Clinical trial results:
A 24 week randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of once daily linagliptin, 5 milligrams orally, as add on to basal insulin in elderly Type 2 Diabetes Mellitus patients with insufficient glycaemic control

Summary

EudraCT number	2014-000904-88
Trial protocol	GR ES DK GB FI DE BE IE
Global end of trial date	25 April 2017

Results information

Result version number	v1
This version publication date	10 May 2018
First version publication date	10 May 2018

Trial information

Trial identification

Sponsor protocol code	1218.149

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02240680
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, 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 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2017
Global end of trial reached?	Yes
Global end of trial date	25 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy, safety, and tolerability of linagliptin 5 mg once daily compared with placebo as add-on therapy for 24 weeks to stable basal insulin treatment in elderly (≥60 years) patients with type 2 diabetes mellitus and insufficient glycaemic control.

Protection of trial subjects:

Safety was to be ensured by monitoring the patients for AEs clinically, by laboratory testing, and by home blood glucose monitoring (HBGM). Patients who were not adequately controlled could have their permitted background medication adjusted or new antidiabetic medications introduced to ensure their safety. In case the patient developed any condition/disease or AE which did not allow – according to investigator's judgement – the patient's safe continuation of the trial, the patient was to be prematurely discontinued from the trial. Symptoms that could be attributed to hypoglycaemia were to be closely monitored during the trial. General risks associated with participating in this trial were related to trial-specific procedures such as blood sampling. The amount of blood taken during the whole course of the trial was considered to be of no or negligible risk to the patients. The trial design with a 1-week placebo run-in phase is a well-established design for trials in type 2 diabetes. Daily monitoring of blood glucose was performed by patients with the HBGM device and patients were to be discontinued if there was any indication that the patient was not stable enough. Thus the risk of the 1-week placebo treatment was minimal.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 2014
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: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Colombia: 12
Country: Number of subjects enrolled	Denmark: 31
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Japan: 108
Country: Number of subjects enrolled	Mexico: 33
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	Poland: 31

Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 133
Worldwide total number of subjects	525
EEA total number of subjects	194

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)	32
From 65 to 84 years	475
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

This was randomised, double blinded, placebo controlled, parallel study. Total 525 patients with type 2 diabetes mellitus (T2DM) and insufficient glycaemic control were screened. 302 patients were randomised into two groups. The trial was extended to 52 weeks for Japanese patients. 102 patients were identified and observed for the extended period.

Pre-assignment

Screening details:

All patients 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 to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Overall Study (Up to 24 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst

Blinding implementation details:

The randomised period of this trial was double blind, i.e. after randomisation neither the patient nor the investigator nor anyone involved in analysing trial data or with an interest in this double blind trial were aware of a treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Up to 24 weeks)

Arm description:

Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks

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

Dosage and administration details:

Oral adminstration of placebo tablets (Matching Linagliptin) once daily up to 24 weeks.

Arm title	Linagliptin 5 milligram (Up to 24 weeks)

Arm description:

Patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 24 weeks.

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

Dosage and administration details:

Oral adminstation of Linagliptin 5 milligram film coated tablets once daily up to 24 weeks

Number of subjects in period 1[1]	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)
Started	151	151
Completed	136	143
Not completed	15	8
Adverse event, serious fatal	-	1
Consent withdrawn by subject	3	1
Adverse event, non-fatal	6	5
Other than specified	1	-
Lost to follow-up	1	-
Protocol deviation	4	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomized after successfully completing the screening period and received at least one dose of the trial medication.

Period 2

Period 2 title	Japanese Patients (Up to 52 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst

Blinding implementation details:

The randomised period of this trial was double-blind, i.e. after randomisation neither the patient nor the investigator nor anyone involved in analysing trial data or with an interest in this double-blind trial were aware of a treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Up to 52 weeks)

Arm description:

Only Japanese patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 52 weeks

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

Dosage and administration details:

Oral adminstration of placebo tablets (Matching Linagliptin) once daily up to 52 weeks.

Arm title	Linagliptin 5 milligram (Up to 52 weeks)

Arm description:

Only Japanese patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 52 weeks

Arm type	Experimental

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

Dosage and administration details:

Oral adminstation of Linagliptin 5 milligram film coated tablets once daily up to 52 weeks.

Number of subjects in period 2[2]	Placebo (Up to 52 weeks)	Linagliptin 5 milligram (Up to 52 weeks)
Started	50	52
Completed	42	45
Not completed	8	7
Consent withdrawn by subject	1	-
Adverse event, non-fatal	6	7
Protocol deviation	1	-

Notes:

[2] - 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 issue is because of the trial design. We do not have two period in the study but had to present the data in two periods because of the extension of time period for Japanese patients

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (Up to 24 weeks)
Reporting group description:	
Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks	
Reporting group title	Linagliptin 5 milligram (Up to 24 weeks)
Reporting group description:	
Patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 24 weeks.	

Reporting group values	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)	Total
Number of subjects	151	151	302
Age categorical Units: Subjects			
Age Continuous			
Data of age collected for all included patients in the study.			
Units: Years			
arithmetic mean	72.5	72.3	
standard deviation	± 5.6	± 5.1	-
Sex: Female, Male			
Data of Gender collected of all patients included in the study.			
Units: Subjects			
Female	60	59	119
Male	91	92	183
Race (NIH/OMB)			
Data for Race of patients collected under protocol for all included patients in the study.			
Units: Subjects			
American Indian or Alaska Native	7	4	11
Asian	52	52	104
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	10	8	18
White	81	84	165
More than one race	1	2	3
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Data for Ethnicity of patients collected under protocol for all included patients in the study.			
Units: Subjects			
Hispanic or Latino	19	15	34
Not Hispanic or Latino	132	136	268
Unknown or Not Reported	0	0	0
Hemoglobin A1c (HbA1c) at baseline			
HbA1c values measured at baseline in percent. HbA1c is a form of hemoglobin, a blood pigment that carries oxygen, which is bound to glucose. The term HbA1c also refers to glycated hemoglobin. High levels of HbA1c (Normal range is less than 6%) indicate poorer control of diabetes than level in normal range.			
Units: Percentage (%) of HbA1c			

arithmetic mean	8.1	8.2	
standard deviation	± 0.7	± 0.8	-

End points

End points reporting groups

Reporting group title	Placebo (Up to 24 weeks)
Reporting group description:	
Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks	
Reporting group title	Linagliptin 5 milligram (Up to 24 weeks)
Reporting group description:	
Patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 24 weeks.	
Reporting group title	Placebo (Up to 52 weeks)
Reporting group description:	
Only Japanese patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 52 weeks	
Reporting group title	Linagliptin 5 milligram (Up to 52 weeks)
Reporting group description:	
Only Japanese patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 52 weeks	

Primary: Change from baseline in Hemoglobin A1c (HbA1c) after 24 weeks of treatment.

End point title	Change from baseline in Hemoglobin A1c (HbA1c) after 24 weeks of treatment.
End point description:	
This outcome has measured difference between HbA1c values from baseline to 24 weeks post treatment. The term 'baseline' refers to the last observation prior to the administration of any randomised study medication. HbA1c is a form of hemoglobin, a blood pigment that carries oxygen, which is bound to glucose. The term HbA1c also refers to glycated hemoglobin. High levels of HbA1c (Normal range is less than 6%) indicate poorer control of diabetes than level in normal range. Population set used for analysis: Full analysis set observed cases (FAS (OC)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. These analyses used available data as observed while patients were on treatment. All values collected after a patient started rescue medication were excluded from the analysis.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113[1]	134[2]		
Units: Percentage (%) of HbA1c				
least squares mean (standard error)	-0.38 (± 0.07)	-1.01 (± 0.06)		

Notes:

[1] - Full analysis set observed cases (FAS (OC))

[2] - Full analysis set observed cases (FAS (OC))

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed model repeated measures (MMRM) included treatment, week and interaction as fixed effects, baseline HbA1c, daily basal insulin dose as covariates

Comparison groups	Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks)
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[3] - MMRM including fixed effects treatment, week and treatment by week interaction linear covariates baseline HbA1c, baseline daily basal insulin and baseline HbA1c by week interaction and random effect for patient. Within−patient errors are modelled by unstructured covariance matrix. Adjusted mean is based on all patients in the model (not only patients with a baseline and week 24 measurement).

Secondary: Percentage of patients experiencing at least one hypoglycaemia accompanied by a prespecified glucose value.

End point title	Percentage of patients experiencing at least one hypoglycaemia accompanied by a prespecified glucose value.

End point description:

Hypoglycaemia accompanied by a prespecified glucose value is defined as any investigator reported hypoglycaemia (event or AE) with a reported blood glucose level of less than 54 milligram/deciLitre (3.0 millimole/Litre) or any investigator reported symptomatic hypoglycaemic AE with a reported blood glucose level of less or equal 70 milligram/deciLitre (3.9millimole/Litre) or any severe hypoglycaemic AE. Severe hypoglycaemia is an event that requires the assistance of another person to actively administer carbohydrates or glucagon because the patient is unable to take the substance on his or her own. The confidence intervals mentioned in measure of dispersion are exact 95% confidence interval by Clopper and Pearson. The proportion of patients with at least one hypoglycaemia accompanied by a glucose value less than 54mg/dL alone has also represented separately according to American Diabetes Association definition of clinically significant hypoglycaemia.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147[4]	149[5]		
Units: Percentage of patients (%)				
number (confidence interval 95%)				
Prespecified glucose value	23.8 (17.2 to 31.5)	30.9 (23.6 to 39.0)		

Glucose value <54 mg/dL	15.0 (9.6 to 21.8)	16.8 (11.2 to 23.8)		

Notes:

[4] - Full analysis set observed cases (FAS (OC))

[5] - Full analysis set observed cases (FAS (OC))

Statistical analyses

Statistical analysis title	Statistical Analysis 2-Prespecified glucose value

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. The logistic regression analysis showed that patients treated with linagliptin and placebo were equally likely to observe occurrence of hypoglycaemia.The dispersion value standard error of the mean is actually standard error for odds ratio.

Comparison groups	Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks)
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1594
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.464
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.861
upper limit	2.491
Variability estimate	Standard error of the mean
Dispersion value	0.397

Statistical analysis title	Statistical Analysis 3- Glucose value < 54mg/dL

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. The logistic regression analysis showed that patients treated with linagliptin and placebo were equally likely to observe occurrence of hypoglycaemia.The dispersion value standard error of the mean is actually standard error for odds ratio.

Comparison groups	Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks)
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.672
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.149
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.604
upper limit	2.188

Variability estimate	Standard error of the mean
Dispersion value	0.377

Notes:

[6] - The proportion of patients with at least one hypoglycaemia accompanied by a glucose value less than 54mg/dL alone has also represented separately according to American Diabetes Association definition of clinically significant hypoglycaemia.

Secondary: Proportions of patients with HbA1c<8.0%

End point title	Proportions of patients with HbA1c<8.0%

End point description:

This is the proportion of patients with HbA1c on treatment <8.0% after 24 weeks of treatment. The confidence intervals mentioned in method of dispersion are exact 95% CI by Clopper and Pearson. Population set used for analysis: Full analysis set (Non-completers considered failure)(FAS (NCF)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. This analyses regarded missing values for binary efficacy endpoints as failure.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[7]	87[8]		
Units: Percentage of patients (%)				
number (confidence interval 95%)	40.2 (29.9 to 51.3)	70.1 (59.4 to 79.5)		

Notes:

[7] - Full analysis set (Non-completers considered failure)(FAS (NCF))

[8] - Full analysis set (Non-completers considered failure)(FAS (NCF))

Statistical analyses

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. This analysis showed that patients teated with linagliptin were more likely to achieve these responses than in the placebo group.The dispersion value standard error of the mean is actually standard error for odds ratio.

Comparison groups	Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks)
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.468
upper limit	10.206

Variability estimate	Standard error of the mean
Dispersion value	1.818

Secondary: Proportion of patients with HbA1c on treatment <7.0%

End point title	Proportion of patients with HbA1c on treatment <7.0%

End point description:

This is the proportion of patients with HbA1c on treatment <7.0% after 24 weeks of treatment. The confidence intervals mentioned in method of dispersion are exact 95% CI by Clopper and Pearson. Population set used for analysis: Full analysis set (Non-completers considered failure)(FAS (NCF)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. This analyses regarded missing values for binary efficacy endpoints as failure.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[9]	143[10]		
Units: Percentage of patients (%)				
number (confidence interval 95%)	14.6 (9.3 to 21.4)	37.8 (29.8 to 46.2)		

Notes:

[9] - Full analysis set (Non-completers considered failure)(FAS (NCF))

[10] - Full analysis set (Non-completers considered failure)(FAS (NCF))

Statistical analyses

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. This analysis showed that patients teated with linagliptin were more likely to achieve these responses than in the placebo group.The dispersion value standard error of the mean is actually standard error for odds ratio.

Comparison groups	Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks)
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.689
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.485
upper limit	8.848

Variability estimate	Standard error of the mean
Dispersion value	1.519

Secondary: Proportion of patients with HbA1c lowering by at least 0.5%.

End point title	Proportion of patients with HbA1c lowering by at least 0.5%.

End point description:

The proportions of patients who attained lowering of HbA1c by ≥0.5% from baseline after 24 weeks of treatment were analysed. The confidence intervals mentioned in method of dispersion are exact 95% CI by Clopper and Pearson. Population set used for analysis: Full analysis set (Non-completers considered failure)(FAS (NCF)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. This analyses regarded missing values for binary efficacy endpoints as failure.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[11]	103[12]		
Units: Percentage of patients (%)				
number (confidence interval 95%)	37.4 (29.6 to 45.8)	69.1 (61.0 to 76.4)		

Notes:

[11] - Full analysis set (Non-completers considered failure)(FAS (NCF))

[12] - Full analysis set (Non-completers considered failure)(FAS (NCF))

Statistical analyses

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. This analysis showed that patients teated with linagliptin were more likely to achieve these responses than in the placebo group.The dispersion value standard error of the mean is actually standard error for odds ratio.

Comparison groups	Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks)
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.731
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.302
upper limit	6.048

Variability estimate	Standard error of the mean
Dispersion value	0.92

Secondary: Change from baseline in Fasting Plasma Glucose (FPG)

End point title	Change from baseline in Fasting Plasma Glucose (FPG)

End point description:

This outcome has measured difference between FPG values from baseline to 24 weeks post treatment. The term 'baseline' refers to the last observation prior to the administration of any randomised study medication. Population set used for analysis: Full analysis set observed cases (FAS (OC)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. These analyses used available data as observed while patients were on treatment. All values collected after a patient started rescue medication were excluded from the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo (Up to 24 weeks)	Linagliptin 5 milligram (Up to 24 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[13]	134[14]		
Units: milligram/decilitre				
least squares mean (standard error)	0.2 (± 3.6)	-11.3 (± 3.3)		

Notes:

[13] - Full analysis set observed cases (FAS (OC))

[14] - Full analysis set observed cases (FAS (OC))

Statistical analyses

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Adjusted mean of all differences between HbA1c at baseline and after 24 weeks. It is based on all patients in the model (not only patients with a baseline and week 24 measurement).

Comparison groups	Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0178
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	-2
Variability estimate	Standard error of the mean
Dispersion value	4.8

Notes:

[15] - MMRM including fixed effects treatment, week and treatment by week interaction, linear covariates baseline HbA1c, baseline daily basal insulin, baseline FPG and baseline FPG by week interaction and random effect for patient. Within−patient errors are modelled by unstructured covariance matrix. Adjusted mean is based on all patients in the model (not only patients with a baseline and week 24 measurement).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration up to 24 weeks, until 7 days after last drug administration for overall population. And from first drug administration up to 52 weeks, until 7 days after last drug administration for Japanese population.

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence, including an exacerbation of a preexisting condition, in a patient in a clinical investigation who received a pharmaceutical product. A treated set (TS) was used for AE analysis. TS includes patients who were dispensed study medication and taken at least one dose of investigational treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Linagliptin 5 mg (Up to 24 weeks)

Reporting group description:

Patients were orally administered with Linagliptin 5 mg film-coated tablets once daily up to 24 weeks.

Reporting group title	Placebo (Up to 24 weeks)

Reporting group description:

Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks

Reporting group title	Placebo (Up to 52 weeks)

Reporting group description:

Japanese patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 52 weeks

Reporting group title	Linagliptin 5mg (Up to 52 weeks)

Reporting group description:

Japanese patients were orally administered with Linagliptin 5 mg film-coated tablets once daily up to 52 weeks.

Serious adverse events	Linagliptin 5 mg (Up to 24 weeks)	Placebo (Up to 24 weeks)	Placebo (Up to 52 weeks)
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 151 (12.58%)	21 / 151 (13.91%)	7 / 50 (14.00%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Colorectal cancer			

subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Enchondromatosis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Gastric cancer			
subjects affected / exposed	0 / 151 (0.00%)	0 / 151 (0.00%)	0 / 50 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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			
Deep vein thrombosis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Intermittent claudication			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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			
Asthma			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Cough			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Dyspnoea			
subjects affected / exposed	0 / 151 (0.00%)	2 / 151 (1.32%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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			
Lipase increased			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Femoral neck fracture			

subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Multiple fractures			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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 / 151 (0.00%)	0 / 151 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 151 (0.00%)	0 / 151 (0.00%)	1 / 50 (2.00%)
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 myocardial infarction			
subjects affected / exposed	0 / 151 (0.00%)	0 / 151 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Arrhythmia			

subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Atrial fibrillation			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Bradycardia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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 arrest			
subjects affected / exposed	2 / 151 (1.32%)	0 / 151 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 151 (1.32%)	1 / 151 (0.66%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 151 (0.00%)	2 / 151 (1.32%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	1 / 151 (0.66%)	1 / 151 (0.66%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral arteriosclerosis			

subjects affected / exposed	0 / 151 (0.00%)	0 / 151 (0.00%)	0 / 50 (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 / 151 (0.00%)	0 / 151 (0.00%)	0 / 50 (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
Dizziness			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 151 (0.00%)	0 / 151 (0.00%)	0 / 50 (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
Lumbar radiculopathy			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 151 (0.00%)	0 / 151 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Diabetic retinopathy			
subjects affected / exposed	2 / 151 (1.32%)	0 / 151 (0.00%)	0 / 50 (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
Glaucoma			

subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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			
Ascites			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Haemorrhoids			
subjects affected / exposed	0 / 151 (0.00%)	0 / 151 (0.00%)	0 / 50 (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
Inguinal hernia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 151 (1.32%)	0 / 151 (0.00%)	0 / 50 (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

Haematuria			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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 impairment			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 151 (1.32%)	1 / 151 (0.66%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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
Erysipelas			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Klebsiella sepsis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	0 / 50 (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
Pneumonia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 151 (0.66%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	0 / 50 (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

Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 151 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Linagliptin 5mg (Up to 52 weeks)		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 52 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enchondromatosis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intermittent claudication			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			

subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Lipase increased				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Spinal compression fracture				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain stem infarction				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral arteriosclerosis				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxic-ischaemic encephalopathy				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar radiculopathy				

subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetic retinopathy			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Inguinal hernia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Klebsiella sepsis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Linagliptin 5 mg (Up to 24 weeks)	Placebo (Up to 24 weeks)	Placebo (Up to 52 weeks)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 151 (47.68%)	58 / 151 (38.41%)	19 / 50 (38.00%)
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 151 (1.32%)	1 / 151 (0.66%)	0 / 50 (0.00%)
occurrences (all)	2	1	0

Large intestine polyp			
subjects affected / exposed	2 / 151 (1.32%)	0 / 151 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 151 (1.99%)	1 / 151 (0.66%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 151 (3.31%)	6 / 151 (3.97%)	3 / 50 (6.00%)
occurrences (all)	5	6	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 151 (4.64%)	4 / 151 (2.65%)	0 / 50 (0.00%)
occurrences (all)	9	4	0
Urinary tract infection			
subjects affected / exposed	10 / 151 (6.62%)	9 / 151 (5.96%)	1 / 50 (2.00%)
occurrences (all)	11	11	1
Viral upper respiratory tract infection			
subjects affected / exposed	11 / 151 (7.28%)	8 / 151 (5.30%)	3 / 50 (6.00%)
occurrences (all)	12	9	4
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	51 / 151 (33.77%)	38 / 151 (25.17%)	14 / 50 (28.00%)
occurrences (all)	142	162	107

Non-serious adverse events	Linagliptin 5mg (Up to 52 weeks)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 52 (71.15%)		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Large intestine polyp			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Reproductive system and breast			

disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	 3 / 52 (5.77%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 2 / 52 (3.85%) 2		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	 5 / 52 (9.62%) 6 1 / 52 (1.92%) 1 11 / 52 (21.15%) 16		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	 20 / 52 (38.46%) 58		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2015	The amendment was implemented after approval by the IEC/IRB/competent authority. The main changes introduced by the amendment were: *There was a change in Coordinating Investigator *The inclusion criteria were modified to allow patients from 60 years old (lower age limit) and with a lower HbA1c limit of 7.0% to be eligible for the trial *There was a change in the secondary endpoint regarding the proportion of patients with HbA1c <7.5% at the end of the trial – this was changed to HbA1c <7.0% *The key secondary endpoint was designated as a secondary endpoint *The sample size was reduced to 300 patients, with 100 randomised patients required in Japan *Exclusion criteria no. 1 was clarified for dementia scores excluding patients from undergoing further additional assessment, thereby excluding these patients from participation clarify the Saint Louis University Mental Status Examination scores for mild neurocognitive disorder *Exclusion criteria no. 4 was modified to add STEMI and/or unstable angina pectoris *Exclusion criteria no.10 was modified to add meglitinides and bromocriptine *The permitted antidiabetic therapy that was to be considered rescue therapy was clarified *The definition of hypoglycaemia as ≤70 mg/dL was clarified *The process for AESIs was updated and clarified *It was clarified that the results of pharmacogenetic sampling would be reported separately from the main clinical trial report

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For patients in Japan, a local protocol amendment was introduced, and according to it the study was extended to 52 weeks for Japanese population only.

Notes: