

**Clinical trial results:**

A phase IIIb, multicentre, multinational, randomized, double-blind, placebo controlled, parallel group study to evaluate the glycemic and renal efficacy of once daily administration of linagliptin 5 milligram (mg) for 24 weeks in type 2 diabetes patients, with micro- or macroalbuminuria (30-3000mg/g creatinine) on top of current treatment with Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor Blocker – MARLINA (Efficacy, safety & Modification of Albuminuria in type 2 diabetes subjects with Renal disease with LINAgliptin)

Summary

EudraCT number	2012-002603-17
Trial protocol	DE ES FI DK
Global end of trial date	17 December 2015

Results information

Result version number	v1 (current)
This version publication date	23 December 2016
First version publication date	23 December 2016

Trial information**Trial identification**

Sponsor protocol code	1218.89
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01792518
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 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	21 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2015
Global end of trial reached?	Yes
Global end of trial date	17 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to investigate the glycaemic efficacy and safety of linagliptin (5 mg once daily) after 24 weeks of treatment in patients with type 2 diabetes mellitus and albuminuria on top of current therapy with Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB). The study was designed to test the superiority of treatment with linagliptin versus placebo. The key secondary objective of the study was to investigate the superiority of treatment with linagliptin versus placebo in terms of renal efficacy after 24 weeks of treatment in this population.

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. Rescue medication was allowed for all patients as required.

Background therapy:

All patients had to take Anti-hypertensive background therapy (ACEi or ARB). Anti-diabetic background therapies were allowed, up to 2 oral treatments in combination with or without basal insulin.

Evidence for comparator:

Placebo matching Linagliptin

Actual start date of recruitment	26 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	Canada: 86
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Japan: 90
Country: Number of subjects enrolled	Taiwan: 101
Country: Number of subjects enrolled	Korea, Republic of: 82
Country: Number of subjects enrolled	Philippines: 96
Country: Number of subjects enrolled	Finland: 50
Country: Number of subjects enrolled	United States: 97

Country: Number of subjects enrolled	Vietnam: 85
Worldwide total number of subjects	819
EEA total number of subjects	182

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)	508
From 65 to 84 years	311
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Randomized, double-blind, placebo controlled, parallel group study to evaluate glycemic and renal efficacy of Linagliptin 5 mg for 24 weeks in type 2 diabetes patients. Of the 819 enrolled patients, 500 patients entered the 2-week placebo run-in period, 360 patients were randomised and treated (Placebo: 178 patients, Linagliptin: 182 patients).

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended a specialist site which ensured that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The placebo run-in period of this trial was an open-label period. The randomised period of this trial was performed double-blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients received 1 matching placebo tablet to Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

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

Dosage and administration details:

Patients received 1 matching placebo tablet to Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

Arm title	Linagliptin 5 mg
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Arm description:

Patients received 1 tablet of Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

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

Dosage and administration details:

Patients received 1 tablet of Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

Number of subjects in period 1^[1]	Placebo	Linagliptin 5 mg
Started	178	182
Completed	170	175
Not completed	8	7
Adverse event, serious fatal	-	1
Consent withdrawn by subject	2	-
Adverse event, non-fatal	3	3
Other Reason	-	1
Lost to follow-up	3	1
Protocol deviation	-	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 the patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Patients received 1 matching placebo tablet to Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group title	Linagliptin 5 mg
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Reporting group description:

Patients received 1 tablet of Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group values	Placebo	Linagliptin 5 mg	Total
Number of subjects	178	182	360
Age categorical Units: Subjects			

Age Continuous			
Treated Set (TS) - including all patients treated with at least one dose of randomised trial medication.			
Units: Years			
arithmetic mean	60.1	61	
standard deviation	± 9.3	± 10	-
Gender, Male/Female			
Treated Set (TS) - including all patients treated with at least one dose of randomised trial medication.			
Units: Participants			
Female	65	66	131
Male	113	116	229

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Patients received 1 matching placebo tablet to Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.	
Reporting group title	Linagliptin 5 mg
Reporting group description: Patients received 1 tablet of Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.	

Primary: HbA1c Change From Baseline After 24 Weeks Double-blind Randomized Treatment

End point title	HbA1c Change From Baseline After 24 Weeks Double-blind Randomized Treatment
End point description: Change from baseline in Glycated haemoglobin (HbA1c) [%] after 24 weeks of treatment with double-blind trial medication. The term "baseline" refers to the last observation before the start of any randomised trial treatment. The number of participants analysed displays the number of participants with available data at the timepoint of interest. Full Analysis Set (FAS) - including all randomised patients who were treated with at least one dose of study drug, had a baseline HbA1c and a baseline Urinary Albumin Creatinine Ratio (UACR), and at least one on treatment HbA1c or UACR assessment. Observed Case (OC): Values after the use of rescue medication were set to missing.	
End point type	Primary
End point timeframe: Baseline and 24 weeks	

End point values	Placebo	Linagliptin 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156 ^[1]	161 ^[2]		
Units: Percentage of HbA1c				
least squares mean (standard error)	-0.03 (± 0.06)	-0.63 (± 0.06)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Superiority of Linagliptin 5 mg vs. placebo: change in HbA1c is analysed using mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c, baseline log ₁₀ (UACR), baseline HbA1c by visit and baseline log ₁₀ (UACR) by visit as linear covariates and treatment, visit, visit by treatment interaction as fixed effects. The Unstructured covariance structure has been used to fit the mixed model.	
Comparison groups	Placebo v Linagliptin 5 mg

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.43
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[3] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Linagliptin 5 mg minus Placebo.

Secondary: The time weighted average of percentage change from baseline in UACR during the course of 24 weeks of treatment

End point title	The time weighted average of percentage change from baseline in UACR during the course of 24 weeks of treatment
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End point description:

The time weighted average of percentage change from baseline in UACR (mg/g creatinine) during the course of 24 weeks of treatment. The term "baseline" for UACR refers to the geometric mean of UACR values measured at Visits 2 and 3. The number of participants analysed displays the number of participants with available data at the timepoint of interest. The Least Squares Means are adjusted geometric means. Full Analysis Set (FAS) - including all randomised patients who were treated with at least one dose of study drug, had a baseline HbA1c and a baseline Urinary albumin creatinine ratio (UACR), and at least one on treatment HbA1c or UACR assessment. Last Observation Carried Forward (LOCF). Values after the patient started rescue medication were excluded from analysis (and imputed with an LOCF procedure).

End point type	Secondary
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End point timeframe:

Baseline and 24 weeks

End point values	Placebo	Linagliptin 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173 ^[4]	178 ^[5]		
Units: mg/g creatinine				
least squares mean (confidence interval 95%)	0.9487 (0.8857 to 1.0162)	0.8902 (0.8318 to 0.9526)		

Notes:

[4] - FAS

[5] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Superiority of Linagliptin 5 mg vs. placebo: change in UACR is analysed using analysis of covariance

model. Model includes baseline HbA1c and baseline log10 (UACR) as linear covariates and treatment as fixed effect.

Comparison groups	Placebo v Linagliptin 5 mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.1954
Method	ANCOVA
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.03

Notes:

[6] - Ratio of relative change for Linagliptin 5 mg over placebo is presented.

Secondary: The change from baseline in estimated glomerular filtration rate (eGFR) after 24 weeks of treatment

End point title	The change from baseline in estimated glomerular filtration rate (eGFR) after 24 weeks of treatment
End point description:	The change from baseline in estimated glomerular filtration rate (eGFR) as assessed by chronic kidney disease epidemiology collaboration (CKD-EPI) equation (cystatin C) after 24 weeks of treatment. The term "baseline" refers to the last observation before the start of any randomised trial treatment. The number of participants analysed displays the number of participants with available data at the timepoint of interest. This outcome measure is a secondary safety endpoint. Treated Set (TS) - including all patients treated with at least one dose of randomised trial medication.
End point type	Secondary
End point timeframe:	Baseline and 24 weeks

End point values	Placebo	Linagliptin 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156 ^[7]	162 ^[8]		
Units: milliliter/minute/1.73 square metre				
least squares mean (standard error)	-2.35 (± 1.92)	-4.98 (± 1.89)		

Notes:

[7] - TS

[8] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	Change in eGFR is analysed using mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c, baseline log10 (UACR), baseline eGFR, baseline HbA1c by visit, baseline log10 (UACR) by visit and baseline eGFR by visit as linear covariates and treatment, visit, visit by treatment interaction as fixed effects. The Unstructured covariance structure has been used to fit the mixed model.

Comparison groups	Placebo v Linagliptin 5 mg
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	= 0.3306
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.95
upper limit	2.68
Variability estimate	Standard error of the mean
Dispersion value	2.7

Notes:

[9] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as Linagliptin 5 mg minus Placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 28 days after the last drug administration, up to 240 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Linagliptin 5 mg
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Reporting group description:

Patients received 1 tablet of Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

Reporting group title	Placebo
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Reporting group description:

Patients received 1 matching placebo tablet to Linagliptin 5 mg, administered orally, once every day for 24 weeks during the double blind treatment period.

Serious adverse events	Linagliptin 5 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 182 (9.34%)	8 / 178 (4.49%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic occlusion			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis ischaemic			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral nerve injury			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpericardiotomy syndrome			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 182 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seizure			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			

subjects affected / exposed	2 / 182 (1.10%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal fistula			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 182 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 182 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site infection			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 182 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 182 (0.00%)	2 / 178 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1

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

Non-serious adverse events	Linagliptin 5 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 182 (21.43%)	27 / 178 (15.17%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 182 (7.14%)	10 / 178 (5.62%)	
occurrences (all)	16	12	
Upper respiratory tract infection			
subjects affected / exposed	4 / 182 (2.20%)	9 / 178 (5.06%)	
occurrences (all)	4	9	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	24 / 182 (13.19%)	10 / 178 (5.62%)	
occurrences (all)	50	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2012	The main changes were: The reference to the standard treatment for diabetic nephropathy therapy in the title has been deleted as angiotensin converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB) were not registered for this indication by regulatory authorities in every country (this change was also made in the entire document accordingly). There was a change in Trial Clinical Monitor (TCM). Some clarifications regarding Ambulatory blood pressure measurement (ABPM) and biomarkers procedures and update of the flowchart (randomisation visit number changed from Visit 3 to Visit 3.1), as well as clarification regarding the procedure for rescue therapy. Denmark has been added in participating countries. Inclusion criterion 2 has been modified to clarify the use of basal insulin and to prohibit the use of Sulphonylurea (SU) and glinide as antidiabetic background therapy (in order to decrease the risks of hypoglycaemia). Inclusion criterion 4 has been modified to allow the screening of the patients on other criteria than exclusively Urinary albumin creatinine ratio (UACR) as it was not systematically measured in each participating country; to describe albuminuria collection; and to clarify the parameter to consider in order to assess patient's eligibility.
22 April 2013	The main changes were: The flow chart has been updated to reflect some clarifications regarding the procedures. Measurement of beta-2-microglobulin has been deleted because of practical reasons and redundancy. SU and glinide were allowed again during the follow-up period. Clarification that Adverse Event (AE) have to be considered under treatment during the 7 days after last trial drug administration and that AEs have to be declared between Visits 7 and 8. The Estimated glomerular filtration rate (eGFR) formula CDK-EPI has been changed to be in agreement with the central laboratory. It was stated that separate Trial Statistical Analysis Plan (TSAPs) for (other) biomarkers analyses were to be written as biomarkers analyses were to be reported separately.
04 December 2013	The main changes were: SU and glinide have been added as potential options for rescue medication as they had been allowed as background therapies; inclusion criteria 2 and 3 and exclusion criterion 13 were modified accordingly in order to facilitate the recruitment. In the inclusion criterion 3, Glycosylated haemoglobin (HbA1c) lower level was decreased from 7% to 6.5% in order to facilitate the recruitment. It was added that pancreatic events will have to be adjudicated in order to better follow up the occurrence of pancreatic events. The use of rescue medication was added as further efficacy endpoint. Clarifications have been added regarding declaration of Serious adverse event (SAEs) and Adverse event of special interest (AESIs) in order to harmonize processes with Boehringer Ingelheim Standard operating procedure (BI SOP). The Full analysis set (FAS) definition has been changed in order to include the Urinary albumin creatinine ratio (UACR) endpoint as an additional requirement. The statistical models have been corrected to include log ₁₀ (UACR) instead of UACR, in regards to the normality of the UACR endpoint. The range of baseline categories for UACR endpoint has been changed in order to be compliant with project specifications.

27 April 2015	<p>The main changes were: The Estimated creatinine clearance (eCrCl) Cockcroft Gault formula has been replaced by eGFR assessed by CKD-EPI equation as this equation is not influenced by Body mass index (BMI) and would then allow a better assessment of GFR in patients with T2DM. As a consequence of the previous change, the endpoint "change from baseline in eGFR as assessed by CKD-EPI equation after 24 weeks of treatment" has been categorised as a secondary safety endpoint and the endpoint "change from baseline in eCrCl as assessed by Cockcroft Gault formula after 24 weeks of treatment" has been categorised as other safety endpoint. The sample size has been reduced to 350 patients based on new clinical study results and a revised statistical assumption to ensure a power of at least $\geq 85\%$. The primary analysis model has been changed from an ANCOVA on the FAS (LOCF) to a MMRM approach on the FAS (OC) based on Food & Drug Administration (FDA) recommendation. The inclusion criterion 2 has been modified to clarify the number of oral antidiabetic therapies allowed in combination with basal insulin. The exclusion criterion 13 has been clarified. 'Transition from baseline macro- or microalbuminuria to either micro- or normal albuminuria after 24 weeks of treatment' has been added as efficacy endpoint to identify patients with improvement of the pre-existing renal impairment condition. Safety endpoints related to ABPM measurements (change from baseline in mean 24 h arterial blood pressure and in mean 24 h pulse rate after 24 weeks of treatment) have been added for consistency with the endpoints on vital signs. The endpoint AESI has been removed as AESIs are already included in the AE analysis.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported