 ^[8]
Week 24 (remaining in the trial)	130	128	128
Week 52 (completed trial)	120	112	113
Completed	120	112	113
Not completed	16	23	21
Adverse event, serious fatal	1	3	1
Consent withdrawn by subject	10	12	13
Lost to follow-up	5	8	7

Number of subjects in period 1	Treatment Naive: Linagliptin 5 mg
Started	135
Week 24 (continuing trial medication)	123
Week 52 (completed trial medication)	116 ^[9]
Week 24 (remaining in the trial)	125
Week 52 (completed trial)	118
Completed	118
Not completed	17
Adverse event, serious fatal	-
Consent withdrawn by subject	9
Lost to follow-up	8

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg at week 52 but not the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg at week 52 but not the trial.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 25 mg at week 52 but not the trial.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 10 mg at week 52 but not the trial.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Linagliptin 5 mg at week 52 but not the trial.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Empagliflozin 25 mg/linagliptin 5 mg at week 52 but not the trial.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completed the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Empagliflozin 10 mg/linagliptin 5 mg at week 52 but not the trial.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completed the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Empagliflozin 10 mg at week 52 but not the trial.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completed the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Linagliptin 5 mg at week 52 but not the trial.

Baseline characteristics

Reporting groups^[1]

Reporting group title	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Reporting group description:	
Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Reporting group description:	
Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Empagliflozin 25 mg
Reporting group description:	
Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Empagliflozin 10 mg
Reporting group description:	
Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Linagliptin 5 mg
Reporting group description:	
Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Reporting group description:	
Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
Reporting group description:	
Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 25 mg
Reporting group description:	
Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 10 mg
Reporting group description:	
Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Linagliptin 5 mg
Reporting group description:	
Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral	

Notes:

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

Justification: The baseline characteristics represents the number of patients randomized and analyzed whereas the worldwide number represents the number of patients enrolled.

Reporting group values	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 25 mg
Number of subjects	137	136	141
Age categorical Units: Subjects			

Age Continuous			
Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: years			
arithmetic mean	57.1	56.2	55.4
standard deviation	± 10.2	± 10.3	± 10.1
Gender, Male/Female			
Units: participants			
Female	64	52	75
Male	73	84	66

Reporting group values	Metformin Background: Empagliflozin 10 mg	Metformin Background: Linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects	140	132	137
Age categorical Units: Subjects			

Age Continuous			
Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: years			
arithmetic mean	55.9	56.3	54.3
standard deviation	± 10.5	± 9.9	± 10
Gender, Male/Female			
Units: participants			
Female	59	65	65
Male	81	67	72

Reporting group values	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg	Treatment Naive: Empagliflozin 10 mg
Number of subjects	136	135	134
Age categorical Units: Subjects			

Age Continuous			
Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: years			
arithmetic mean	55.2	55.7	53.8
standard deviation	± 9.7	± 9.5	± 10.4

Gender, Male/Female			
Units: participants			
Female	62	57	70
Male	74	78	64

Reporting group values	Treatment Naive: Linagliptin 5 mg	Total	
Number of subjects	135	1341	
Age categorical			
Units: Subjects			

Age Continuous			
Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken.			
Units: years			
arithmetic mean	53.7		
standard deviation	± 11.4	-	
Gender, Male/Female			
Units: participants			
Female	60	620	
Male	75	721	

End points

End points reporting groups

Reporting group title	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Reporting group description: Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Reporting group description: Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Empagliflozin 25 mg
Reporting group description: Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Empagliflozin 10 mg
Reporting group description: Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral	
Reporting group title	Metformin Background: Linagliptin 5 mg
Reporting group description: Study population on a stable background of metformin defined as pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Reporting group description: Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
Reporting group description: Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 25 mg
Reporting group description: Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Empagliflozin 10 mg
Reporting group description: Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral	
Reporting group title	Treatment Naive: Linagliptin 5 mg
Reporting group description: Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral	

Primary: Change from baseline in glycosylated hemoglobin (HbA1c) for Metformin Background patients

End point title	Change from baseline in glycosylated hemoglobin (HbA1c) for Metformin Background patients ^[1]
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End point description:

Glycosylated hemoglobin (HbA1c) is a measurement of the percentage of hemoglobin that is glycated. The change from baseline in HbA1c is calculated as the week 24 HbA1c minus the baseline HbA1c. Since HbA1c is measured as a percentage the change from baseline is also a percentage. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all Metformin Background patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

End point type	Primary
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End point timeframe:

Baseline and 24 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 25 mg	Metformin Background: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134 ^[2]	135 ^[3]	140 ^[4]	137 ^[5]
Units: % change from baseline				
least squares mean (standard error)	-1.19 (± 0.06)	-1.08 (± 0.06)	-0.62 (± 0.06)	-0.66 (± 0.06)

Notes:

[2] - FAS (LOCF)

[3] - FAS (LOCF)

[4] - FAS (LOCF)

[5] - FAS (LOCF)

End point values	Metformin Background: Linagliptin 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	128 ^[6]			
Units: % change from baseline				
least squares mean (standard error)	-0.7 (± 0.06)			

Notes:

[6] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Empa 25
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c ($p < 0.0001$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.0038$), geographical region ($p < 0.0001$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

Comparison groups	Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c ($p < 0.0001$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.0038$), geographical region ($p < 0.0001$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.32
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Empa 10
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c ($p < 0.0001$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.0038$), geographical region ($p < 0.0001$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

Comparison groups	Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
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Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c (p<0.0001) as linear covariate(s) and baseline eGFR (MDRD) (p=0.0038), geographical region (p<0.0001), treatment (p<0.0001) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.

Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.09

Primary: Change from baseline in glycosylated hemoglobin (HbA1c) for Treatment Naive patients

End point title	Change from baseline in glycosylated hemoglobin (HbA1c) for Treatment Naive patients ^[7]
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End point description:

Glycosylated hemoglobin (HbA1c) is a measurement of the percentage of hemoglobin that is glycated. The change from baseline in HbA1c is calculated as the week 24 HbA1c minus the baseline HbA1c. Since HbA1c is measured as a percentage the change from baseline is also a percentage. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all treatment naive patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

End point type	Primary
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End point timeframe:

Baseline and 24 weeks

Notes:

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

Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg	Treatment Naive: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134 ^[8]	135 ^[9]	133 ^[10]	132 ^[11]
Units: % change from baseline				
least squares mean (standard error)	-1.08 (± 0.07)	-1.24 (± 0.07)	-0.95 (± 0.07)	-0.83 (± 0.07)

Notes:

[8] - FAS (LOCF)

[9] - FAS (LOCF)

[10] - FAS (LOCF)

[11] - FAS (LOCF)

End point values	Treatment Naive: Linagliptin 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	133 ^[12]			
Units: % change from baseline				
least squares mean (standard error)	-0.67 (± 0.07)			

Notes:

[12] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Naive: Empa/Lina 25/5 versus Empa 25
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c (p<0.0001) as linear covariate(s) and baseline eGFR (MDRD) (p=0.8627), geographical region (p=0.0008), treatment (p<0.0001) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

Comparison groups	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1785
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Naive: Empa/Lina 10/5 versus Empa 10
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c ($p < 0.0001$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.8627$), geographical region ($p = 0.0008$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

Comparison groups	Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Naive: Empa/Lina 25/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c ($p < 0.0001$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.8627$), geographical region ($p = 0.0008$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

Comparison groups	Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	-0.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Naive: Empa/Lina 10/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline HbA1c ($p < 0.0001$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.8627$), geographical region ($p = 0.0008$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

Comparison groups	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg v Treatment Naive: Linagliptin 5 mg
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Change from baseline in fasting plasma glucose at week 24 for Metformin Background patients

End point title	Change from baseline in fasting plasma glucose at week 24 for Metformin Background patients ^[13]
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End point description:

Change from baseline in fasting plasma glucose at week 24 for Metformin Background patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all Metformin Background patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

End point type	Secondary
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End point timeframe:

Baseline and 24 Weeks

Notes:

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

Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 25 mg	Metformin Background: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133 ^[14]	134 ^[15]	139 ^[16]	136 ^[17]
Units: mg/dL change from baseline				
least squares mean (standard error)	-35.25 (± 2.53)	-32.18 (± 2.52)	-18.83 (± 2.47)	-20.84 (± 2.5)

Notes:

[14] - FAS (LOCF)

[15] - FAS (LOCF)

[16] - FAS (LOCF)

[17] - FAS (LOCF)

End point values	Metformin Background: Linagliptin 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	127 ^[18]			
Units: mg/dL change from baseline				
least squares mean (standard error)	-13.05 (± 2.59)			

Notes:

[18] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Empa 25
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Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ($p < 0.0001$), baseline HbA1c ($p = 0.6082$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.3685$), geographical region ($p = 0.0104$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

Comparison groups	Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-16.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.37
upper limit	-9.48
Variability estimate	Standard error of the mean
Dispersion value	3.54

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Lina 5
Statistical analysis description:	
Model for Week 24 includes baseline fasting plasma glucose (p<0.0001), baseline HbA1c (p=0.6082) as linear covariate(s) and baseline eGFR (MDRD) (p=0.3685), geographical region (p=0.0104), treatment (p<0.0001) as fixed effect(s).	
Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.	
Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-22.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.3
upper limit	-15.1
Variability estimate	Standard error of the mean
Dispersion value	3.62

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Empa 10
Statistical analysis description:	
Model for Week 24 includes baseline fasting plasma glucose (p<0.0001), baseline HbA1c (p=0.6082) as linear covariate(s) and baseline eGFR (MDRD) (p=0.3685), geographical region (p=0.0104), treatment (p<0.0001) as fixed effect(s).	
Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.	
Comparison groups	Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-11.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.31
upper limit	-4.37
Variability estimate	Standard error of the mean
Dispersion value	3.55

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Lina 5
Statistical analysis description:	
Model for Week 24 includes baseline fasting plasma glucose (p<0.0001), baseline HbA1c (p=0.6082) as linear covariate(s) and baseline eGFR (MDRD) (p=0.3685), geographical region (p=0.0104), treatment (p<0.0001) as fixed effect(s).	
Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.	
Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-19.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.21
upper limit	-12.03
Variability estimate	Standard error of the mean
Dispersion value	3.61

Secondary: Change from baseline in fasting plasma glucose at week 24 for Treatment Naive patients

End point title	Change from baseline in fasting plasma glucose at week 24 for Treatment Naive patients ^[19]
End point description:	
Change from baseline in fasting plasma glucose at week 24 for Treatment Naive patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all treatment naive patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.	
End point type	Secondary
End point timeframe:	
Baseline and 24 Weeks	

Notes:

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

Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg	Treatment Naive: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134 ^[20]	135 ^[21]	133 ^[22]	132 ^[23]

Units: mg/dL change from baseline				
least squares mean (standard error)	-29.55 (\pm 2.67)	-28.21 (\pm 2.66)	-24.24 (\pm 2.68)	-22.39 (\pm 2.69)

Notes:

[20] - FAS (LOCF)

[21] - FAS (LOCF)

[22] - FAS (LOCF)

[23] - FAS (LOCF)

End point values	Treatment Naive: Linagliptin 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	133 ^[24]			
Units: mg/dL change from baseline				
least squares mean (standard error)	-5.92 (\pm 2.68)			

Notes:

[24] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Naive: Empa/Lina 25/5 versus Empa 25
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Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ($p < 0.0001$), baseline HbA1c ($p = 0.4591$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.7413$), geographical region ($p = 0.1504$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

Comparison groups	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1605
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.74
upper limit	2.11
Variability estimate	Standard error of the mean
Dispersion value	3.78

Statistical analysis title	Naive: Empa/Lina 10/5 versus Empa 10
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Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ($p < 0.0001$), baseline HbA1c ($p = 0.4591$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.7413$), geographical region ($p = 0.1504$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

Comparison groups	Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1246
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.25
upper limit	1.61
Variability estimate	Standard error of the mean
Dispersion value	3.78

Statistical analysis title	Naive: Empa/Lina 25/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ($p < 0.0001$), baseline HbA1c ($p = 0.4591$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.7413$), geographical region ($p = 0.1504$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

Comparison groups	Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-23.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.06
upper limit	-16.21
Variability estimate	Standard error of the mean
Dispersion value	3.78

Statistical analysis title	Naive: Empa/Lina 10/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ($p < 0.0001$), baseline HbA1c ($p = 0.4591$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.7413$), geographical region ($p = 0.1504$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.

Comparison groups	Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
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Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-22.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.71
upper limit	-14.88
Variability estimate	Standard error of the mean
Dispersion value	3.77

Secondary: Change from baseline in body weight for Metformin Background patients

End point title	Change from baseline in body weight for Metformin Background patients ^[25]
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End point description:

Change from baseline in body weight for Metformin Background patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all Metformin Background patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

End point type	Secondary
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End point timeframe:

Baseline and 24 Weeks

Notes:

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

Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 25 mg	Metformin Background: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134 ^[26]	135 ^[27]	140 ^[28]	137 ^[29]
Units: kg change from baseline				
least squares mean (standard error)	-2.99 (± 0.31)	-2.6 (± 0.3)	-3.18 (± 0.3)	-2.53 (± 0.3)

Notes:

[26] - FAS (LOCF)

[27] - FAS (LOCF)

[28] - FAS (LOCF)

[29] - FAS (LOCF)

End point values	Metformin Background: Linagliptin 5 mg			
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Subject group type	Reporting group			
Number of subjects analysed	128 ^[30]			
Units: kg change from baseline				
least squares mean (standard error)	-0.69 (± 0.31)			

Notes:

[30] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Empa 25
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Statistical analysis description:

Model for Week 24 includes baseline weight ($p < 0.0001$), baseline HbA1c ($p = 0.1610$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.3685$), geographical region ($p = 0.0162$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

Comparison groups	Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6604 ^[31]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	1.03
Variability estimate	Standard error of the mean
Dispersion value	0.43

Notes:

[31] - Not an alpha protected test.

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline weight ($p < 0.0001$), baseline HbA1c ($p = 0.1610$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.3685$), geographical region ($p = 0.0162$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	-1.44
Variability estimate	Standard error of the mean
Dispersion value	0.44

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Empa 10
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Statistical analysis description:

Model for Week 24 includes baseline weight ($p < 0.0001$), baseline HbA1c ($p = 0.1610$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.3685$), geographical region ($p = 0.0162$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

Comparison groups	Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8757 ^[32]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.77
Variability estimate	Standard error of the mean
Dispersion value	0.43

Notes:

[32] - Not an alpha protected test.

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Lina 5
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Statistical analysis description:

Model for Week 24 includes baseline weight ($p < 0.0001$), baseline HbA1c ($p = 0.1610$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.3685$), geographical region ($p = 0.0162$), treatment ($p < 0.0001$) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.

Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.77
upper limit	-1.05
Variability estimate	Standard error of the mean
Dispersion value	0.44

Secondary: Change from baseline in body weight for Treatment Naive patients

End point title	Change from baseline in body weight for Treatment Naive patients ^[33]
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End point description:

Change from baseline in body weight for Treatment Naive patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all treatment naive patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

End point type	Secondary
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End point timeframe:

Baseline and 24 Weeks

Notes:

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

Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg	Treatment Naive: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134 ^[34]	135 ^[35]	133 ^[36]	132 ^[37]
Units: kg change from baseline				
least squares mean (standard error)	-2 (± 0.36)	-2.74 (± 0.36)	-2.13 (± 0.36)	-2.27 (± 0.37)

Notes:

[34] - FAS (LOCF)

[35] - FAS (LOCF)

[36] - FAS (LOCF)

[37] - FAS (LOCF)

End point values	Treatment Naive: Linagliptin 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	133 ^[38]			
Units: kg change from baseline				
least squares mean (standard error)	-0.78 (± 0.36)			

Notes:

[38] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Naive: Empa/Lina 25/5 versus Empa 25
Statistical analysis description:	
Model for Week 24 includes baseline weight ($p < 0.0001$), baseline HbA1c ($p = 0.0023$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.0316$), geographical region ($p = 0.0134$), treatment ($p = 0.0031$) as fixed effect(s).	
Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.	
Comparison groups	Treatment Naive: Empagliflozin 25 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.801 ^[39]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	1.14
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[39] - Not an alpha protected test.

Statistical analysis title	Naive: Empa/Lina 10/5 versus Empa 10
Statistical analysis description:	
Model for Week 24 includes baseline weight ($p < 0.0001$), baseline HbA1c ($p = 0.0023$) as linear covariate(s) and baseline eGFR (MDRD) ($p = 0.0316$), geographical region ($p = 0.0134$), treatment ($p = 0.0031$) as fixed effect(s).	
Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.	
Comparison groups	Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3616 ^[40]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	0.54
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[40] - Not an alpha protected test.

Statistical analysis title	Naive: Empa/Lina 25/5 versus Lina 5
Statistical analysis description:	
Model for Week 24 includes baseline weight (p<0.0001), baseline HbA1c (p=0.0023) as linear covariate(s) and baseline eGFR (MDRD) (p=0.0316), geographical region (p=0.0134), treatment (p=0.0031) as fixed effect(s).	
Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.	
Comparison groups	Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0178
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.51

Statistical analysis title	Naive: Empa/Lina 10/5 versus Lina 5
Statistical analysis description:	
Model for Week 24 includes baseline weight (p<0.0001), baseline HbA1c (p=0.0023) as linear covariate(s) and baseline eGFR (MDRD) (p=0.0316), geographical region (p=0.0134), treatment (p=0.0031) as fixed effect(s).	
Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.	
Comparison groups	Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	-0.95
Variability estimate	Standard error of the mean
Dispersion value	0.51

Secondary: Occurrence of treat to target efficacy response for Metformin

Background patients

End point title	Occurrence of treat to target efficacy response for Metformin Background patients ^[41]
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End point description:

Occurrence of the treat-to-target efficacy response for Metformin Background patients measured as HbA1c < 7.0% after 24 weeks of treatment for patients with HbA1c ≥ 7.0% at baseline.

Full Analysis Set (FAS) with non-completers considered failures (NCF). FAS- Metformin background patients randomised and treated who had a baseline (HbA1c ≥ 7% at baseline are included) and at least 1 on treatment HbA1c value with NCF approach, in which missing data due to premature discontinuation of a patient were considered as failure.

End point type	Secondary
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End point timeframe:

24 Weeks

Notes:

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

Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg	Metformin Background: Empagliflozin 25 mg	Metformin Background: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	123 ^[42]	128 ^[43]	132 ^[44]	125 ^[45]
Units: % of patients satisfying HbA1c < 7.0%				
number (confidence interval 95%)	61.8 (52.6 to 70.4)	57.8 (48.8 to 66.5)	32.6 (24.7 to 41.3)	28 (20.3 to 36.7)

Notes:

[42] - FAS (NCF)

[43] - FAS (NCF)

[44] - FAS (NCF)

[45] - FAS (NCF)

End point values	Metformin Background: Linagliptin 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	119 ^[46]			
Units: % of patients satisfying HbA1c < 7.0%				
number (confidence interval 95%)	36.1 (27.5 to 45.4)			

Notes:

[46] - FAS (NCF)

Statistical analyses

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Empa 25
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Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 25/5 versus Empa 25.

Comparison groups	Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.191
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.319
upper limit	7.573

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Empa 10
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Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 10/5 versus Empa 10

Comparison groups	Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.474
upper limit	8.184

Statistical analysis title	Metformin: Empa/Lina 25/5 versus Lina 5
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Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 25/5 versus Lina 5.

Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.495

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.92
upper limit	6.363

Statistical analysis title	Metformin: Empa/Lina 10/5 versus Lina 5
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Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 10/5 versus Lina 5.

Comparison groups	Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0005
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.795
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.562
upper limit	5.001

Secondary: Occurrence of treat to target efficacy response for Treatment Naive patients

End point title	Occurrence of treat to target efficacy response for Treatment Naive patients ^[47]
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End point description:

Occurrence of the treat-to-target efficacy response for Treatment Naive patients measured as HbA1c < 7.0% after 24 weeks of treatment for patients with HbA1c ≥ 7.0% at baseline.

Full Analysis Set (FAS) with non-completers considered failures (NCF). FAS-treatment naive patients randomised and treated who had a baseline (HbA1c ≥ 7% at baseline are included) and at least 1 on treatment HbA1c value with NCF approach, in which missing data due to premature discontinuation of a patient were considered as failure.

End point type	Secondary
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End point timeframe:

24 Weeks

Notes:

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

Justification: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

End point values	Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg	Treatment Naive: Empagliflozin 25 mg	Treatment Naive: Empagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	121 ^[48]	122 ^[49]	118 ^[50]	121 ^[51]
Units: % of patients satisfying HbA1c <7.0%				
number (confidence interval 95%)	55.4 (46.1 to 64.4)	62.3 (53.1 to 70.9)	41.5 (32.5 to 51)	38.8 (30.1 to 48.1)

Notes:

[48] - FAS (NCF)

[49] - FAS (NCF)

[50] - FAS (NCF)

[51] - FAS (NCF)

End point values	Treatment Naive: Linagliptin 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	127 ^[52]			
Units: % of patients satisfying HbA1c <7.0%				
number (confidence interval 95%)	32.3 (24.3 to 41.2)			

Notes:

[52] - FAS (NCF)

Statistical analyses

Statistical analysis title	Naive: Empa/Lina 25/5 versus Empa 25
Statistical analysis description:	
Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.	
Odds ratio for Empa/Lina 25/5 versus Empa 25.	
Comparison groups	Treatment Naive: Empagliflozin 25 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0224
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.893
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.095
upper limit	3.274

Statistical analysis title	Naive: Empa/Lina 10/5 versus Empa 10
Statistical analysis description:	
Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.	
Odds ratio for Empa/Lina 10/5 versus Empa 10.	
Comparison groups	Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.961
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.697
upper limit	5.169

Statistical analysis title	Naive: Empa/Lina 25/5 versus Lina 5
Statistical analysis description:	
Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.	
Odds ratio for Empa/Lina 25/5 versus Lina 5.	
Comparison groups	Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.768
upper limit	5.314

Statistical analysis title	Naive: Empa/Lina 10/5 versus Lina 5
Statistical analysis description:	
Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.	
Odds ratio for Empa/Lina 10/5 versus Lina 5.	
Comparison groups	Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.303
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.462
upper limit	7.522

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first trial medication intake until 7 days after last drug intake during the 52-week study period.

Adverse event reporting additional description:

One patient was randomized to treatment with Empa/Lina 25/5 but was treated with Empa 10 from the start of trial for 6 weeks. For efficacy, the patient was analyzed as randomized (Empa/Lina 25/5) and for safety the patient was analyzed as first medication taken (Empa 10).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Empagliflozin 25 mg/Linagliptin 5 mg
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Reporting group description:

Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral

Reporting group title	Empagliflozin 10 mg/Linagliptin 5 mg
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Reporting group description:

Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral

Reporting group title	Empagliflozin 25 mg
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Reporting group description:

Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral

Reporting group title	Empagliflozin 10 mg
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Reporting group description:

Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral

Reporting group title	Linagliptin 5 mg
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Reporting group description:

Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral

Serious adverse events	Empagliflozin 25 mg/Linagliptin 5 mg	Empagliflozin 10 mg/Linagliptin 5 mg	Empagliflozin 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 273 (4.40%)	16 / 272 (5.88%)	19 / 276 (6.88%)
number of deaths (all causes)	0	2	3
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoid cystic carcinoma			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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	1 / 273 (0.37%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Lung neoplasm			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Metastases to peritoneum			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Ovarian cancer			

subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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 cancer			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Varicose vein			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Finger amputation			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 273 (0.00%)	2 / 272 (0.74%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectocele			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
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			
Acute respiratory failure			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Pulmonary embolism			

subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Mental status changes			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Investigations			
Troponin increased			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Chemical injury			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Fibula fracture			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Lower limb fracture			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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

Rib fracture			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Seroma			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Angina unstable			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Coronary artery disease			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Coronary artery occlusion			

subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Hypertensive heart disease			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Palpitations			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Silent myocardial infarction			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Cerebral infarction			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Dementia Alzheimer's type			

subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Encephalopathy			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lethargy			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Abdominal strangulated hernia			

subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Intestinal perforation			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Mechanical ileus			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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 chronic			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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 / 273 (0.00%)	0 / 272 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic mass			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Skin and subcutaneous tissue disorders			

Diabetic foot			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Calculus ureteric			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Myofascial pain syndrome			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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

Osteoarthritis			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Cellulitis			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Cystitis			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 273 (0.00%)	1 / 272 (0.37%)	0 / 276 (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
Encephalitis viral			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Meningitis tuberculous			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peritonitis			

subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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 viral			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Pyelonephritis chronic			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 273 (0.37%)	0 / 272 (0.00%)	0 / 276 (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
Urinary tract infection			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Dehydration			

subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (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
Hypokalaemia			
subjects affected / exposed	0 / 273 (0.00%)	0 / 272 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Empagliflozin 10 mg	Linagliptin 5 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 275 (5.82%)	10 / 267 (3.75%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoid cystic carcinoma			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal carcinoma			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			

subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (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 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Finger amputation			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectocele			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin increased			

subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chemical injury			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seroma			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			

subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 275 (0.36%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			

subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (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	2 / 275 (0.73%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			

subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 275 (0.36%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (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			
Diabetic foot			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hydronephrosis			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myofascial pain syndrome			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (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			
Bacterial infection			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis viral			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis tuberculous			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			

subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 275 (0.00%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 275 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Empagliflozin 25 mg/Linagliptin 5 mg	Empagliflozin 10 mg/Linagliptin 5 mg	Empagliflozin 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 273 (29.30%)	86 / 272 (31.62%)	70 / 276 (25.36%)
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 273 (5.86%)	15 / 272 (5.51%)	13 / 276 (4.71%)
occurrences (all)	18	27	18
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 273 (1.83%)	14 / 272 (5.15%)	13 / 276 (4.71%)
occurrences (all)	6	16	17
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 273 (6.59%)	16 / 272 (5.88%)	10 / 276 (3.62%)
occurrences (all)	19	18	13
Upper respiratory tract infection			
subjects affected / exposed	19 / 273 (6.96%)	19 / 272 (6.99%)	18 / 276 (6.52%)
occurrences (all)	23	23	22
Urinary tract infection			
subjects affected / exposed	27 / 273 (9.89%)	29 / 272 (10.66%)	25 / 276 (9.06%)
occurrences (all)	35	38	36
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	8 / 273 (2.93%)	8 / 272 (2.94%)	12 / 276 (4.35%)
occurrences (all)	8	12	17

Non-serious adverse events	Empagliflozin 10 mg	Linagliptin 5 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 275 (30.18%)	94 / 267 (35.21%)	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 275 (6.91%)	24 / 267 (8.99%)	
occurrences (all)	24	28	
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	10 / 275 (3.64%) 13	12 / 267 (4.49%) 12	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	16 / 275 (5.82%) 18	20 / 267 (7.49%) 29	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	13 / 275 (4.73%) 15	16 / 267 (5.99%) 19	
Urinary tract infection subjects affected / exposed occurrences (all)	30 / 275 (10.91%) 34	27 / 267 (10.11%) 31	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	12 / 275 (4.36%) 14	24 / 267 (8.99%) 28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2012	<p>The amendment dated 27 Jan 2012 (approximately 5 months after trial initiation) introduced the following sponsor-initiated changes and clarifications after being approved by the IRB/IEC/CA: The protocol was revised to update the new co-ordinating investigator information in the trial. Increased number of entered patients: As per FDA request, the modified ITT population was to be used as the full analysis set, changed from the ITT population which included all randomised patients. The modified ITT population included all randomised patients who were treated with at least 1 dose of trial medication, had a baseline HbA1c measurement, and had at least 1 on-treatment HbA1c measurement. Considering the anticipated patient discontinuation in the trial before the first on-treatment HbA1c measurement, additional 30 patients were to be entered in the trial. The Screening study day in the flowchart was modified to clarify that the maximum time allowed from Visit 1 date to Visit 3 was 35 days.</p> <p>Description of DILI (drug-induced liver injury), definition of always serious AEs, and an appendix with further instruction on DILI handling were added in the protocol to fulfil the recommendation of the current FDA guidance. The CEC responsibility description was revised to clarify and reflect the current FDA guidance regarding evaluation of cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Known hypersensitivity or allergy to DPP4-inhibitors was added as exclusion criteria according to the FDA recommendation. A secondary analysis of the change from baseline in HbA1c after 24 weeks of treatment for the full analysis set including completers only was added according to FDA recommendation.</p>
11 December 2012	<p>The amendment dated 11 Dec 2012 (approximately 15.5 months after trial initiation) introduced the following sponsor-initiated changes and clarifications from logistical or administrative aspects which were implemented without the approval from IRB/IEC/CA: The other exploratory endpoint investigating the treat-to-target efficacy response of HbA1c <7.0% after 24 weeks of treatment was redefined as a key secondary endpoint. The endpoint was included into the confirmatory testing structure performed at 24 weeks. For the key secondary endpoint of change in body weight after 24 weeks of treatment, the comparison between the FDCs and empagliflozin was removed and redefined as other efficacy endpoint. Detailed information on DBL, treatment unblinding, and data planned to be analysed for the Week 24 confirmatory analysis were added to clarify that all confirmatory statistical analyses on the primary and key secondary endpoints were to be performed at Week 24. Laboratory tests were added and description for the clinical evaluation of liver injury was corrected to be consistent with the ISF DILI checklist and DILI laboratory kit.</p>
07 June 2013	<p>The amendment dated 07 Jun 2013 (approximately 1 year and 9 months after trial initiation) introduced the following sponsor-initiated changes and was implemented immediately in order to eliminate hazard and required IRB/IEC/CA to be notified of change with request for approval. Treatment discontinuation instructions were updated to include the criterion "if pancreatitis was suspected, the study treatment was to be stopped". This amendment was introduced after the DBL of primary analysis on 20 Mar 2013; hence it was not included in the primary analysis report.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported