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

Summary

EudraCT number	2012-002271-34
Trial protocol	PT DE ES IT
Global end of trial date	30 March 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2016
First version publication date	09 April 2016

Trial information

Trial identification

Sponsor protocol code	1275.10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01778049
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	173 Binger Strasse, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2015
Global end of trial reached?	Yes
Global end of trial date	30 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to investigate the efficacy, safety, and tolerability of linagliptin 5 mg (lina 5) compared with placebo, each administered as add-on therapy to empagliflozin (25 mg [empa 25] or 10 mg [empa 10]) and metformin, over 24 weeks in patients with type 2 diabetes (T2DM), who had met the HbA1c inclusion criterion (HbA1c ≥7% and ≤10.5%) after 16 weeks of open-label (OL) treatment with empa 25 OL or empa 10 OL and metformin background treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Germany: 111
Country: Number of subjects enrolled	Italy: 138
Country: Number of subjects enrolled	Portugal: 22
Country: Number of subjects enrolled	Russian Federation: 62
Country: Number of subjects enrolled	Spain: 131
Country: Number of subjects enrolled	Ukraine: 131
Country: Number of subjects enrolled	Argentina: 343
Country: Number of subjects enrolled	Canada: 148
Country: Number of subjects enrolled	United States: 211
Worldwide total number of subjects	1324
EEA total number of subjects	402

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)	1023
From 65 to 84 years	298
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Subjects randomised to 16 week(wk) open-label (OL) treatment with either empagliflozin (empa) 25 or empa 10 treatment, thereafter subjects entered to 1 wk open label placebo (Plc) add-on period in order to complete further eligibility evaluations before being randomised into one of the 24 wk double-blind treatment groups.

Pre-assignment

Screening details:

This was a randomised, double-blind, multi-national, parallel group trial. In this trial the treatment effects of linagliptin (lina) 5 compared with Plc were analysed as add-on to either empa 25 or empa 10. All trial treatments were administered in addition to metformin background treatment.

Period 1

Period 1 title	Open label treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial medications during the initial 16 week treatment period and the placebo add-on period were open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Empa 10 mg OL

Arm description:

Subjects were orally administered once daily empa 10 mg film-coated (1 tablet) for 16 wk during OL treatment period, thereafter patients received once daily fixed dose combination (FDC) placebo (1 tablet) matching to FDC empa 10 mg/lina 5 mg in addition to empa 10 mg for one week during open label placebo add-on treatment period.

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

Dosage and administration details:

Subjects were orally administered once daily empagliflozin (empa) 10 mg film-coated tablet for 16 weeks during open-label treatment period.

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

Dosage and administration details:

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

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

Dosage and administration details:

After 16 week open label treatment, subjects were orally administered once daily placebo tablet matching to empa 10 mg (in combination with placebo to linagliptin (lina) 5 mg, 1 FDC tablet) in addition to empa 10 mg for 1 week.

Arm title	Empa 25 mg OL

Arm description:

Subjects were orally administered once daily empa 25 mg film-coated (1 tablet) for 16 week during OL treatment period, thereafter patients received once daily FDC placebo (1 tablet) matching to FDC empa 25 mg/lina 5 mg in addition to empa 25 mg for one week during open label placebo add-on treatment period.

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

Dosage and administration details:

Subjects were orally administered once daily empagliflozin (empa) 25 mg film-coated tablet for 16 weeks during open-label (OL) treatment period.

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

Dosage and administration details:

After 16 week open label treatment period, subjects were orally administered once daily placebo tablet matching to empa 25 mg (in combination with placebo to linagliptin (lina) 5 mg, 1 FDC tablet) in addition to empa 25 mg for 1 week.

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

Dosage and administration details:

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

Number of subjects in period 1	Empa 10 mg OL	Empa 25 mg OL
Started	352	354
Completed	256	226
Not completed	96	128
Other reason not defined above	77	94
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	10
Adverse event, non-fatal	5	14
Lost to follow-up	4	3

Lack of efficacy	1	1
Protocol deviation	5	5

Period 2

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lina5 (E10)

Arm description:

Subjects were orally administered FDC empa 10 mg/lina 5 mg (1 tablet) and placebo matching to empa 10 mg (1 tablet) for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

Subjects were orally administered once daily empa 10 mg tablet (in combination with lina 5 mg, 1 FDC tablet) in addition to empa 10 mg for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

Subjects were orally administered once daily lina 5 mg tablet (in combination with empa 10 mg, 1 FDC tablet) for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

Subjects were orally administered placebo matching to empa 10 mg for 24 weeks during the double-blind treatment period.

Arm title	Plc (E10)

Arm description:

Subjects were orally administered empa 10 mg (1 tablet) and matching placebo to FDC empa 10 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Plc (E10) were not treated. Although actual number of subjects started is 130, 128 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

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

Dosage and administration details:

Subjects were orally administered empa 10 mg for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

Subjects were orally administered once daily placebo tablet matching to lina 5 mg (in combination with placebo to empa 10 mg, 1 FDC tablet) for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

Subjects were orally administered once daily placebo tablet matching to empa 10 mg (in combination with placebo to lina 5 mg, 1 FDC tablet) for 24 weeks during the double-blind treatment period.

Arm title	Lina5 (E25)

Arm description:

Subjects were orally administered FDC empa 25 mg/lina 5 mg (1 tablet) and placebo matching to empa 25 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Lina5 (E25) were not treated. Although actual number of subjects started is 114, 112 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

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

Dosage and administration details:

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

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

Dosage and administration details:

Subjects were orally administered placebo matching to empa 25 mg for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

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

Arm title	Plc (E25)

Arm description:

Subjects were orally administered empa 25 mg (1 tablet) and matching placebo to FDC empa 25 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

Subjects were orally administered empa 25 mg for 24 weeks during the double-blind treatment period.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Notes:

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

Justification: In this study, Period 1 evaluates open label treatment period which referred to as pre-treatment analysis , thus period 2 double blind treatment period was selected as a baseline period to define the baseline characteristics of this trial.

Number of subjects in period 2[2][3]	Lina5 (E10)	Plc (E10)	Lina5 (E25)
Started	126	128	112
Completed	111	118	102
Not completed	15	10	10
Other reason not defined above	4	2	2
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	4	5	3
Lost to follow-up	4	1	5

Protocol deviation	2	-	-
Lack of efficacy	-	-	-

Number of subjects in period 2[2][3]	Plc (E25)
Started	112
Completed	105
Not completed	7
Other reason not defined above	1
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Lost to follow-up	2
Protocol deviation	-
Lack of efficacy	1

Notes:

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

Justification: Baseline characteristics are based on the last measurement prior to the administration of any double-blind randomised study medication. In this study the term “baseline” was not used to refer to measurements prior to the administration of open-label medication. Such measurements were referred to as “pre-treatment".

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

Justification: This study was conducted in two phases, open label (OL) and double blind (DB) phase. Subjects received OL treatment for 16 weeks and thereafter patients entered a 1 week open-label placebo add-on period in order to complete further eligibility evaluations before being randomised into one of the 24 week DB treatment groups. The patients who were eligible were only randomised to DB treatemet period, thus the inconsistency within the number of subjects completed the preceding period is observed.

Baseline characteristics

Reporting groups	
Reporting group title	Lina5 (E10)
Reporting group description:	
Subjects were orally administered FDC empa 10 mg/lina 5 mg (1 tablet) and placebo matching to empa 10 mg (1 tablet) for 24 weeks during the double-blind treatment period.	
Reporting group title	Plc (E10)
Reporting group description:	
Subjects were orally administered empa 10 mg (1 tablet) and matching placebo to FDC empa 10 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Plc (E10) were not treated. Although actual number of subjects started is 130, 128 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.	
Reporting group title	Lina5 (E25)
Reporting group description:	
Subjects were orally administered FDC empa 25 mg/lina 5 mg (1 tablet) and placebo matching to empa 25 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Lina5 (E25) were not treated. Although actual number of subjects started is 114, 112 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.	
Reporting group title	Plc (E25)
Reporting group description:	
Subjects were orally administered empa 25 mg (1 tablet) and matching placebo to FDC empa 25 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period.	

Reporting group values	Lina5 (E10)	Plc (E10)	Lina5 (E25)
Number of subjects	126	128	112
Age categorical Units: Subjects			

Age Continuous |			
The Treated set (TS) was used for the double-blind treatment period. The treated set (TS) consisted of all patients who were randomised and treated with at least one dose of study drug during the double-blind part of the trial. The TS was the basis of the safety analyses for the double-blind period.			
Units: years			
arithmetic mean	56.6	56.6	56.4
standard deviation	± 9.5	± 9.5	± 9.9
Gender, Male/Female Units: participants			
Female	55	56	58
Male	71	72	54

Reporting group values	Plc (E25)	Total	
Number of subjects	112	478	
Age categorical Units: Subjects			

Age Continuous |			
The Treated set (TS) was used for the double-blind treatment period. The treated set (TS) consisted of all patients who were randomised and treated with at least one dose of study drug during the double-blind part of the trial. The TS was the basis of the safety analyses for the double-blind period.			
Units: years			
arithmetic mean	56.2		

standard deviation	± 10.7	-	

Gender, Male/Female Units: participants			
Female	47	216	
Male	65	262	

End points

End points reporting groups

Reporting group title	Empa 10 mg OL

Reporting group description:

Subjects were orally administered once daily empa 10 mg film-coated (1 tablet) for 16 wk during OL treatment period, thereafter patients received once daily fixed dose combination (FDC) placebo (1 tablet) matching to FDC empa 10 mg/lina 5 mg in addition to empa 10 mg for one week during open label placebo add-on treatment period.

Reporting group title	Empa 25 mg OL

Reporting group description:

Subjects were orally administered once daily empa 25 mg film-coated (1 tablet) for 16 week during OL treatment period, thereafter patients received once daily FDC placebo (1 tablet) matching to FDC empa 25 mg/lina 5 mg in addition to empa 25 mg for one week during open label placebo add-on treatment period.

Reporting group title	Lina5 (E10)

Reporting group description:

Subjects were orally administered FDC empa 10 mg/lina 5 mg (1 tablet) and placebo matching to empa 10 mg (1 tablet) for 24 weeks during the double-blind treatment period.

Reporting group title	Plc (E10)

Reporting group description:

Subjects were orally administered empa 10 mg (1 tablet) and matching placebo to FDC empa 10 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Plc (E10) were not treated. Although actual number of subjects started is 130, 128 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Lina5 (E25)

Reporting group description:

Subjects were orally administered FDC empa 25 mg/lina 5 mg (1 tablet) and placebo matching to empa 25 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Lina5 (E25) were not treated. Although actual number of subjects started is 114, 112 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Plc (E25)

Reporting group description:

Subjects were orally administered empa 25 mg (1 tablet) and matching placebo to FDC empa 25 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period.

Primary: Change from baseline of HbA1c after 24 weeks of treatment

End point title	Change from baseline of HbA1c after 24 weeks of treatment

End point description:

Change from baseline in Glycated haemoglobin (HbA1c) [%] after 24 wk of treatment with double-blind trial medication, i.e. HbA1c change from baseline at week 24. The term "baseline" refers to the last measurement prior to the administration of any double-blind randomised study medication. It was not used to refer to measurements prior to the administration of open-label medication. Such measurements will be referred to as "pre-treatment". Observed Case (OC): This method analyse only available data that were observed while patients were on treatment, i.e., excluding the missing data. All values measured after rescue medication taken were set to missing. Full Analysis Set (FAS): Includes all patients in the Treated set who had a baseline HbA1c assessment and at least one on-treatment HbA1c assessment during the double-blind part of the trial.

End point type	Primary

End point timeframe:

Baseline and 24 weeks

End point values	Lina5 (E10)	Plc (E10)	Lina5 (E25)	Plc (E25)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	111[1]	110[2]	98[3]	98[4]
Units: Percentage of HbA1c				
least squares mean (standard error)	-0.53 (± 0.07)	-0.21 (± 0.07)	-0.58 (± 0.07)	-0.1 (± 0.07)

Notes:

[1] - FAS (OC)

[2] - FAS (OC)

[3] - FAS (OC)

[4] - FAS (OC)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Superiority of lina 5 (E10) vs. Plc (E10): change in HbA1c using a restricted maximum likelihood (REML)- based mixed model repeated measures (MMRM) approach. The model includes baseline HbA1c as linear covariate & baseline estimated glomerula filtration rate (eGFR), geographical region, treatment, visit, visit by treatment interaction as fixed effects.

Comparison groups	Lina5 (E10) v Plc (E10)
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0013
Method	Mixed Model Repeated Measure (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[5] - The unstructured covariance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the adjusted mean difference calculated as Lina 5 (E10) minus Plc (E10) value.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Superiority of lina 5 (E25) vs.Plc (E25): change in HbA1c using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. The model includes baseline HbA1c as linear covariate & baseline eGFR, geographical region, treatment, visit, visit by treatment interaction as fixed effects.

Comparison groups	Lina5 (E25) v Plc (E25)
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.28
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[6] - The unstructured covariance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the adjusted mean difference value calculated as Lina 5 (E25) minus Plc (E25).

Secondary: Change from baseline in FPG (mmol/L) after 24 weeks

End point title	Change from baseline in FPG (mmol/L) after 24 weeks

End point description:

Change from baseline in fasting plasma glucose (FPG) (mmol/L) after 24 weeks of treatment with double-blind trial medication, i.e. FPG change from baseline at Week 24.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Lina5 (E10)	Plc (E10)	Lina5 (E25)	Plc (E25)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108[7]	107[8]	93[9]	94[10]
Units: mmol/L				
least squares mean (standard error)	-0.44 (± 0.18)	0.21 (± 0.18)	-0.68 (± 0.15)	-0.24 (± 0.15)

Notes:

[7] - FAS (OC)

[8] - FAS (OC)

[9] - FAS (OC)

[10] - FAS (OC)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Superiority of lina5 (E10) vs. Plc (E10): change in FPG using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. The model includes baseline HbA1c & baseline eGFR as linear covariates, geographical region, treatment, visit, visit by treatment interaction as fixed effects.

Comparison groups	Lina5 (E10) v Plc (E10)
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0103
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[11] - The unstructured covariance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the adjusted mean difference value calculated as Lina 5 (E10) minus Plc (E10).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Superiority of lina5 (E25) vs. Plc (E25): change in FPG using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. The model includes baseline HbA1c & baseline eGFR as linear covariates, geographical region, treatment, visit, visit by treatment interaction as fixed effects.

Comparison groups	Lina5 (E25) v Plc (E25)
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.0452
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[12] - The unstructured covariance structure has been used to fit the mixed model. Mean Difference (Final Values) is actually the adjusted mean difference value calculated as Lina 5 (E25) minus Plc (E25).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 7 days after the last drug administration, up to 212 days (OL treatment period) and 205 days (double blind treatment period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	empa 10 mg OL

Reporting group description:

Subjects were orally administered once daily empa 10 mg film-coated (1 tablet) for 16 wk during OL treatment period, thereafter patients received once daily fixed dose combination (FDC) placebo (1 tablet) matching to FDC empa 10 mg/lina 5 mg in addition to empa 10 mg for one week during open label placebo add-on treatment period.

Reporting group title	empa 25 mg OL

Reporting group description:

Subjects were orally administered once daily empa 25 mg film-coated (1 tablet) for 16 week during OL treatment period, thereafter patients received once daily FDC placebo (1 tablet) matching to FDC empa 25 mg/lina 5 mg in addition to empa 25 mg for one week during open label placebo add-on treatment period.

Reporting group title	Lina5 (E10)

Reporting group description:

Subjects were orally administered FDC empa 10 mg/lina 5 mg (1 tablet) and placebo matching to empa 10 mg (1 tablet) for 24 weeks during the double-blind treatment period.

Reporting group title	Plc (E10)

Reporting group description:

Subjects were orally administered empa 10 mg (1 tablet) and matching placebo to FDC empa 10 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Plc (E10) were not treated. Although actual number of subjects started is 130, 128 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Lina5 (E25)

Reporting group description:

Subjects were orally administered FDC empa 25 mg/lina 5 mg (1 tablet) and placebo matching to empa 25 mg (1 tablet) for 24 weeks during the double-blind treatment period. Two subjects randomised to Lina5 (E25) were not treated. Although actual number of subjects started is 114, 112 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Plc (E25)

Reporting group description:

Subjects were orally administered empa 25 mg (1 tablet) and matching placebo to FDC empa 25 mg/lina 5 mg (1 tablet) for 24 weeks during the double-blind treatment period.

Serious adverse events	empa 10 mg OL	empa 25 mg OL	Lina5 (E10)
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 352 (3.41%)	12 / 354 (3.39%)	4 / 126 (3.17%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Prostatic adenoma			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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
Subclavian vein thrombosis			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
General disorders and administration site conditions			
Calcinosis			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Chest pain			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
Death			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
General physical health deterioration			

subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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
Metrorrhagia			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Pharyngeal lesion			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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
Investigations			
Amylase increased			

subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
Skull fractured base			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
Atrial fibrillation			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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
Myocardial infarction			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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

Myocardial ischaemia			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
Tachycardia			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum intestinal			

subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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 polyp			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	2 / 352 (0.57%)	0 / 354 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Vomiting			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 352 (0.57%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Dermatitis bullous			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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
Dyshidrotic eczema			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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			
Back pain			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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
Neck pain			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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

Bronchitis			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Gangrene			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Infectious colitis			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	0 / 126 (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
Osteomyelitis			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 352 (0.00%)	0 / 354 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	0 / 126 (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 / 352 (0.00%)	0 / 354 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Plc (E10)	Lina5 (E25)	Plc (E25)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 128 (3.91%)	3 / 112 (2.68%)	4 / 112 (3.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Prostatic adenoma			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Calcinosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Chest pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Death			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 112 (0.00%)	0 / 112 (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
Metrorrhagia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Pharyngeal lesion			
subjects affected / exposed	0 / 128 (0.00%)	1 / 112 (0.89%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase increased			

subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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			
Fall			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fractured base			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Atrial fibrillation			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Atrial flutter			
subjects affected / exposed	0 / 128 (0.00%)	1 / 112 (0.89%)	0 / 112 (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 / 128 (0.78%)	0 / 112 (0.00%)	0 / 112 (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
Myocardial infarction			
subjects affected / exposed	1 / 128 (0.78%)	0 / 112 (0.00%)	0 / 112 (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

Myocardial ischaemia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 112 (0.89%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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 haemorrhage			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 128 (0.78%)	0 / 112 (0.00%)	0 / 112 (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
Ischaemic stroke			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum intestinal			

subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal polyp			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Vomiting			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Liver injury			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Skin and subcutaneous tissue disorders			

Dermatitis bullous			
subjects affected / exposed	0 / 128 (0.00%)	1 / 112 (0.89%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyshidrotic eczema			
subjects affected / exposed	0 / 128 (0.00%)	1 / 112 (0.89%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Haemarthrosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 128 (0.78%)	0 / 112 (0.00%)	0 / 112 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Rotator cuff syndrome			
subjects affected / exposed	1 / 128 (0.78%)	0 / 112 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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

Bronchitis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Gangrene			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Infectious colitis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Osteomyelitis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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
Urinary tract infection			
subjects affected / exposed	0 / 128 (0.00%)	0 / 112 (0.00%)	0 / 112 (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

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

Non-serious adverse events	empa 10 mg OL	empa 25 mg OL	Lina5 (E10)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 352 (13.35%)	38 / 354 (10.73%)	22 / 126 (17.46%)
Investigations			
Lipase increased			
subjects affected / exposed	15 / 352 (4.26%)	10 / 354 (2.82%)	4 / 126 (3.17%)
occurrences (all)	15	10	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 352 (4.83%)	5 / 354 (1.41%)	8 / 126 (6.35%)
occurrences (all)	18	5	11
Urinary tract infection			
subjects affected / exposed	16 / 352 (4.55%)	23 / 354 (6.50%)	10 / 126 (7.94%)
occurrences (all)	17	26	13

Non-serious adverse events	Plc (E10)	Lina5 (E25)	Plc (E25)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 128 (7.81%)	18 / 112 (16.07%)	21 / 112 (18.75%)
Investigations			
Lipase increased			
subjects affected / exposed	1 / 128 (0.78%)	7 / 112 (6.25%)	7 / 112 (6.25%)
occurrences (all)	1	7	7
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 128 (2.34%)	2 / 112 (1.79%)	8 / 112 (7.14%)
occurrences (all)	3	2	8
Urinary tract infection			
subjects affected / exposed	6 / 128 (4.69%)	11 / 112 (9.82%)	7 / 112 (6.25%)
occurrences (all)	9	14	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2013	Stopping of trial treatment in case of changes in metformin background treatment or with suspected pancreatitis (included in the linagliptin labelling) were added as discontinuation criteria. Minor corrections and clarifications for consistency within the CTP and within the development program were introduced.
27 November 2013	Based upon comments in an advice letter received from health authority on 24 Apr 2013 the primary analysis model was changed from ANCOVA (LOCF) to MMRM (OC). According to published literature, MMRM analysis appears to be a superior approach for controlling Type I error rates and minimizing bias as compared to single imputation approaches such as LOCF ANCOVA analysis particularly in the presence of missing completely at random or missing at random data [R10-5462]. The MMRM approach included treatment, baseline renal function, region, visit, and visit-by-treatment interaction as fixed effects, and HbA1c baseline as linear covariate. An unstructured covariance structure was used to model the within-patient errors. Subsequent changes to the sensitivity analyses of the primary endpoint included the analysis of the primary endpoint using an ANCOVA model. The analysis of the key secondary endpoint and the subgroup analyses were updated accordingly. For consistency with the TSAP, the planned analyses were updated by adding definitions of the different analysis sets (SCR, OLS, and OLFAS). The description of the trial objective and the trial design was amended to clarify the use of FDCs of empagliflozin and linagliptin. External independent committees were set-up for the adjudication of safety relevant events (pancreatic events, hepatic events, cancer assessments). To match new requirement for public disclosure AEs, hypoglycaemic events, AESIs and cardiovascular events were part of the safety assessment without being classified as further endpoints [001-MCS-40-106_RD-03]. Processes for expedited AE reporting were updated and clarified. Administration of herbal/nutritional supplements/medication that interfered with the investigational products was included as a reason for patient withdrawal. Administrative changes including updates and clarifications on AE reporting requirements including the definition of the REP, minor corrections and further clarifications were introduced.
11 June 2014	This revision of the CTP involved only minor administrative aspects and clarifications and did not require IRB/IEC approval.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported