Clinical Trial Protocol

Doc. No.:
c02155180-06

EudraCT No.:	2011-004148-23
BI Trial No.:	1218.22
BI Investigational Product(s):	Linagliptin (BI 1356)
Title:	A multicenter, international, randomized, parallel group, double-blind, placebo-controlled **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA
Clinical Phase:	IV
Trial Clinical Monitor:	**Phone** **Fax**
	Phone: Fax:
Co-ordinating Investigators:	
	Phone: Fax:
	Phone: Fax:
	Phone: Fax:
Status:	**Final Protocol (Revised Protocol (based on global amendment 2))**
Version and Date:	**Version: 3.0** **Date: 22 November 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Trajenta®			
Name of active ingredient: Linagliptin (BI 1356)			
Protocol date: 5 February 2013	**Trial number:** 1218.22		**Revision date:** **22 November 2016**
Title of trial:	A multicenter, international, randomized, parallel group, double-blind, placebo-controlled **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA		
Co-ordinating Investigators	Phone: Fax: Phone: Fax: Phone: Fax:		
Trial site(s):	Approximately 600		
Clinical phase:	IV		
Objective(s):	The primary objective is to demonstrate non-inferiority (by means of comparing the upper limit of a two-sided 95% confidence interval with the non-inferiority margin of 1.3) of treatment with linagliptin in comparison to placebo (as add-on therapy on top of standard of care) with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint (i.e. cardiovascular (CV) death ~~[including fatal stroke, fatal MI and sudden death]~~, non-fatal stroke **or** non-fatal myocardial infarction (MI) ~~(excluding silent MI)~~ ~~and hospitalisation for unstable angina pectoris)~~ in patients with type 2 diabetes mellitus (T2DM). If non-inferiority has been demonstrated, then the primary composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to the composite renal endpoint (i.e. renal death, sustained end-stage renal disease (ESRD), sustained decrease in estimated ~~global~~ **glomerular** filtration rate (eGFR) ≥~~50~~ **40**% from baseline), will be investigated separately with a test on superiority.		

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Methodology:	This randomized, double-blind, placebo controlled, parallel group study compares treatment with linagliptin (5 mg once daily) to treatment with placebo (matching tablets once daily) as add-on therapy to standard of care.
No. of patients:	
total entered:	An estimated ~~8300~~ **7000** randomized patients to obtain a minimum of ~~625~~ **611** primary endpoint events.
each treatment:	An estimated ~~4150~~ **3500** randomized patients per treatment group.
Diagnosis :	T2DM
Criteria for inclusion:	1. Documented diagnosis of T2DM before visit 1(screening). 2. Male or female patients who are drug-naïve or pre-treated with any antidiabetic background medication, excluding treatment with GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors if ≥ consecutive 7 days. 3. Stable antidiabetic background medication (unchanged daily dose) for at least 8 weeks prior to randomization. If insulin is part of the background therapy, the average daily insulin dose should not have changed by more than 10% within the 8 weeks prior to randomization compared with the daily insulin dose at randomization. 4. HbA1c of ≥ 6.5% and ≤ 10.0% at visit 1 (screening) 5. Age ≥ 18 years at visit 1(screening). *For Japan only: Age ≥ 20 years at visit 1* 6. Body Mass Index (BMI) ≤ 45 kg/m^2 at visit 1 (screening) 7. Signed and dated written informed consent by date of visit 1(screening) in accordance with Good Clinical Practice (GCP) and local legislation prior to any study related procedure 8.High risk of CV events defined by: • Albuminuria (micro or macro) and previous macrovascular disease: defined according to section 3.3.2 **and/or** • Impaired renal function with predefined UACR: for criteria see section 3.3.2 Refer to section 3.3.3 for exclusion criteria.
Test product(s):	Linagliptin
dose:	5 mg
mode of admin.:	Tablets per os
Comparator product:	Placebo
dose:	NA
mode of admin.:	Tablets per os
Duration of treatment:	Estimated ~~48~~ **54** months treatment period from first patient randomized, depending on observed number of primary endpoint events.

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Criteria for efficacy:

The primary endpoint in this trial is time to the first occurrence of any of the following **by** adjudicat**ion**~~ed~~ **confirme**d components of the primary composite endpoint (4 **3**-point MACE): CV death ~~(including fatal stroke, fatal MI and sudden death)~~, non-fatal MI ~~(excluding silent MI)~~ **or** non-fatal stroke ~~and hospitalisation for unstable angina pectoris~~.

The key secondary endpoint~~s are~~ **is** time to the first occurrence of **any of the following by adjudication confirmed components:**

- ~~CV death (including fatal stroke, fatal MI and sudden death), non-fatal MI (excluding silent MI), non-fatal stroke (3-point MACE)~~
- Composite renal endpoint (renal death, sustained ESRD, sustained decrease of ~~50~~ **40**% or more in eGFR)

The primary endpoint (4 **3**-point MACE) will be tested for non-inferiority. Thereafter, **if non-inferiority has been demonstrated**, the 4 **3**-point MACE and the combined composite renal endpoint will be tested separately ~~(= in parallel)~~ for superiority. ~~In case the 4-point MACE and/or the composite renal endpoint is significantly superior, the 3-point MACE will be tested for superiority.~~

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Criteria for safety:	Secondary and tertiary CV and renal endpoints are described above and in Section 7. In addition, incidence and intensity of adverse events, physical examination, vital signs, electrocardiogram (ECG) and change from baseline in laboratory parameters will be assessed.
Statistical methods:	For the primary analyses a Cox proportional hazards regression model of time to first event with factor treatment and geographical region will be conducted. The primary analyses will be performed on the ~~full analysis set~~ **Treated Set** following the intent-to-treat principle. The first null hypothesis states that linagliptin is inferior to placebo by a hazard ratio of at least 1.3 regarding the primary composite endpoint. The study is powered to reject that hypothesis. If the non-inferiority test with margin 1.3 has revealed a significant result, then two separate hypothesis tests for a) the primary composite endpoint b) the composite renal endpoint (i.e. renal death, sustained ESRD, sustained decrease in estimated GFR ≥ ~~50~~ **40**% from baseline) will be tested for superiority ~~in parallel~~, each with the Cox proportional hazards regression model for time to first event. **To adjust for multiplicity a sequentially**

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rejective multiple test procedure will be applied.			

FLOW CHART

Trial period	**Screening**	**Treatment period**						**FU**
Visit	**1**	**2**	**3**	**4**	**5**	**6 to N**	**EOT[C]**	**FU[D]**
Week	**-2**	**0**	**12**	**36**	**60**	**84 to N[B]**	**-**	**-**
Days from randomization	**-14[A]**	**0**	**84**	**252**	**420**	**588 to N[B]**	**-**	**EOT + 30**
Time window (days)[O]	**+13 [A]**		**±7**	**±14**	**±14**	**±14**	**±14**	**+7**
Informed consent	X							
In-/exclusion criteria	X	X						
Medical history/ concomitant diagnoses	X							
Demographics	X							
Physical examination[F]		X		X		X	X	X[D]
Vital signs	X	X	X	X	X	X	X	X[D]
Height	X[E]							
Weight	X[E]			X	X	X	X	
Waist circumference		X		X	X	X	X	
12-lead-ECG[H]		X		X	X	X	X	X[D]
Pregnancy Test[I]		X		X	X	X	X	
Fasted home blood glucose monitoring[J]		X	X	X	X	X	X	
Safety laboratory[K]	X	X	X	X	X	X	X	X[D]
UACR[Q]	X	X[A]		X		X[K]	X	X[D]
HbA_{1c}	X	X	X	X	X	X	X	
Lipid panel		X		X		X[K]	X	X[D]
eGFR[L]	X	X	X	X	X	X	X	X[D]
Pharmacogenetic sampling[P]		X						
Adverse events/outcome events [M]	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Randomization (IRT)[N]		X						
Dispense study medication (IRT)[N]		X	X	X	X	X		
Return study medication/ medication compliance check			X	X	X	X	X	

Flow Chart (continued)

A Randomization may be done as soon as the visit 1 (safety) laboratory results and eGFR are known and all other eligibility criteria are met. If the UACR result at visit 2 is required to fulfil inclusion criterion 8, randomization may be postponed until the laboratory results are known. It's not required to repeat visit 2 assessments if the patient returns to the clinic for randomization.

B A clinic visit will be scheduled every 24 weeks until study end.

C The study is event driven. The number of confirmed adjudicated primary endpoint events will be continuously monitored during the trial. Based on the available number of events the projected number of expected future events will be calculated. As soon as the projection reliably suggests that the total number of patients with a by adjudication confirmed primary endpoint event will reach ~~625~~ **611** ~~within the next 24 weeks~~, the trial team will perform respective actions to stop the trial. From this time point on, all patients are expected to perform their last visit (EOT visit) within the ~~regular~~ **proposed** time schedule, ~~which means within the next 24 weeks~~ **communicated via an investigator letter**. A follow-up visit will take place ~~one week~~ **30 days** after the end of treatment (EOT visit).

Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception , collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.

If a patient who prematurely discontinued study drug is not willing to return to the pre-defined study visits, at minimum a yearly telephone call (preferably every 6 months) and a telephone call at study end will be required, to document the occurrence of outcome events and vital status. If possible, other adverse events and concomitant therapy changes since last visit ~~might~~ **should** be recorded (refer to section 3.3.4).

D All patients will have a follow up visit ~~one week~~ **30 days** following regular or premature completion of the treatment period. The follow-up visit may be performed as a phone visit for patients who did not prematurely discontinue study medication and who do not have abnormalities at the EOT visit (only adverse events/outcome events and changes in concomitant therapy to be obtained).

E Body Mass Index will be calculated automatically.

F A complete, head-to-toe physical examination (e.g. evaluation of the body and its functions using inspection, palpation, percussion, and auscultation) will be done.

G

H In addition to the visits indicated, electrocardiogram (ECG) should be recorded in case of respective cardiac symptoms (indicating rhythm disorders or cardiac ischemia).

I For female patients (local urine pregnancy test in women of child bearing potential). More frequent testing can be done if required by local regulations/authorities.

J Distribution of glucometer and testing supplies with instructions at randomization (visit 2). During the treatment period, weekly finger stick glucose measurements are recommended (fasted). During the whole trial participation, additional measurements should be done if necessary and in case of hypo- or hyperglycaemia related symptoms. The patient should be instructed to bring their HBGM device and diary to the clinic for an additional measurement (fasted).

K At visit 1 safety laboratory includes ALT, AST, alkaline phosphatase and creatinine to check for eligibility in addition to lipase**,** urine albumin, urine creatinine and HbA_{1c} as specified in the flow chart. At randomization (visit 2) baseline laboratory will be obtained. See section 5.2.3 for to be obtained laboratory parameters. As of visit 6: yearly (every other visit) lipid profile (Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides), urine albumin and urine creatinine.

L Estimated ~~creatinine clearance~~ **glomerular filtration rate (eGFR)** will be calculated using the MDRD formula. This formula considers the race as an adjustment factor, therefore, the race must be known (and will be collected) for accurate estimation. In case of an eGFR decrease of $\geq 40\%$ since baseline (visit 2) and again in case of an eGFR decrease of $\geq 50\%$ since baseline (visit 2) an additional visit 4**-8** weeks after detection should be scheduled to collect a blood sample for repeat analysis of creatinine (eGFR). An additional sample of creatinine should also be taken between the visits if a signal of increasing creatinine is reported to the study site by others (e.g., GPs from local labs).

M In case of a stroke the reported value from the modified Rankin Scale will be collected approximately one week after stroke onset and 3 months after stroke onset. This might require an additional contact.

N Interactive Response Technology (IRT) will allocate medication kit numbers at all study visits from visit 2 till study end. At visit 2 patients will receive one treatment box sufficient for 12 weeks treatment (plus one week reserve). As of visit 3 patients will receive two medication boxes sufficient for 24 weeks treatment (plus two weeks reserve).

O The protocol allows a time window of +/- 7 days for visit 3 and +/- 14 days for all scheduled visits in the treatment period after visit 3. To ensure sufficient medication, visits after visit 3 should be scheduled within 182 days and visit 3 should take place no later than 91 days after visit 2.

P To allow possible retrospective pharmacogenetic analyses, all patients eligible for randomization will be asked for a blood sample with a separate informed consent. The pharmacogenetic sample should preferably be taken at visit 2, but could also be taken at any later visit, depending on availability of the respective informed consent. Pharmacogenetic sampling is voluntary and is not a prerequisite for participation in the study.

Q Urine Albumin Creatinine Ratio (UACR) will be calculated at the central lab, and should be measured on a first morning void specimen wherever possible.

TABLE OF CONTENTS

ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme inhibitor
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALD	Approximate Lethal Dose
ALT	Alanine Transaminase (SGPT)
AP	Alkaline Phosphatase
ARB	Angiotensin Receptor Blocker
AST	Aspartate transaminase (SGOT)
BI	Boehringer Ingelheim
BMI	Body Mass Index (weight in kg divided by height in meters squared)
BP	Blood Pressure
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CCDS	Company Core Data Sheet
CEC	Clinical Event Committee
CES-D	Center for Epidemiologic Studies Depression scale
~~CHF~~	~~Congestive Heart Failure~~
CKD	Chronic Kidney Disease
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRF	Case Report Form
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTSU	Clinical Trial Supply Unit
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DPP-4	Dipeptidyl-peptidase 4
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular filtration Rate
EOT	End of Treatment
ESRD	End Stage Renal Disease
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl-transferase (GGT)
GI	GastroIntestinal
GIP	Glucose-dependent Insulinotropic Peptide
GLP-1	Glucagon-like Peptide 1
HbA_{1c}	Glycosylated Haemoglobin

HBGM	Home Blood Glucose Monitoring
βHCG	beta Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HR	Hazard Ratio
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intention To Treat
IUDs/IUSs	Intra Uterine Devices/Systems
LDL	Low Density Lipoprotein
LDH	Lactate Dehydrogenase
MACE	Major Adverse Cardiovascular Events
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial infarction
MMSE	Mini-Mental State Examination
NGSP	National Glycohemoglobin Standardization Program
NI	Non-Inferiority
OAD	Oral antidiabetic drug
OS	**On-treatment Set**
PCI	Percutaneous Coronary Intervention
p.o.	per os (oral)
PPS	Per Protocol Set
PR	Pulse Rate
PV	Protocol Violation
SAE	Serious Adverse Event
SC	Steering Committee
SGLT-2	Sodium Glucose Linked Transporter
SOP	Standard Operating Procedure
SU	Sulfonylurea
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 diabetes mellitus
TIA	Transient Ischemic Attack
TMT	Trial Making Test
TS	**Treated Set**
TSAP	Trial Statistical Analysis Plan
UACR	Urine Albumin Creatinine Ratio
ULN	Upper Limit of Normal
~~VEGF~~	~~Vascular endothelial growth factor~~
VFT	Verbal Fluency Test

1. INTRODUCTION

Linagliptin is an orally available inhibitor of the enzyme dipeptidyl-peptidase IV (DPP-4) facilitating a decrease of blood glucose levels in patients with type 2 diabetes mellitus (T2DM).

1.1 MEDICAL BACKGROUND

T2DM is a chronic metabolic disease defined by elevated glucose levels that is associated with an increased risk for acute and/or late complications related to the micro- and macrovascular circulation. For instance, T2DM is the leading cause for end stage renal disease (ESRD) worldwide and a major cause of new cases of blindness and visual impairment. The elevated risk for macrovascular disease is primarily related to increased risk for athero-thrombosis that leads to increased morbidity and premature mortality from cardiovascular (CV) disease [R10-0116, P08-06509] and an important predictor for CV diseases is chronic kidney disease (CKD) which often co-exist. Studies suggest that 70-75% of all deaths in people with diabetes can be attributed to CV complications [R10-0117].

Strategies for glycaemic management of T2DM; guidelines and limitations

Patients with T2DM are usually treated by combinations of lifestyle and pharmacological interventions and several international guidelines for the treatment of T2DM have been issued [R07-1076, P10-00533, R09-1164, R09-6397, R08-1310, R10-4077, P08-01788]. Most guidelines suggest that the therapeutic goal for glycosylated haemoglobin (HbA1c) should be 6.5-7.0%, which by the use of available tools seem hard to obtain after more than 5-10 years of diabetes duration. A survey in the US (National Health and Nutrition Examination Survey [NHANES] 2003-2004) found that only 57% of participants had HbA1c < 7.0% [R10-0133]. Poor control was also noted among the 7000 individuals with T2DM in the Cost of Diabetes in Europe – Type 2 study where only 31% achieved the < 6.5% HbA1c goal for HbA1c [R10-0134]. Reasons for this are, amongst other factors, related to a progressive failure of the pancreatic ß-cells to compensate for an endogenous insulin resistance by an adequately increased insulin secretion, and the lack of treatment with sustainable effects. Ample evidence tells that lifestyle modification alone, or oral monotherapy, are not sufficient to maintain target levels of glycaemic control in most patients over time. In guidance for the clinician on which pharmacological compounds to use to achieve glycaemic goals amongst patients with T2DM the international guidelines differs slightly [R07-1076, P10-00533, R09-1164, R09-6397, R08-1310, R10-4077, P08-01788]. In general however, all bodies recommend that metformin should be first line treatment. Despite some limitations, this compound is the most widely used with a good safety profile, with some evidence suggesting cardio protective properties [R09-6405, R09-6406], and without associated cardiotoxicity. Most other drugs on the market lack such documentation.

As a second line treatment, because of the progressive loss of ß-cell function in patients with T2DM, traditional insulin secretagogues such as the sulfonylurea's (SUs) that stimulate insulin secretion in a non-glucose-dependent manner are widely used; in fact, they are the most commonly used second line therapy. However, treatment with SUs carries an increased risk for hypoglycaemia and weight gain [R09-6400], and as is the case for metformin, are

also associated with a lack of sustainable effect [R09-6400]. Therefore, international treatment guidelines have endorsed use of other drugs, e.g. insulins, glitazones, glinides and alpha-glucosidase inhibitors, to be used as 2nd line or 3rd line in certain settings. However, most of these drugs also have side effects that limit their use, such as hypoglycaemia, weight gain, gastrointestinal (GI) side effects and peripheral oedema. In addition to morbidity associated with each of these side effects, they could also have adverse CV implications. Hypoglycaemia and weight gain were recently postulated as contributors to the adverse mortality outcomes in the "Action to Control Cardiovascular Risk in Diabetes" (ACCORD) trial [R09-6407]. In addition, serious hypoglycaemia was the 2nd strongest predictor for incident myocardial infarction (MI) in the Veterans Affairs Diabetes trial (VADT)[R09-6408].

Since CV risk signals with drugs to treat T2DM have historically been observed at relatively late stages, just before or even after the drugs have reached the market, regulatory authorities such as the US Food and Drugs Administration (FDA) have issued a guidance to industry in order to rule out potential excessive CV morbidity and mortality associated with all new drugs for the treatment of T2DM [R09-2151]. Such an assessment could involve dedicated trials. It is therefore of interest to explore novel treatment options that offer glycaemic reduction without an associated increased CV risk.

Of note is that data from recent years indicates a decrease in the age-specific mortality rates due to CV diseases (although the increased relative CV risk between subjects with T2DM and without still is high and increased 2-4 fold), a reduction in renal complications seems not to occur. Establishing treatment options for T2DM that potentially not only reduce overall glycaemic burden, but also potentially could address current unmet medical need in prevention and/or treatment of macro-/microvascular complications could therefore have huge implications for T2DM patient care as there currently are insufficient and low-quality evidence on the effectiveness of individual oral antidiabetic drugs (OADs) on the development or progression of CV complications and nephropathy, as underscored also in the recent systematic review on the 'Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes', sponsored by the Agency for Healthcare Research and Quality [R11-4860].

Emerging treatment for T2DM; DPP- 4 inhibitors

The incretin effect is a phenomenon where glucose-dependent insulin secretion is augmented by intestinally derived peptides (i.e. incretins) that are released in the presence of glucose or nutrients in the gut and thereby contribute to the maintenance of long term and post-meal glycaemic control in a glucose-dependent manner. Glucagon-like peptide 1 (GLP-1) is an important member of the incretin hormone family, and together with glucose-dependent insulinotropic peptide (GIP), accounts for more than 50% of the incretin effect in humans [R09-6409]. These hormones are almost instantaneously inactivated by the enzyme DPP-4. DPP-4 is widely expressed in many tissues including kidney, liver, intestine, lymphocytes and vascular endothelial cells. Since postprandial GLP-1 secretion has been reported to be attenuated in T2DM [R09-6409], a prolongation of the half life of GLP-1 by DPP-4 inhibition has been proven as a therapeutic target to improve glycaemic control in patients with T2DM. Besides its stimulatory effects on insulin secretion dependent on the actual

plasma glucose concentration [R09-6409], resulting in a reduction of HbA_{1c}, GLP-1 has also been shown to inhibit glucagon secretion, to delay gastric emptying, to induce satiety, to affect weight loss, and, in animal models, to maintain long-term ß-cell function. The potential benefit of maintenance of ß-cell function is of particular interest, that if also the case in humans, would represent an important clinical finding. However, no long term studies in humans have confirmed this. An added interesting feature of this therapeutic option is that it seems to be associated with no weight gain and a very low risk of hypoglycaemia.

Study proposal

In this large-scale intervention trial we will test the impact of treatment with the DPP-4 inhibitor linagliptin head-to-head versus placebo on long-term CV safety as well as the potential preventive impact on CV and renal complications. The study will be given the acronym CARMELINA (CArdiovascular Safety & Renal Microvascular outcomE with LINAgliptin in patients with type 2 diabetes mellitus at high vascular risk).

1.2 DRUG PROFILE

The DPP-4 inhibitor compound linagliptin was discovered by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

Linagliptin is a potent inhibitor of DPP-4 activity and prolongs the half-life of GLP-1. This has been shown in vitro, in various animal models, and in clinical trials. Linagliptin is an orally available compound with a low risk for hypoglycaemic episodes [U04-1767].

~~In general pharmacological tests, linagliptin exhibited good tolerability in a variety of physiological systems. No genotoxic effect was observed in any of the tests performed with linagliptin or with its major metabolite CD 1790. The single dose (acute) toxicity of linagliptin after oral administration was low as indicated by an Approximate Lethal Dose (ALD50) between 1000 and 2000 mg/kg. In repeat dose toxicity studies, a wide margin of safety was demonstrated. This was also true with respect to exposure to the major metabolite CD 1750.~~

~~Linagliptin shows nonlinear pharmacokinetics, both after oral and intravenous administration in the therapeutic dose range, with a less than dose-proportional increase in plasma concentrations. After oral administration of a 5 mg dose, linagliptin is rapidly absorbed, with peak plasma concentrations (median Tmax) occurring approximately 1.5 hours post dose.~~

~~Clearance, volume of distribution, and amount excreted unchanged in urine increase with increasing doses, which may be a result of nonlinear protein binding in the therapeutic plasma concentration range. Linagliptin is predominantly excreted unchanged in faeces. Renal excretion is considered to be a minor elimination pathway of linagliptin at therapeutic dose levels.~~

~~The long terminal half-life of >100 hours does not reflect the effective half-life, as steady state is reached within 2-7 days. Time to steady state decreases dose-dependently from 4-7~~

~~days to 2 days for once daily dosing of 1-10 mg linagliptin. The accumulation factors of C_{max} and AUC range from 1.2-2 upon multiple dosing.~~
~~No adjustment of linagliptin dosage based on the intrinsic factors age, BMI, weight, gender or race is considered necessary. Linagliptin showed no clinically relevant interaction with either the CYP 3A4 substrate simvastatin, with metformin, pioglitazone, glyburide, or empagliflozin (BI 10773). After strong inhibition of P-gp and CYP 3A4 by ritonavir linagliptin AUC and Cmax increased approximately twofold and threefold, respectively. Since linagliptin has a large safety window and no obvious change in the safety profile was seen under concomitant administration of P-gp and/or CYP3A4 inhibitors in phase II and III, these changes are considered to be not clinically relevant.~~

~~There is no effect of food on the extent of absorption. Only the rate of absorption was slightly reduced (median Tmax increased from 1.02 to 2.99 hours and Cmax reduced by about 15%) when linagliptin was given with food, which was considered to be of no clinical relevance. No dose adjustment of linagliptin in patients with any degree of hepatic or renal impairment is suggested as the pharmacokinetics of linagliptin did not relevantly change with decreasing hepatic function and the exposure changes seen at steady state in patients decreased renal function are considered as not clinically relevant.~~

~~In all trials to date in patients with T2DM, more than 5955 patients have received linagliptin 5 mg. Inhibition of DPP-4 activity by linagliptin also translated into an increase in plasma GLP-1 levels. In addition, linagliptin exhibited excellent tolerability at all dose levels in phase II studies with an absence of a dose dependent increase in adverse events.~~
~~In phase II and III clinical trials in patients with T2DM, the overall incidence of adverse events (AEs) with linagliptin 5 mg was comparable to placebo (linagliptin 5 mg: 52.5%, placebo: 51.6%). In addition, the number of patients with AEs leading to discontinuation of trial drug (linagliptin 5 mg: 2.3%, placebo: 2.8%) and with investigator defined drug-related AEs (linagliptin 5 mg: 8.3%, placebo: 9.1%) did not differ significantly between linagliptin and placebo.~~

~~The most frequently reported adverse events (≥ 5%) in both treatment groups were nasopharyngitis (4.7% placebo, 5.9% linagliptin 5 mg), hyperglycaemia (10.6% placebo, 5.1% linagliptin 5 mg) and hypoglycaemia (5.1% placebo and 7.8% linagliptin 5 mg)~~

~~The increased incidence of hypoglycaemia observed in the phase II and III studies nearly exclusively came from trial 1218.18 where linagliptin was added to a background therapy of metformin and SU where hypoglycemia rates after 24 weeks were observed to be 14.8% for placebo, and 22.8% for linagliptin 5 mg. When linagliptin was administered as monotherapy there was no difference between the placebo group and linagliptin with regard to the occurrence of 'hypoglycaemia'. Also the addition of linagliptin to a metformin background did not appear to increase the frequency of hypoglycaemia.~~

~~The incidence of serious adverse events (SAEs) in the phase II and III studies was 3.1% in patients treated with linagliptin 5 mg and 3.8% in patients treated with placebo.~~

~~Consistency of efficacy of linagliptin 5 mg has been shown in a number of phase III double~~

~~blind placebo-controlled efficacy trials, in reduction of HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose etc. These trials have tested linagliptin as monotherapy, on a background of metformin, and as add-on therapy to metformin plus SU and initial combination with metformin in the factorial design trial.~~

~~For further information about the drug profile of linagliptin, please refer to EU SPC or US PI, or another regulatory label document.~~

Clinical Pharmacokinetics

In earlier PK trials, linagliptin showed nonlinear PK in the therapeutic dose range, with a less than dose proportional increase in plasma concentrations. Clearance, volume of distribution, and amount excreted unchanged in urine increased with increasing doses, possibly due to nonlinear protein binding. Linagliptin was predominantly excreted unchanged in faeces. Renal excretion was considered to be a minor elimination pathway. No dose adjustment of linagliptin based on hepatic impairment, renal impairment, age, body mass index (BMI), weight, gender, or race is considered necessary. Linagliptin showed no clinically relevant interaction with metformin, pioglitazone, glyburide or empagliflozin.

Clinical efficacy and safety

Treatment with 5 mg linagliptin once daily has resulted in clinically meaningful and statistically significant reductions in HbA_{1c}, FPG, and postprandial glucose. There is a consistent pattern in the improvement in HbA_{1c} levels when linagliptin was used in patients with different background therapies. These findings demonstrate efficacy for up to 18 to 24 weeks duration for different background therapies and are further supported by trials of longer duration up to 104 weeks.

Overall, in phase III studies the overall incidence of adverse events (AEs), drug related AEs, AEs of severe intensity, AEs leading to discontinuation, and serious AEs (Serious Adverse Event, SAEs) were very similar across studies, with linagliptin being mostly comparable with placebo. For description of side effects of linagliptin refer to the current Investigator's Brochure [U04-1767] and the local prescribing information for linagliptin.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The aim of the present study is to investigate the long–term impact on CV morbidity and mortality of treatment with linagliptin in a selected population of patients with T2DM and compare outcomes against placebo, on a background of standard of care. To date, this has not been tested in long-term trials of linagliptin. Since this is the case for other DPP-4 inhibitors approved for the treatment of T2DM, several long-term studies are presently ongoing. There are currently no safety signals that indicate that linagliptin should be inferior to placebo with respect to CV safety [P12-00933]. A recent meta-analysis of the marketed DPP-4 inhibitors, on the contrary, indicates actually a potential beneficial CV effect of DPP-4 inhibitors as a class, although this meta-analysis mainly included trials of shorter duration with patients who were not at a particular high CV risk, limiting the findings to hypothesis generation [R09-6410]; thus this requires further studies.

The rationale to assess microvascular outcomes, in particular renal safety with the aim of demonstrating renal benefits, is derived from the hypothesis based on pre-clinical and limited clinical data, that GLP-1 based therapies, and in particular linagliptin, may have a direct impact on the integrity of the endothelium and podocytes of the glomerula and the proximal tubular cells as well as endothelial function and last, that linagliptin has a relatively high tissue distribution, including in the kidney, albeit all these features currently remains to be demonstrated.

As the study population of this trial are patients with high CV risk, all with various degrees of end-organ damage (i.e., renal impairment) it is conceivable that the study will include patients at all stages of T2DM duration since in fact many patients are being diagnosed with T2DM for the first time at the occasion of a CV event [R12-1135]. Therefore, antidiabetic treatment naïve, as well as patients with all kind of approved background antidiabetic treatment (including insulins) are eligible. The only exceptions are patients on DPP-4 inhibitors and/or GLP-1 receptor agonists and/or sodium glucose linked transporter (SGLT-2) inhibitors. Taking into consideration linagliptins mode of action, there is not an option in this trial to combine study drug (i.e., placebo or linagliptin) with a GLP-1 receptor analogue as the DPP4 inhibitor and GLP1 receptor analogue combination is not approved or indicated (per label of all GLP-1 products and DPP4 inhibitors). Also concomitant use of an SGLT-2 inhibitor is not allowed since this is a new class of drug that is and hithereto undescribed in terms of CV benefit-risk ratio in order to reduce complexity of interpretation of study outcome. Further, as this trial would like to address the impact on CV outcomes of linagliptin compared to placebo in a high CV risk population, some with high degree of renal impairment, where most likely the use of SGLT-2 inhibitors will be restricted, SGLT-2 inhibitors would only be an applicable therapy for a subset of the study cohort.

The study has two arms: linagliptin or placebo as add-on to antidiabetic treatment naive patients or other allowed antidiabetic treatments. The study design is described in more detail in Section 3.1.

The planned eligibility criteria will hence target a trial population with a short to long T2DM duration with a high CV risk (e.g., due to previous macrovascular disease and albuminuria (micro or macro) and/or renal impairment and predefined urine albumin creatinine ratio [UACR]). Thereby, it will assess the CV safety profile of linagliptin as compared with placebo in a broad (> 50% of patients with T2DM and CV complications are assumed to have some degree of renal impairment and some others > 20% have renal impairment alone) and relevant population of patients with T2DM. This study design therefore concurs with the recent FDA guidance for target populations in whom to specifically assess CV safety of novel OADs for the treatment of T2DM [R09-2151]. This study will also be an integral part of the ongoing CV safety assessment for linagliptin and data will be used to support regulatory submission.

Functional assessment of post-stroke recovery outcome of linagliptin versus placebo when provided on top of standard of care will also be evaluated using a simple one-tick box questionnaire (Rankin modified test scale), which could further advance our understanding of important issues in the management of patients with T2DM (Section 5.3.2).

2.2 TRIAL OBJECTIVES

The primary objective is to demonstrate non-inferiority (by means of comparing the upper limit of a two-sided 95% confidence interval with the non-inferiority margin of 1.3) of treatment with linagliptin in comparison with placebo (as add-on therapy on top of standard of care) with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint (i.e. CV death ~~[including fatal stroke, fatal MI and sudden death]~~, non-fatal stroke **or** non-fatal MI ~~(excluding silent MI)~~ ~~and hospitalisation for unstable angina pectoris~~) in patients with T2DM.

If non-inferiority has been demonstrated, then the primary composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to ~~the~~ **first occurrence of any of the adjudicated components of the** composite renal endpoint (i.e. renal death, sustained ESRD, sustained loss in estimated glomerular filtration rate (eGFR) ≥ ~~50~~ **40**% from baseline), will be investigated with a test on superiority.
The CV and renal superiority tests will be performed separately, with ~~no~~ **an** upfront imbalance regarding the assigned alpha-levels.

~~If linagliptin is superior with regard to the primary endpoint and/or the composite renal endpoint, a further test will evaluate the superiority of linagliptin with regard to the 3-component Major Adverse Cardiovascular Events (MACE) endpoint (CV death [including fatal stroke, fatal MI and sudden death], non-fatal stroke, non-fatal MI [excluding silent MI]).~~
For a description of the endpoints chosen and statistical analyses to assess these objectives, please refer to Section 5 and Section 7.

2.3 BENEFIT - RISK ASSESSMENT

Potential general benefits for study participants in this trial irrespective of investigational drug received are 1) improvements in glycaemic control, 2) improvements of other CV risk factors and 3) general medical benefit from careful and close monitoring by medical personnel and home blood glucose monitoring during the study.

General risks associated with participating are related to trial specific procedures such as blood sampling that can be associated with bruising and pain. The amount of blood taken during the whole course of the trial is not believed to be associated with any discomfort for the patients.

Investigational drug specific risk

Linagliptin from its clinical phase III testing has shown a safety profile similar to placebo. It carries a low risk for inducing hypoglycaemia and is generally weight neutral. Safety will be ensured by monitoring the patients for AEs both clinically and by laboratory testing. If any investigator should have a clinical concern, the safety of the patients will be of paramount importance. Given the large safety margin derived from the toxicology studies, the wide therapeutic window of linagliptin (120-fold recommended clinical dose), the high tolerability observed in previous trials in subjects with T2DM, and the monitoring throughout the trial the sponsor is of the opinion that the risks for the participating patients are minimal and justified.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomized, double-blind, and placebo controlled study compares treatment with linagliptin (5 mg once daily) with placebo treatment (matching tablets once daily) as add-on therapy to standard of care background antidiabetic treatment as specified in Section 3.3.2.

The trial is event driven and will run until ~~625~~ **611** patients with a by adjudication confirmed primary endpoint event are observed (Section 7.6), with an estimated ~~8300~~ **7000** randomized patients to be observed for an estimated study duration of ~~48~~ **54** months, beginning with the randomization of the first patient. The anticipated recruitment period is 36 months. In case the number of primary endpoint events is not or may not be reached within this period the trial duration ~~and/or the number of patients~~ will be increased until the defined number of adjudicated primary endpoint events is reached.

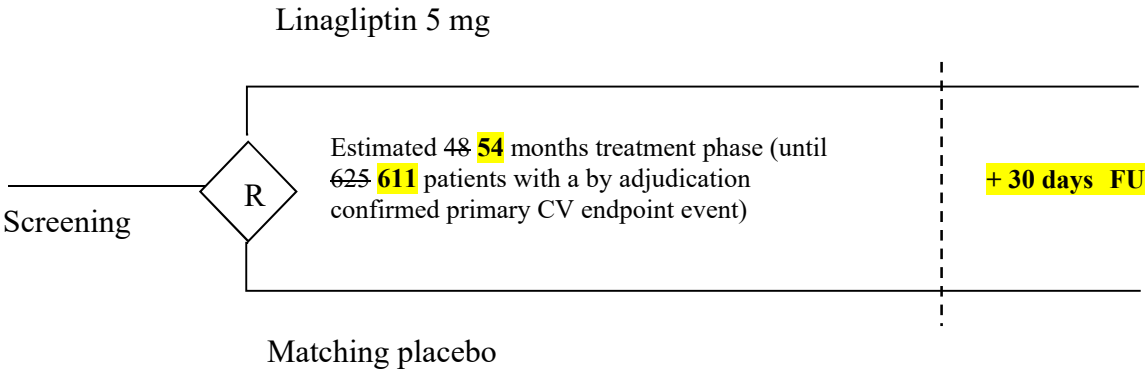

Figure 3.1: 1 Treatment periods and treatment groups in the trial design

For all patients, site visits are scheduled at regular time intervals (see flow chart). The estimated treatment duration for the first randomized patient is ~~48~~ **54** months. The number of confirmed adjudicated primary endpoint events will be continuously monitored during the trial. Based on the available number of events the projected number of expected future events will be calculated. As soon as the projection reliably suggests that the total number of patients with a by adjudication confirmed primary endpoint event will reach ~~625~~ **611** ~~within the next 24 weeks~~, the trial team will perform respective actions to stop the trial. From this time point on, all patients are expected to perform their last visit (EOT visit) within the ~~regular~~ **proposed** time schedule, ~~which means within the next 24 weeks~~ **communicated via an investigator letter.**

The End of Treatment visit (EOT) activities will be performed when a patient discontinues study medication treatment permanently. The EOT activities are not required for temporary interruptions of study drug. All patients will have a follow up visit ~~one week~~ **30 days** following discontinuation of study drug, irrespective whether they complete the treatment period or pre-maturely discontinue study treatment. Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted

if a patient is willing to return to the pre-defined study visits, with exception of collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.

If a patient who prematurely discontinued study drug is not willing to return to the pre-defined study visits, at minimum a yearly telephone call (preferably every 6 months) and a telephone call at study end will be required, to document the occurrence of outcome events and vital status. If possible, other AE's and concomitant therapy changes since last visit might be recorded. Every attempt will be made by the investigator to ensure patients continue participating in the study during study drug interruptions and after discontinuation of study drug. The ITT analysis requires that all study patients be followed until study end even if the study drug was temporarily interrupted or discontinued.

Patients will have a follow up visit ~~one week~~ **30 days** following regular or premature completion of the treatment period. The follow-up visit may be performed as a phone visit for patients who did not prematurely discontinue study medication and who do not have abnormalities at the EOT visit (only AEs/outcome events and changes in concomitant therapy to be obtained).

In case early study termination is to be performed (e.g. based on recommendation by the Data Monitoring Committee [DMC]), a reasonable timeframe to stop the trial (perform last patient visits) will be defined and communicated to the investigators.

3.1.1 Administrative structure of the trial

The study is sponsored by Boehringer Ingelheim (BI).

Co-ordinating Investigators who will (co) chair the Steering Committee (SC) will be nominated.

Documents on principal investigators and other important participants at each site, especially their curricula vitae, will be filed in the Clinical Trial Master File (CTMF).

CRO's will be assigned for central laboratory, interactive response technology (IRT), ECG analyses and conduct of the trial.

The following committees will participate in the conduct of the trial, their specific functions are summarised below:

Steering Committee
A SC will have a scientific and clinical advisory function in the study. The SC is comprised of university- and sponsor-based scientists with clinical and methodological expertise. Details on the composition of the committee, its procedures and interactions are provided in a separate SC Charter.

Data Monitoring Committee
An independent DMC will review safety and efficacy data and will make recommendations whether to continue or terminate the study. The DMC analyses and operations will be formally separated from the sponsor, the investigators, and the SC. Details on the composition of the committee, its procedures and interactions are provided in a separate DMC Charter.

Clinical Event Committee
The study is set up with prospective centralized blinded adjudication of all cardio/cerebrovascular trigger events. The prospectively defined adjudication process will assess cardiac and neurological vascular events through an independent, blinded, external Clinical Event Committee (CEC). Details on the composition of the committee, its procedures and interactions are provided in a separate CEC charter.

Additionally, separate independent, blinded, external committees will be set up for adjudication of renal events and pancreatic events. The adjudication process for renal events and pancreatic events will be clarified in ~~a separate~~ **the** CEC charter.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A wide variety of antidiabetic medications are available for the treatment of T2DM, but it is unclear how these drugs compare with respect to long term CV risk and microvascular outcomes [R11-4860]. The aim of this study is to have patients with T2DM on various antidiabetic background therapies represented to evaluate the long term CV and microvascular safety of linagliptin in a real life clinical setting.

The placebo-controlled design is considered ethically acceptable on the basis of appropriate criteria for patient discontinuation, ability to change background treatment to maintain, or obtain, sufficient level of glycaemic control as defined in relevant local and regional guidelines for optimized standard of care.

The treatment period is planned until the necessary number of by adjudication confirmed primary endpoint events is observed, to demonstrate non-inferiority of linagliptin compared to placebo when added on to standard of care.

Treatment with linagliptin will be compared against placebo. The treatment goal for HbA_{1c} in this trial, according to most international guidelines, will be a target of $\leq 7.0\%$, using open-label titration and addition of non-study therapies in both arms to achieve this goal throughout the trial. During the trial, additional therapy will be allowed, and encouraged, if $HbA_{1c} > 7.5\ \%$ during the trial treatment phase in accordance with guidelines. This is considered important to ensure that an optimal level of standard of care is reached in both arms of the trial. However, the decision to titrate or initiate medication to optimize glycaemic control will remain with the investigator and the patients' health care providers in accordance with appropriate local treatment guidelines.

The protocol also encourages the investigators and the patients' health care providers to treat all other CV risk factors (e.g. lipid levels, blood pressure, albuminuria, unhealthy lifestyle, smoking) according to an optimal level of local/regional standard of care. In a high CV risk population with renal impairment (i.e., albuminuria or eGFR [modification of diet in renal disease (MDRD) formula] 15-75 mL/min/1.73 m^2), this usually implies liberal use (if tolerated or not contraindicated) of statins, beta-blockers, calcium channel blockers, platelet inhibitors etc. This should be conducted in the context of local or regional guidance for primary or secondary CV risk prevention.

As in management of any patient with diabetic nephropathy and hypertension, the investigator may consider referral to a physician experienced in the care of kidney disease and hypertension for uncertainty about treatment. In particular it is expected that the patients at least are treated with either an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy (if one class is not tolerated, the other should be substituted) and that the target blood pressure (BP) goal is < 130/80 mmHg. When ACE inhibitors, ARBs, or diuretics are used, additional monitoring apart from the 24 week assessments in the protocol of serum creatinine, is at the investigators discretion.

The background medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations. The investigator can adjust the antihypertensive therapy, or other needed therapy, according to local and international recommendations, if better BP control is warranted during the course of the trial.

3.3 SELECTION OF TRIAL POPULATION

An appropriate number of patients will be screened (synonym enrolled) for the trial in approximately 600 study centres in up to 35 countries to ensure that an estimated ~~8300~~ **7000** patients are randomized (~~4150~~ **3500** to each treatment group) and evaluable. Investigators who fail to randomize at least one study subject in the first 12 weeks of the trial may be excluded from further participation. If enrolment is delayed, additional centres may be initiated.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all centres when a sufficient number of patients have been randomized to trial treatment. Investigators will be notified when screening is complete and will not be allowed to recruit additional patients thereafter. Patients who have completed visit 1 procedures prior to notification of the termination of recruitment will be allowed to be randomized in the study, if they meet all eligibility criteria. Subject eligibility will be based upon a complete medical history including a physical examination and clinical laboratory tests. Judgement of the clinical relevance of a concomitant disease is at the discretion of the investigator.

Re-screening and/or re-testing (of assessments) is permitted once.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the investigator site file (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

Patients with documented diagnosis of T2DM at high risk of CV events and meeting all other eligibility criteria can be enrolled in the study.

3.3.2 Inclusion criteria

1) Documented diagnosis of T2DM before visit 1 (screening).
2) Male or female patients who are drug-naïve or pre-treated with any antidiabetic background therapy, excluding treatment with GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors if ≥ 7 consecutive days.
3) Stable antidiabetic background medication (unchanged daily dose) for at least 8 weeks prior to randomization. If insulin is part of the background therapy, the average daily insulin dose should not have been changed by more than 10% within the 8 weeks prior to randomization compared with the daily insulin dose at randomization.
4) HbA1c of ≥ 6.5% and ≤ 10.0% at visit 1 (screening).
5) Age ≥ 18 years at visit 1 (screening). *For Japan only: Age ≥ 20 years at Visit 1.*
6) Body Mass Index (BMI) ≤ 45 kg/m^2 at visit 1 (screening).
7) Signed and dated written informed consent by date of visit 1 (screening) in accordance with GCP and local legislation prior to any study related procedure.
8) High risk of CV events (**I and/or II**):

I.		**Albuminuria (UACR ≥ 30 mg/g creatinine or ≥ 30 µg/min [microgram albumin per minute] or ≥ 30 mg/24 h [milligram albumin per 24 hours] in two out of three unrelated spot urine or timed samples in the last 24 months prior to randomization)* <u>AND</u> previous macrovascular disease, defined as either one or more:**
	a	Confirmed history of MI (> 2 months prior to Visit 1)
	b	Advanced coronary artery disease, defined by any one of the following: • ≥ 50% narrowing of the luminal diameter in 2 or more major coronary arteries by coronary angiography, MRI angiography or CT angiography; *Definition of major coronary arteries: LAD (Left Anterior Descending). CX (Circumflex) or RCA (right coronary artery)* • Left main stem coronary artery with ≥ 50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography; • Prior percutaneous or surgical revascularization of ≥ 2 major coronary arteries at least 2 months prior to Visit 1 (screening); • The combination of prior percutaneous or surgical revascularization of 1 major coronary artery at least 2 months prior to visit 1 (screening), and ≥ 50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography of at least 1 additional major coronary artery.

	c	High-risk single-vessel coronary artery disease, defined as the presence of ≥ 50% narrowing of the luminal diameter of one major coronary artery by coronary angiography, MRI angiography or CT angiography in patients not revascularised**:** **AND** at least one of the following: • A positive non invasive stress test, confirmed by either: o a positive ECG exercise tolerance test in patients without left bundle branch block, Wolff-Parkinson-White syndrome, left ventricular hypertrophy with repolarization abnormality, or paced ventricular rhythm, atrial fibrillation in case of abnormal ST-T segments; o a positive stress echocardiogram showing induced regional systolic wall motion abnormalities; o a positive nuclear myocardial perfusion imaging stress test showing stress-induced reversible perfusion abnormality; o a positive cardiac stress perfusion MRI showing a stress induced perfusion defect; • Patient discharged from hospital with a documented diagnosis of unstable angina pectoris between 2 and 12 months prior to visit 1 (screening).
	d	History of ischemic or haemorrhagic stroke (>3 months prior to visit 1)
	e	Presence of carotid artery disease (symptomatic or not) documented by either: o imaging techniques with at least one lesion estimated to be ≥50% narrowing of the luminal diameter; o prior percutaneous or surgical carotid revascularization.
	f	Presence of peripheral artery disease documented by either: o previous limb angioplasty, stenting or bypass surgery; o previous limb or foot amputation due to macrocirculatory insufficiency; o angiographic evidence of peripheral artery stenosis ≥ 50% narrowing of the luminal diameter in at least one limb (definition of peripheral artery: common iliac artery, internal iliac artery, external iliac artery, femoral artery, popliteal artery).
II.		**Evidence of impaired renal function with predefined UACR, with or without CV co-morbidities, defined as follows (and/or criteria):** • Impaired renal function (as defined by MDRD formula) with an eGFR:15- <45 mL/min/1.73 m^2 at visit 1 (screening) with any UACR. • Impaired renal function (as defined by MDRD formula) with an eGFR ≥ 45-75 mL/min/1.73 m^2 at visit 1 (screening) with an UACR > 200 mg/g creatinine or > 200 µg/min (microgram albumin per minute) or > 200 mg/24 h [milligram albumin per 24 hours] demonstrated in two out of three unrelated spot urine or timed samples in the last 24 months prior to randomization*.

*If the UACR result at Visit 2 is required to fulfil inclusion criterion 8, randomization may be postponed until the laboratory results are known.

Note: To ensure appropriate representation of patients from the different CV risk categories, the trial team will monitor the proportion of patients being recruited into these categories (trial level, and by region and/or country if appropriate). In consultation with the SC, limitation of recruitment of a particular category may be arranged (trial level, or per region and/or country level). This process will be implemented to ensure a proper distribution of CV risk categories worldwide.

3.3.3 Exclusion criteria

1) Type 1 diabetes mellitus.
2) Treatment (≥ 7 consecutive days) with GLP-1 receptor agonists, other DPP-4 inhibitors or SGLT-2 inhibitors prior to informed consent. Note: This also includes clinical trials where these antidiabetic drugs have been provided to the patient.
3) Active liver disease or impaired hepatic function, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase (AP) ≥3 x upper limit of normal (ULN) as determined at Visit 1.
4) eGFR <15 ml/min/**1.73 m^2** (severe renal impairment or ESRD, MDRD formula), as determined during screening at Visit 1 and/or the need for maintenance dialysis.
5) Any previous (or planned within next 12 months) bariatric surgery (open or laparoscopic) or intervention (gastric sleeve).
6) Pre-planned coronary artery re-vascularisation (PCI, CABG) or any previous PCI and/or CABG ≤ 2 months prior informed consent
7) Known hypersensitivity or allergy to the investigational products or its excipients.
8) Any previous or current alcohol or drug abuse that would interfere with trial participation in the opinion of the investigator.
9) Participation in another trial with an investigational drug ongoing or within 2 months prior to visit 1 (screening)*.
10) Pre-menopausal women (last menstruation ≤ 1 year prior to informed consent) who:
    - are nursing or pregnant,
    - or are of child-bearing potential and are not practicing an acceptable method of birth control (acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems (IUDs/IUSs), oral, implantable or injectable contraceptives, sexual abstinence (if allowed by local authorities), double barrier method and vasectomised partner) or do not plan to continue using acceptable method of birth control throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial.
11) Patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, have a life expectancy less than 5 years for non-CV causes, or have cancer other than non-melanoma

skin cancer within last 3 years, or has any other condition than mentioned which in the opinion of the investigator, would not allow safe participation in the study.

12) Acute coronary syndrome (ACS), diagnosed ≤ 2 months prior to visit 1 (screening).
13) Stroke or TIA ≤ 3 months prior to visit 1 (screening).

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

This is a long-term safety **outcome** study **and every effort should be made by the site staff to encourage patients to remain in the study and on study drug if medically safe.** Patients who discontinue study drug prematurely should be observed until study end ~~as if they were still receiving blinded study treatment~~. Patients who prematurely discontinue study drug **should** remain in the study. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of , collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.

If a patient who prematurely discontinued study drug is not willing to return at the pre-defined regular visit schedule, at minimum a yearly telephone call (preferably every 6 months) and a telephone call at study end will be ~~asked for~~ **required**, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit ~~might~~ **should** be recorded. Every attempt will be made by the investigator to ensure patients continue participating in the study during study drug interruptions and after discontinuation of study drug.

Patients who prematurely discontinue study medication ~~during the treatment phase~~ are allowed to restart the study medication at any time if appropriate in the opinion of the investigator and if not contraindicated. In this study, patients are allowed to have multiple study drug interruptions. There is no limit on either the number of study drug interruptions or the maximum length of any study drug interruption. **Investigators should routinely consider re-starting study drug at every visit following study drug discontinuation.**

A patient should be instructed to stop the study drug only after discussion between sponsor representative and investigator, if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at study assessments).

Early discontinuation of study medication is not a criterion for withdrawal of consent for participating in the study.

If a patient becomes pregnant during the trial, the study treatment will be stopped, the patient will be followed up during the study and until birth or termination of the pregnancy (see further details in Section 5.2.2.2).

If pancreatitis is suspected, the study treatment should be stopped.

~~An individual patient is to be withdrawn from the study and follow-up assessments only if the patient actively withdraws consent, without the need to justify the decision.~~

A patient has the right to withdraw informed consent for participation at any time for any reason. However, withdrawal of consent from study participation should be very rare and unusual. Because of this, the investigator should be involved in the discussions with the patient regarding a withdrawal of consent. Additionally, the investigator should discuss the withdrawal of consent with the sponsor representative prior to stopping study participation.

Patients that are not actively taking study drug may be less motivated to adhere to the study visit schedule. Investigators and site staff should work to detect early signs of losing interest and readily present such patients (not actively taking study drug) with the following options to encourage continued participation:

Option 1 Continue to attend regularly scheduled study visits at the site until the study ends

Option 2 Conduct all remaining study visits over the phone

Option 3 Discontinue participation in remaining study activities but permit collection of vital status and CV outcome events at minimum at the end of the study through the patient or alternative person designated by the patient (e.g., family, spouse, partner, legal representative, or physician) even if only by telephone

Option 4 Discontinue participation in remaining study activities but permit collection of vital status at minimum at the end of the trial through the patient, alternative person designated by the patient, or through review of patient's medical information from alternative sources (e.g., doctor's notes, hospital records, etc.)

Patients will be asked to choose the most rigorous form of follow-up that they are willing to comply with.

Patients who refuse all four of the above are considered to have fully withdrawn informed consent to participate in the study. A patient should be withdrawn from the study and all follow up assessments only if the patient refused all four options and withdraws informed consent, without the need to justify the decision. Where allowed, patients should be followed-up for vital status.

If the patient withdraws informed consent for participation in the study, the study will end for that patient. The patient should stop taking study medication and should be asked to complete the EOT and follow-up procedures as described in the Flow Chart. Completing these procedures is strongly recommended for the patient's safety. ~~A patient could be instructed to stop the study treatment only after discussion between sponsor representative and investigator, if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at study assessments).~~ Patients that withdraw **informed consent** ~~or discontinue from the study after randomization~~ will not be replaced.

If a patient is lost, every effort should be made by the Investigator and site staff to contact and locate the patient before the patient is declared lost to follow-up. Investigators and site staff should use every possible allowable means to locate patients

who have missed visits. The sponsor might involve third party vendor in compliance with local legislation.

3.3.4.2 Discontinuation of the trial by the sponsor

BI reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1) Failure to meet expected enrolment goals overall or at a particular trial site,
2) Emergence of any efficacy/safety information that could significantly affect continuation of the trial
3) Violation of good clinical practice (GCP), the clinical trial protocol (CTP), or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The study medication will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator product(s)

The characteristics of the test products are below.

Substance:	Linagliptin ~~(BI linagliptin)~~
Pharmaceutical form:	**film-coated** tablet
Source:	Boehringer Ingelheim ~~Pharma GmbH & Co. KG~~
Unit Strength:	5 mg
Route of administration:	p.o., once daily

Substance:	Placebo matching linagliptin 5 mg
Pharmaceutical form:	**film-coated** tablet
Source:	Boehringer Ingelheim ~~Pharma GmbH & Co. KG~~
Unit Strength:	-
Route of administration:	p.o., once daily

4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into the randomized treatment period, treatment assignment will be by means of a third-party phone/web-based randomization on visit 2.

Patient assignment to the treatment groups will be determined by a computer generated random sequence using IRT. Details are described in the manual for IRT procedures, which is available in the ISF. Details of the process of treatment allocation can be found in Section 7.5.

The assigned medication number(s) will be entered in the electronic case record form (eCRF), and the corresponding medication kit(s) should be given to the patient.

4.1.3 Selection of doses in the trial

The dose of 5 mg linagliptin was selected based on the results from previous dose finding studies and represents the approved dose for linagliptin.

4.1.4 Drug assignment and administration of doses for each patient

Patients will continue with their standard background antidiabetic therapy throughout the entire study with an unchanged dose unless medical emergencies or other plausible reasons (e.g. renal impairment, lactacidosis, heart failure, dose intolerance, hypoglycaemia or hyperglycaemia) necessitates changes (at the discretion of the investigator). In case of contrast exposure for investigation of coronary artery pathology or other vessel assessment, metformin is allowed to be temporally held according to regional/local guidelines.

Therefore, during the treatment phase it is investigator judgement to change the background medication dose, as the background medication of the trial is standard of care treatment with hypoglycaemic targets as defined by guidelines. Medication for optimising glycaemic control could also be initiated provided protocol criteria are met (see section 4.2.1).

Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin may be considered.

Medication will be dispensed in a double-blind-manner as either 5 mg linagliptin or matching placebo. IRT will allocate medication kit numbers at all study visits from visit 2 till study end. At visit 2 patients will receive one treatment box sufficient for 12 weeks treatment (plus one week reserve). As of visit 3 (till study end) patients will receive two medication boxes sufficient for 24 weeks treatment (plus two weeks reserve). The protocol allows a time window of +/- 7 days for visit 3 and +/- 14 days for all scheduled visits in the treatment period after visit 3. To ensure sufficient medication, visits after visit 3 should be scheduled within 182 days and visit 3 should take place no later than 91 days after visit 2.

The patients will be instructed to bring their home blood glucose monitoring (HBGM) devices to each visit for measurement of fasted glucose.

Administration of the study medication is once daily. Patients should be instructed to take their trial medication with water. To ensure a dose interval of about 24 hours, the medication should be taken at the same time every day. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken. Study medication can be taken with or without food.

In some situations, it might be necessary to interrupt study medication temporarily. Patients are encouraged to re-start study treatment after an interruption if appropriate in the opinion of the investigator and if not contraindicated.

Patients should be instructed to be fasted and not to take their trial medication in the morning of visit days as they will be dosed whilst in the clinic. Patients who fail to do so should have the visit rescheduled as soon as possible, reminding the patient about the expectations at the study visit. Background and/or optimizing hypoglycaemic control medication will be taken as prescribed including visit days.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in analyzing or with an interest in this double blind study will remain blinded with regard to the randomized treatment assignments until after database lock.

The randomization code will be kept secret by Clinical Trial Support up to database lock. Refer to Section 4.1.5.2 for rules of breaking the code for an individual or for all patients in

emergency situations.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorized Pharmacovigilance representatives and not be shared further.

For Japan only: in this blinded trial, an emergency code break will be available to the Investigator via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate CRF page. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

The DMC will have access to unblinded data, refer to Section 3.1 and Section 7.3.4.

4.1.5.2 Procedures for emergency unblinding

In the event of a medical emergency that requires identification of an individual patient's treatment, investigators will be able to access this information via IRT. The monitor or the onsite monitor/CRA should be contacted immediately (preferably before unblinding takes place) and the reason for unblinding the patient's treatment should be documented in the medical records. The patient could continue with study medication after unblinding.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. All study medication will be contained in medication boxes identified with the trial number and medication number. Each medication box will contain sufficient BI linagliptin tablets or matching placebo tablets for 12 weeks treatment (plus one week reserve).

Trial drug will be supplied on a per visit basis. Supply will be managed by IRT.

Examples of the labels will be available in the ISF.

4.1.7 Storage conditions

The study medication must be kept in its original packaging under the recommended storage conditions indicated on the label. ~~All trial medication should be stored according to the storage conditions as specified on the label and in the original package.~~ Patients should be

instructed not to remove the trial medication from the blisters until immediately prior to the time of intake to protect tablets from humidity and light. Patients will be reminded to keep the study drug out of the sight and reach of children.

A temperature log must be maintained at sites. If storage conditions are found to be outside the specific range, the monitor or designee, IRT and the BI clinical trial supply unit (CTSU) must be contacted immediately in order to clarify whether the trial medication can still be used.

4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor.

The investigator, pharmacist and/or investigational drug storage manager will receive the investigational drugs when all country specific required approvals are in place and all required country specific essential documents are in house e.g.:

- approval of the study protocol by the independent review board (IRB) / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor representative and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol,
- if applicable: availability of the proof of a medical licence for the principal investigator,
- For USA: availability of Form 1572.

The investigator, pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator, pharmacist and/or investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP, plus kits assigned by IRT and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor, the investigator, pharmacist and/or investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

The following text is only applicable for Japan:

The investigator / pharmacist / investigational drug storage manager will receive the

investigational drugs delivered by the sponsor representative after IRB / ethics committee approval of the study and completion of a clinical trial contract between the sponsor representative and the Head of Trial Centre.

The investigator / pharmacist / investigational drug storage manager should return the unused and collected investigational drugs (including the empty boxes) to the sponsor after unblinding the trial.

In case investigational drugs are returned before unblinding of the trial, the investigator / pharmacist / investigational drug storage manager should seal the opened box (excluding empty boxes) for the patient, and before returning the unused and collected investigational drugs (including the empty boxes) to the sponsor. When returning the investigational drugs, the investigator / pharmacist / investigational drug storage manager should exercise utmost caution to assure that the sponsor representative and other relevant trial staff members remain blinded to the patient's name on the package (box or label) of the investigational drugs.
Upon completion of the trial, the investigator / pharmacist / investigational storage manager submits to the sponsor representative a copy of the investigational drug dispensing and return log. When submitting the copy, the investigator / pharmacist / investigational drug storage manager should exercise caution to assure that the sponsor representative and other relevant trial staff members remain blind to the patient's name.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Glycaemic control, emergency procedures, and additional treatment(s)

The use of medication for optimization of glycaemic control as standard of care will be permitted in this trial. This medication can include all types of approved antidiabetic medication except for DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors. The dose of glycaemic optimization medication will be according to local labelling at the investigator's discretion and in accordance with local/international guidelines.

The use of medication for optimizing glycaemic control in case of hyperglycaemia is advised when during the treatment period:

- the patient has a glucose level >180 mg/dl (>10.0 mmol/L) after an overnight fast;
- the patient has an HbA_{1c} > 7.5% (58 mmol/mol).

The above results for FPG should be confirmed, meaning that there is a minimum of two measurements on two different days.

The use of medication optimizing glycaemic control has to be taken in accordance with the prescribing information and will be recorded in the eCRF. Patients who have to be treated with other medication than specified in the protocol should discontinue study treatment, but will remain in the trial.

Any additional treatment, that does not qualify as a medication optimizing glycaemic control, and is considered necessary for the patient's welfare may be given at the discretion of the investigator. Exceptions to this are the restrictions described in Section 4.2.2.

Handling of hypoglycaemic episodes can be done according to the guidelines and standard of care used by the treating physicians. These episodes need to be documented on the appropriate pages of the eCRF.

All concomitant (additional) medications and other therapies will be recorded on the appropriate pages of the eCRF.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The use of other ~~DDP~~ **DPP**4 inhibitors and/or injectable GLP-1 receptor agonists and/or SGLT-2 inhibitors (next to background therapy and any additional anti-diabetic therapy) will be prohibited during the course of the study.

If any restricted treatments or any other concomitant drugs interfering with the study medication are given during the conduct of the trial, the study medication can be discontinued temporarily, or if needed permanently.

4.3 TREATMENT COMPLIANCE

Patients will be asked to bring all trial medication (boxes, including blisters with or without any remaining tablets) with them to each trial visit. The tablets will be counted by the investigator or his/her designate and compliance will be calculated. The compliance check will be based on the number of ~~capsules~~ **tablets** missing (i.e. actually taken) in relation to the number of ~~capsules~~ **tablets** that should have been taken.

Compliance should be between 80% and 120%. Compliance should be emphasised with a goal of at least 80% compliance rate. However, randomized patients will not be discontinued for lack of compliance without prior discussion with the monitor or designee.

Patients who are not compliant with their medication should again be carefully interviewed and again re-informed about the purpose and the conduct of the trial.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoint(s) of efficacy

The primary endpoint in this trial is time to the first occurrence of any of the following **by** adjudicat**ion**~~ed~~ **confirmed** components of the primary composite endpoint (4 **3**-point MACE): CV death ~~(including fatal stroke, fatal MI and sudden death),~~ non-fatal MI ~~(excluding silent MI)~~ **or** non-fatal stroke ~~and hospitalisation for unstable angina pectoris~~.

The key secondary endpoint~~s are~~ **is** time to the first occurrence of **any of the following by adjudication confirmed components:**

- ~~CV death (including fatal stroke, fatal MI and sudden death), non-fatal MI (excluding silent MI), non-fatal stroke (3-point MACE)~~
- Composite renal endpoint (renal death, sustained ESRD, sustained decrease of ~~50~~ **40**% or more in eGFR)

~~At the final analysis the~~ **The** primary endpoint (4 **3**-point MACE) will be tested for non-inferiority. Thereafter**, if non-inferiority has been demonstrated,** the 4 **3**-point MACE and the combined composite renal endpoint will be tested separately ~~(= in parallel)~~ for superiority. ~~In case the 4-point MACE and/or composite renal endpoint is significantly superior, the 3-point MACE will then be tested for superiority.~~

Even after occurrence of a non-fatal endpoint, the patient should be followed-up until the end of the study in order to document other endpoints/variables.

*** Silent MI is an investigator reported endpoint, and is a trigger term for central adjudication for cardiovascular events. Any investigator reported silent MI that is adjudicated and confirmed as being an MI by the CEC will be counted as MI.**

Albuminuria progression is defined according to change from normoalbuminuria to either microalbuminuria (UACR > 30 mg/g and ≤ 300 mg/g) or clinical proteinuria (UACR > 300 mg/g) or from microalbuminuria (UACR > 30 mg/g and ≤ 300 mg/g) to clinical proteinuria (UACR > 300 mg/g).

5.1.2 Assessment of efficacy

HbA_{1c}:
Blood samples for the determination of HbA_{1c} will be taken according to the Flow Chart. The blood sample can be taken at any time during the visit. The samples will be analysed at a central laboratory or its affiliates having a National Glycohemoglobin Standardization Program (NGSP) Level I certificate. Further details about sample handling, shipment, and assay procedures can be found in the ISF (Lab manual).

FPG:
Blood samples for the determination of FPG will be taken according to the Flow Chart after an overnight fast (at least 10 hours no food and only water). At all respective visits, the samples should be taken before breakfast and before trial drug administration. The samples will be measured with the HBGM device.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Incidence and intensity of adverse events, physical examination, vital signs, ECG and change from baseline in laboratory parameters will be assessed.

5.2.1.1 Reporting waiver for cardiovascular-outcome events

In accordance with ICH-guideline E2A and in order to maintain the integrity of this study, CV outcome events that occur after randomization and represent an SAE are exempted from expedited reporting to health authorities. The medication code will not be broken for the purpose of expedited reporting to regulatory authorities.

CV outcome events are defined as the following components of the primary, **key** secondary and other CV endpoints:

- CV death
- non fatal MI
- silent MI
- non fatal stroke (ischemic/hemorrhagic/etiology unknown)
- hospitalisation for unstable angina pectoris
- hospitalisation ~~due to congestive~~ **for** heart failure ~~(CHF)~~
- transient ischemic attack (TIA)
- coronary revascularisation procedures (PCI and CABG)
- peripheral revascularization procedures

For definitions of the CV outcome events see Appendix 10.2.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment. **An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.**

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE that results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs

patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement that may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

For Japan: An AE which possibly leads to disability will be reported as an SAE. Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms. *For Japan: The reason for the decision on causal relationship needs to be provided in the CRF*.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

If an SAE is reported from a still blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. any active comparator or placebo according to the trial design).

Worsening of underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG*, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF, if they are judged clinically relevant by the investigator.

*Changes in the ECG indicating (silent) MI should be reported as a cardiovascular outcome event.

Hypoglycaemic events

Hypoglycaemic events should be documented according to the following criteria:

- Asymptomatic hypoglycaemia: Event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≥54 mg/dl and ≤70 mg/dl (≥3.0 mmol/l and ≤3.9 mmol/l):
- Asymptomatic hypoglycaemia: Event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration < 54 mg/dl (<3.0 mmol/l)
- Documented symptomatic hypoglycaemia with glucose concentration ≥54 mg/dl and ≤70 mg/dl (≥3.0 mmol/l and ≤3.9 mmol/l): Event accompanied by typical symptoms of hypoglycaemia
- Documented symptomatic hypoglycaemia with glucose concentration < 54 mg/dl (<3.0 mmol/l): Event accompanied by typical symptoms of hypoglycaemia but no need for external assistance
- Severe hypoglycaemic episode: Event with any degree of documented hypoglycemia, requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

All symptomatic hypoglycaemic events, all asymptomatic events with glucose levels less than 3.0 mmol/l and all asymptomatic hypoglycaemic events that are considered as adverse event by the investigator have to be recorded as an adverse event**.**

Adverse Events of Special Interest

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI's need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE.

The following events are considered as adverse events of special interest (AESI):

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis
- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis
- Hepatic events such as ≥ 3 fold ULN of AST and/or ALT in combination with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample, hepatitis, hepatic injury, jaundice and potential Hy's Law cases.

- Renal adverse events such as acute renal failure
- Pancreatitis **(refer to the ISF)**
- Thyroid neoplasm (benign)
- Thyroid cancer
- Pancreatic cancer

~~A list of terms that must be documented as AESI for each topic is provided in the ISF. The renal events and pancreatic events will be adjudicated by independent adjudication committees.~~
~~AESI's, even though they might be non-serious are to be documented in the eCRF within 24 hours of receipt and must be reported to the sponsor/CRO in an expedited manner similar to Serious Adverse Events. For details please see Section 5.2.2.2.~~

Protocol-specified AESIs (as identified by the investigator based on the above definitions for adverse events of special interest) can be classified as serious or non-serious but all these AESIs once identified by the investigator must be reported on an SAE form in an expedited manner similar to SAEs, even if they do not meet any of the SAE seriousness criteria.

Beyond of this, and for the purposes of ongoing pharmacovigilance activities by the sponsor, adverse events based on additional searches for coded preferred terms of adverse events captured in the trial database (such as Special MedDRA Queries (SMQs), and user defined searches (BicMQs)) will be queried to verify with the investigator if the adverse event reported represent a suspected or diagnosed protocol specified AESI. AESIs once identified by the investigator must be reported on an SAE form in an expedited manner similar to SAEs, even if they do not meet any of the SAE seriousness criteria.

These additional searches (summarized under the so called 'overview of protocol defined AESIs and safety topics of interest ') may change according to active pharmacovigilance of linagliptin. The most up to date list of these searches will be included in the ISF and changes will be communicated to all investigators.

Hepatic events:

Patients showing an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample need to be followed up locally according to the "DILI checklist" provided in ISF.

Renal events:

~~Estimated creatinine clearance~~ **eGFR** will be calculated using the MDRD formula. This formula considers the race as an adjustment factor, therefore, the race must be known (and will be collected) for accurate estimation.

In case of an eGFR decrease of ≥ 40% since baseline (visit 2) and again in case of an eGFR decrease of ≥ 50% since baseline (visit 2) an additional visit 4**-8** weeks after detection should

be scheduled (unless detected at the EOT visit at study end) to collect a blood sample for repeat analysis of creatinine for calculation of the eGFR. An additional sample of creatinine should also be taken between the visits interval if a signal of increasing creatinine is reported to the study site by others (e.g., treating physicians from local labs).

Skin lesions:

If skin lesions occur (such as exfoliative rash, skin necrosis, or bullous dermatitis): further follow-up investigations should be done according to medical judgement depending on the clinical course until the patient is recovered and/or a diagnosis is made.

5.2.2.2 Adverse event and serious adverse event reporting

The Investigator shall maintain and keep detailed records of all AEs in their patient files.

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the last per protocol visit) will be collected, documented and reported to the sponsor/CRO by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the last per protocol visit, it should be reported by the investigator to the sponsor if considered relevant by the investigator. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

The investigator must report the following events, immediately (within 24 hours of awareness) to the sponsor/CRO: SAEs, AESI and non-serious AEs relevant for the reported SAE or AESI.

The investigator must document immediately (within 24 hours of awareness) CV outcome events if they occur after randomization on the appropriate eCRF page. CV outcome events which occur prior randomization have to be reported as an (S)AE.

Clinically relevant abnormalities found at physical examination, vital signs or ECG that are not pre-existing prior to signing of informed consent (study inclusion) should be reported as adverse events. If such abnormalities already pre-exist prior to signed informed consent they should be considered as baseline conditions.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer. In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.
The latest list of "Always Serious AEs" can be found in the ISF. A copy of the latest list of "Always Serious AEs" will be provided to you upon request. These events should always be reported as SAEs as described above.

~~BI has set up a list of AEs which are defined to be always serious.~~ In order to support the investigator with the identification of these "always serious adverse events", if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

~~The list of these adverse events can be found in the ISF.~~

For Japan: This information must be also reported immediately to the head of the trial site.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs, **AESIs** and non-serious AEs must include a causal relationship assessment made by the investigator. The SAE form is to be forwarded to the defined unique entry point (contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or Adverse Events of Special Interest becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor/CRO. Drug exposure during pregnancy has to be reported immediately (within 24 hours of awareness) to the defined unique entry point for SAE forms (contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.2.3 Oncological adverse events

Epidemiological evidence suggests that people with diabetes are at a significantly higher risk of several forms of cancer compared with subjects without diabetes [R10-6495]. Currently, it is unclear whether the association between cancer and diabetes is indirect and largely due to shared risk factors (such as the modifiable risk factors: e.g. obesity, diet, physical activity, tobacco smoking, alcohol, or non-modifiable risk factors: e.g. age, gender, race, and

ethnicity), whether it is direct influence (e.g. due to hyperglycaemia), whether it is related to medical therapies used in the treatment of T2DM, or whether T2DM represents a condition with underlying biologic factors that alter cancer risk (e.g. insulin resistance and hyperinsulinemia) [R10-6496, R10-6498, R10-6536, R10-6497, R10-6494].
In order to assess patients with oncological adverse events (benign and malignant) in detail, and in addition to the AESIs thyroid neoplasm (benign), thyroid cancer, and pancreatitic cancer, detailed information will be requested and should be provided by the site. The main focus on oncological adverse events is on the following organ systems, based on [R10-6638] where an increased risk for cancer in the population of patients with T2DM was described:

- Liver
- Endometrium
- Colon and rectum
- Breast
- Bladder
- Prostate

Request for detailed information (e.g. medical history, diagnostic result, laboratory results staging), will be mainly focused on the above listed organ systems, however is not restricted to them. **For details refer to the oncology committee assessment charter.**

5.2.3 Assessment of safety laboratory parameters

The parameters that will be determined are listed below. Analysis will be performed by a central laboratory:

Visit 1 (screening):

- Clinical chemistry: ALT, AST, AP, lipase and creatinine
- Urine analysis: albumin and creatinine

Visit 2 (baseline):

- Haematology: haematocrit, haemoglobin, erythrocyte count, platelet count and total and automates differential leukocyte counts (in absolute counts).
- Clinical chemistry: ALT, AST, γ-GT, AP, lipase, lactate dehydrogenase (LDH), total bilirubin, albumin, potassium, Sodium, creatinine, urea, calcium, inorganic phosphorous, urid acid, cholesterol (total), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides.
- Urine analysis: albumin, creatinine, protein, ketone and leucocytes.

Visit 3 – EOT - FU

- Clinical chemistry: creatinine and lipase
- Urine analysis: albumin and creatinine (visit 4, visit 6 and thereafter yearly).
- Clinical chemistry: cholesterol (total), HDL cholesterol, LDL cholesterol and triglycerides (visit 4, visit 6 and thereafter yearly)

HbA_{1c} will be determined at all scheduled visits, with exception of the FU visit.

Exact date and time of blood and urine sampling should be recorded in the central laboratory requisition form.

UACR will be calculated at the central lab, and should be measured on a first morning void specimen wherever possible. UACR will be performed according to the Flow Chart.

Pregnancy testing (beta Human Chorionic Gonadotropin [βHCG method]) will be performed in female patients of child-bearing potential according to the Flow Chart.

A negative pregnancy test result is required at visit 2 for all female patients of childbearing potential to remain eligible for entry into the treatment phase of the trial and reconfirmed at future visits.

5.2.3.1 Renal function

Renal function will be assessed by the central lab based on the plasma creatinine value measured according to the Flow Chart. The eGFR will be calculated from serum creatinine using the following MDRD formula:

$eGFR = 175 \times (\text{creatinine } (\mu mol/L)/88.4)^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$

Renal impairment will be classified in the following way:

No renal impairment: eGFR ≥ 90 mL/min/1.73m^2;
No renal impairment with evidence of kidney damage (**eGFR ≥ 90 mL/min/1.73m^2 and** UACR ≥30mg/ g creatinine);
Mild renal impairment: eGFR 60-89 mL/min/1.73m^2;
Moderate renal impairment: eGFR 30-59 mL/min/1.73m^2;
Severe renal impairment: eGFR 15-29 mL/min/1.73m^2;
ESRD: eGFR < 15 mL/min/1.73m^2.

Prevalent kidney disease will be defined in the following way:

- **eGFR <60mL/min/1.73m2 and/or UACR >300mg/ g creatinine**

5.2.4 Electrocardiogram

12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded according to the Flow Chart.

The ECGs will be centrally analysed. Additional ECGs may be collected by the investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs, if they are newly discovered after inclusion in the trial.

The recordings will be checked for pathological results by the investigator. Any ECG abnormalities will be carefully monitored and medically treated.

5.2.5 Assessment of other safety parameters

Vital signs and height

Systolic and diastolic blood pressure (DBP) as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position according to the Flow Chart. All recordings should be made using a similar type of and validated certified blood pressure recording instrument on the same arm. See for further details Section 10.3. Height (metres, m) will be measured according to the Flow Chart. Body mass index, BMI (kg/m^2) will be calculated for determination of eligibility at Visit 1.

Weight and Waist circumference

Weight measurements should always be done on a similar approved type of scale for one patient. In order to get comparable body weight values, it should be performed in the following way:

- fasting (except for the screening visit),
- after the urine sampling (weight after bladder voiding),
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc).

Waist circumference measurements should be made around a patient's bare midriff, 1 cm above the iliac crests, after the patient exhales while standing without shoes and with both feet touching and arms hanging freely. The measuring tape should be made of a material that is not easily stretched, such as fibreglass. The tape should be placed perpendicular to the long axis of the body and parallel with the floor and with sufficient tension to conform to the measurement surface [R07-4080].

Physical examination

A head-to toe physical examination (e.g. evaluation of the body and its functions using inspection, palpation, percussion, and auscultation) will be performed by the investigator according to Flow Chart. Documentation of, and findings from the physical examination, must be part of the source documents available at the site.

Home Blood Glucose Monitoring

All patients will be provided with HBGM equipment and supplies for use at home at the randomization visit. Weekly finger stick glucose measurements are recommended. During the whole trial participation, additional measurements should be done if necessary and in case of hypo- or hyperglycaemia related symptoms. Patients will be instructed to bring their HBGM device to visits for an additional measurement of fasted glucose.

More frequent testing can be done if deemed necessary by the investigator or required by local authorities. The respective procedure for illiterate patients (if included) is described in the Appendix 10.1.1.

Instruction on the proper use of the HBGM will be provided by the study staff. The patient will be asked to record the results of the HBGM test on a HBGM diary that will be included in the patient's source document file. Only in the case of linked adverse events or of asymptomatic hypoglycaemia with a measured plasma glucose concentration ≥ 3.0 and ≤ 3.9 mmol/l (≥ 54 and ≤ 70 mg/dL), the single HBGM values will be recorded in the eCRF.

If the results of a HBGM test reveal blood plasma glucose value of > 180 mg/dl (>10.0 mmol/L) after an overnight fast or > 400 mg/dl (22.2 mmol/L) randomly determined and confirmed by a second HBGM (not on the same day) the patient should contact the site for further advice.

During the trial, the patient should also contact the site for advice if the results of a HBGM test reveal blood plasma glucose value of < 70 mg/dL (3.9 mmol/L) after an overnight fast. If the blood glucose level is <54 mg/dL (3.0 mmol/L), the patient should be instructed to eat/drink some carbohydrate.

The HBGM diary should be brought to each visit for review by investigator/trial staff. The HBGM diary should be collected at the visit (if completed) and a new HBGM diary should be given to the patient.

5.3 OTHER

5.3.2 Post stroke functional assessment

To assess clinical disability after stroke the reported value from the modified Rankin Scale, an ordinary scale that is being widely used in clinical practice to rank disability will be collected. It is reported as a single digit from 0-6 (covering the spectrum “no symptoms” to “dead”) approximately one week after stroke onset and 3 months after stroke onset. This might require an additional contact.

5.3.3 Pharmacogenomic evaluation

For DNA Banking an additional blood sample will be requested. The DNA sample derived from the original blood sample will be stored by Boehringer Ingelheim for up to 15 years after the end of the clinical trial. The stored DNA may be analysed at a later time for pharmacogenomic analyses, e.g. to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

5.3.3.1 Methods and timing of Pharmacogenetics sample collection

One (1) blood sample for DNA banking will be taken at visit 2 or later. A maximum of 8.5 mL blood will be collected per PAXgene Blood DNA sampling tube for those patients who signed a separate informed consent concerning the sample banking part. The PAXgene Blood DNA tubes can be stored and shipped at room temperature within 14 days. If a longer storage and shipment period for PAXgene Blood DNA tubes is necessary, the blood samples should be stored at a temperature of -20 degrees Celsius or below. Once frozen, thawing of the samples should be avoided. Detailed instructions for pharmacogenomic sampling, handling and shipment of samples are provided in the ISF/Lab Manual.

Participation in the pharmacogenetic sampling is voluntary and not a prerequisite for participation in the study.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor efficacy and safety aspects in an appropriate way.

The scheduled measurements are appropriate to see drug induced changes in vital signs, laboratory values, and ECG. The endpoints are standard and accepted for evaluation of efficacy and safety of an oral antidiabetic drug, and they are widely used in this kind of study.

Therefore, the appropriateness of all measurements applied in this trial is given.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

The plasma concentration of linagliptin will not be determined.

5.6 BIOMARKER(S)

No additional biomarkers will be determined in this study.

5.7 PHARMACODYNAMICS

No additional pharmacodynamic parameters will be determined in this study.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

The relationship between linagliptin trough plasma concentrations and biomarkers will not be investigated.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits should take place preferably between 7:00 AM and 11:00 AM. If a patient mistakenly takes trial medication in the morning of a visit before attending the clinic or comes in non-fasted where a fasting condition is required (all visits except visit 1), the visit should be rescheduled for another day as soon as possible reminding the patient about the expected conditions. The rescheduled visit must take place in a short enough time-frame so that the patient has sufficient trial medication available.

All patients are to adhere to the visit schedule as specified in the Flow Chart. Some flexibility is allowed in scheduling the visits according to visit time windows as specified in the Flow Chart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule (calculated from randomization visit 2).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The Flow Chart summarizes the investigational procedures to be done at each visit. The procedures are further described below.

6.2.1 Screening period

After the informed consent process is complete and written informed consent is obtained, the patients will be assessed for study eligibility (visit 1) including central laboratory assessments as specified in Section 5.2.3.

Screening will occur at visit 1 and will be registered in IRT.

Those patients who qualify at screening (as determined at visit 1) and meet all inclusion and exclusion criteria prior to randomization (see Sections 3.3.2.and 3.3.3.), will be randomized at visit 2. Randomization may be done as soon as the visit 1 (safety) laboratory results and eGFR are known and all other eligibility criteria are met. No additional medication for optimization of glycaemic control may be initiated during the screening phase.

6.2.2 Treatment period

Randomization will occur at visit 2 using IRT.

Patients will return to the clinic for regularly scheduled study visits after randomization as specified in the Flow Chart. These visits will assess the occurrence of safety and efficacy endpoints, study medication compliance and accountability, concomitant therapy or intervention.

Patient visits should be routinely scheduled in the morning, at approximately the same time at each visit. The actual date/time of trial drug administration at the study visit will be recorded in the eCRF.

At each visit all trial medication will be returned, compliance will be calculated and new trial medication kit(s) will be assigned via IRT and will be dispensed.

This is a **long-term safety** outcome study **and every effort should be made by the site staff to encourage patients to remain in the study and on study drug if medically safe**. All patients, including those who discontinue treatment must be followed up until the end of the study. Patients who prematurely discontinue treatment will continue to be contacted by the investigator at regular intervals (according to the original visit schedule or an alternative reduced schedule negotiated with the patient) either by clinic visits or by phone (refer to section 6.2.3).

Patients who prematurely discontinued study medication during the treatment phase are allowed to restart the study medication at any time if appropriate in the opinion of the investigator and if not contraindicated. **Investigators should routinely consider re-starting study drug at every visit following study drug discontinuation.**

Early discontinuation of study medication is not a criterion for withdrawal of consent for participating in the study.

6.2.3 End of treatment and follow-up period

Patients who discontinue study drug should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception , collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.

If a patient who discontinued study drug is not willing to return to the pre-defined study visits, at minimum a yearly telephone call (preferably every 6 months) and a telephone call at study end will be required, to document the occurrence of outcome events and vital status. If possible, other AE's and concomitant therapy changes since last visit should be recorded. Every attempt will be made by the investigator to ensure patients continue participating in the study during study drug interruptions and after discontinuation of study drug.

Patients that are not actively taking study drug may be less motivated to adhere to the study visit schedule. Investigators and site staff should work to detect early signs of losing interest and readily present such patients (not actively taking study drug) with options to encourage continued participation. Refer to section 3.3.4.1 for options to encourage continued participation and for details regarding patients who are lost-to-follow-up or who have withdrawn informed consent.

~~If the patient withdraws informed consent for study participation, the study participation of the patient will end. The patient should stop taking study medication and should be asked to complete the EOT and follow-up visit activities as described in the Flow Chart. Completing these procedures is strongly recommended for the patient's safety.~~

~~Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of , collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.~~

~~If a patient who prematurely discontinued study drug is not willing to return to the pre-defined study visits, at minimum a yearly telephone call (preferably every 6 months) and a telephone call at study end will be required, to document the occurrence of outcome events and vital status. If possible, other AE's and concomitant therapy changes since last visit might be recorded. Every attempt will be made by the investigator to ensure patients continue participating in the study during study drug interruptions and after discontinuation of study drug.~~

All patients will have a follow up visit ~~one week~~ **30 days** following regular or premature completion of the treatment period. The follow-up visit may be performed as a phone visit for patients who did not prematurely discontinue study medication and who do not have abnormalities at the EOT visit (only adverse events/outcome events and changes in concomitant therapy to be obtained).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Design

This is a multicentre, multinational, randomized, double blind, parallel group, placebo-controlled safety study of linagliptin versus placebo. The trial is event driven and will run with an estimated number of ~~8300~~ **7000** randomized patients for an estimated period of ~~48~~ **54** months beginning with the randomization of the first patient. In case the number of events is not or may not be reached within this period the trial duration and/or the number of patients will be prolonged or increased respectively, to ensure that the required number of ~~625~~ **611** patients with adjudicated primary endpoint events is reached.

Objectives

The study objectives are described in Section 2.2.

For the primary objective the upper bound of the two-sided (1-2*alpha) confidence interval which equals the upper bound of the one-sided (1-alpha) confidence interval will be used to investigate non-inferiority (NI) of linagliptin versus placebo regarding the hazard ratio of the primary endpoint. The non-inferiority margin is chosen as 1.3 (FDA Guidance for Industry - Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, (R09-2151). The overall one-sided significance level is 2.5%.

Primary endpoint

The primary endpoint is time to the first occurrence of any of the following adjudicated components of the composite endpoint (4**3**-point MACE): CV death ~~(including fatal stroke, fatal MI, and sudden death)~~, non-fatal MI ~~(excluding silent MI),~~ **or** non-fatal stroke~~, hospitalisation for unstable angina pectoris~~.

Patients without occurrence of a specific endpoint (composite endpoint or individual components) will be considered censored at their last documented study visit. If any measurement of laboratory data or ECG is available after the last visit of a patient, the date of the respective measurement will be used for censoring of the CV endpoint. If any measurement of eGFR is available after the last visit of a patient, the date of the respective measurement will be used for censoring of the renal endpoint. For all endpoints including the component CV (renal) death, adjudicated CV (renal) death will be counted even if occurred thereafter.

7.2 NULL AND ALTERNATIVE HYPOTHESES

~~An interim analysis will be performed at the one-sided alpha-level of 1.0%, the final analysis at the one-sided alpha-level of 2.12%. At the interim analysis MACE endpoints will be tested~~

~~in a pre-specified order, at the final analysis also the composite renal endpoint will be tested for superiority. The experimentwise (multiple) level alpha is controlled with the following three step gatekeeping hierarchy within the interim and final analysis, respectively.~~

No confirmatory interim analysis for efficacy endpoints will be performed. For the final analysis, the first hypothesis (non-inferiority of the primary endpoint) will be tested at the one-sided alpha-level of ~~2.12%~~ **2.5%.** In case of significance, the null hypothesis is rejected in a confirmatory sense and the next set of hypotheses (two separate hypothesis tests) will be tested: a) test of the primary endpoint for superiority and b) test of the composite renal endpoint for superiority. To adjust for multiplicity ~~the truncated Hochberg~~ **a sequentially rejective** multiple test procedure will be applied **(R16-4473)** ~~with a selected gamma of 0.5 (R12-4087).~~ Both one-sided hypotheses $H_{0(Sup1)}$ and $H_{0(Sup2)}$ will be tested separately**, at the initial alpha-levels of 0.2*alpha for 3-point MACE and 0.8*alpha for the composite renal endpoint, respectively. If both null hypotheses cannot be rejected at these initial alpha-levels, the procedure stops and for none of these endpoints superiority can be declared. After having shown superiority for one of these endpoints, the used alpha can be shuffled to the other test: If $H_{0(Sup2)}$ is rejected at the alpha-level of 0.8*alpha, then $H_{0(Sup1)}$ can be tested at the full alpha-level of 2.5% (one-sided). If $H_{0(Sup1)}$ is rejected at the alpha-level of 0.2*alpha, then $H_{0(Sup2)}$ can be tested at the full alpha-level of 2.5% (one-sided)**. ~~If both tests are significant at the one-sided alpha-level of 1.59% each, superiority of both endpoints (4-point MACE and composite renal endpoint) has been demonstrated. If not, superiority can only be claimed for the endpoint significant at the alpha-level of 1.06%. If superiority of both, the 4-point MACE and the composite renal endpoint has been demonstrated at the one-sided alpha-level of 1.59% each, then superiority of the 3-point MACE can be tested at the alpha-level of 2.12%. If superiority of only one of these endpoints (4-point MACE or composite renal endpoint) has been demonstrated at the one-sided alpha-level of 1.06%, then superiority of the 3-point MACE can be tested at the alpha-level of 0.53%.~~

~~At the interim analysis superiority of the composite renal endpoint will not be tested and therefore all tests on MACE can be performed in the pre-specified order at the alpha-level of 1.0%.~~

If a step is not significant, all subsequent steps may not be interpreted in a confirmatory sense.The sequence of tests is as follows:

1st step:

The primary endpoint (~~4~~ **3**-point MACE) is time to the first occurrence of any of the following adjudicated components of the composite endpoint: CV death ~~(including fatal stroke, fatal MI, and sudden death)~~, non-fatal MI~~,~~ **or** non-fatal stroke~~, hospitalisation for unstable angina pectoris~~.

$H_{0(NI)}$: $HR_{linagliptin\ vs.\ placebo} \geq 1.3$

(Interpretation of $H_{0(NI)}$: Regarding the time to first occurrence of the primary endpoint, the risk (expressed as hazard ratio (HR)) for linagliptin relative to placebo is at least 30% higher.)

vs.

$H_{1(NI)}$: $HR_{linagliptin\ vs.\ placebo} < 1.3$

($H_{1(NI)}$: Regarding the time to first occurrence of the primary endpoint, the risk for linagliptin relative to placebo is less than 30% higher, i.e. linagliptin can be regarded as non-inferior.)

2nd step:

If the null hypothesis of non-inferiority (1st step) can be rejected, then in a second step two confirmatory tests on superiority will be performed ~~at the final analysis~~:

- time to first occurrence of the primary endpoint (4 **3**-point MACE)
- time to first occurrence of the composite renal endpoint

~~At the interim analysis superiority of the composite renal endpoint (i.e. $H_{0(Sup2)}$) will not be tested.~~

$H_{0(Sup1)}$: $HR_{linagliptin\ vs.\ placebo} \geq 1$

($H_{0(Sup1)}$: Regarding the time to first occurrence of the primary endpoint, the risk for linagliptin relative to placebo is higher.)

vs.

$H_{1(Sup1)}$: $HR_{linagliptin\ vs.\ placebo} < 1$

($H_{1(Sup1)}$: Regarding the time to first occurrence of the primary endpoint, the risk for linagliptin relative to placebo is lower.)

$H_{0(Sup2)}$: $HR_{linagliptin\ vs.\ placebo} \geq 1$

($H_{0(Sup2)}$: Regarding the time to first occurrence of the composite renal endpoint, the risk for linagliptin relative to placebo is higher.)

vs.

$H_{1(Sup2)}$: $HR_{linagliptin\ vs.\ placebo} < 1$

($H_{1(Sup2)}$: Regarding the time to first occurrence of the composite renal endpoint, the risk for linagliptin relative to placebo is lower.)

To adjust for multiplicity ~~at the final analysis the truncated Hochberg~~ **a sequentially rejective** multiple test procedure will be applied.

~~3rd step:~~

~~If superiority of the primary endpoint (4-point MACE) and/or the composite renal endpoint has been demonstrated, then as a further confirmatory test superiority is tested with respect to time to first occurrence of the 3-point MACE.~~

~~$H_{0(Sup3)}$: $HR_{linagliptin\ vs.\ placebo} \geq 1$~~

~~($H_{0(Sup3)}$: Regarding the time to first occurrence of the 3-point MACE, the risk for linagliptin relative to placebo is higher.)~~

~~vs.~~

~~$H_{1(Sup3)}$: $HR_{linagliptin\ vs.\ placebo} < 1$~~

~~($H_{1(Sup3)}$: Regarding the time to first occurrence of the 3-point MACE, the risk for linagliptin relative to placebo is lower.)~~

7.3 PLANNED ANALYSES

The primary analyses (including all confirmatory tests described in Section 7.2) will be performed on the ~~full analysis set (FAS)~~ **Treated Set (TS)**. The ~~FAS~~ **TS** will consist of all ~~randomized~~ patients who were treated with at least one dose of study drug.

For the primary and key secondary endpoints a 'classical intention to treat (ITT) analysis on the ~~FAS~~ **TS**' will be done. That means that:

- the analysis set consists of the ~~FAS~~ **TS**,
- the allocated study treatment at randomization will be used for the analysis ('as randomized'),
- all events which occur until study end will be taken into account.

A per protocol set (PPS) of patients following the trial protocol in essential criteria will be created for sensitivity analyses. Patients included in the ~~FAS~~ **TS** who have important protocol violations will be excluded from the PPS. A protocol violation (PV) will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint.

Important protocol violations include:

- Randomized study drug: incorrect study drug taken.
- Severe violation of treatment compliance (defined as compliance with study treatment < 80% for more than 50% of the time between randomization and first endpoint (CV death, non-fatal MI, non-fatal stroke~~, hospitalisation for unstable angina pectoris~~).
- Non-adherence to other specifications of the protocol that could bias the primary composite endpoint (e.g. limited life expectancy (< 5 years) at randomization due to various medical conditions)

Additionally a ~~'30-day treatment'~~ **'on-treatment'** set **(OS)** of patients will be created for sensitivity analysis. The ~~'30-day treatment'~~ **OS** set will include all patients with minimum treatment duration of 30-days.

All patients treated with at least one dose of study drug (the Treated Set) will be included in the safety evaluation~~. In case only randomized patients take study drug, this set is identical to the FAS~~; the safety analyses will be displayed 'as randomized'.

Data recorded on entry into the study and at randomization will be summarized and compared using univariate descriptive statistics.

Additional analyses will be explored in ~~specific~~ subgroups, e.g. depending on characteristics at baseline with respect to the primary and key secondary endpoint~~s~~. **Examples of** ~~C~~covariates that will be explored include:

- Region (North America, Europe, Asia etc.)
- Age (<65, ≥ 65 years)
- Systolic and diastolic blood pressure (**<140**~~160~~ and **< 90**~~100~~ mmHg , **≥ 140**~~160~~ or **≥ 90**~~100~~ mmHg)
- Gender (male, female)
- Prior anti-diabetic treatment (~~none, monotherapy, combination therapy~~ **insulin, no insulin**)
- eGFR < 60 mL/min/1.73 m^2 at baseline
- **Prevalent kidney disease defined as eGFR < 60 mL/min/1.73 m^2 at baseline and/or UACR > 300mg/g creatinine at baseline**

Further details will be given in the trial statistical analysis plan (TSAP).

7.3.1 Primary analyses

A classical ITT-approach on the ~~FAS~~ **TS** will be performed as described above. For the primary analysis a Cox proportional hazards regression model of time to the first event with randomized treatment and geographical region as factors will be applied. Kaplan-Meier estimates by treatment group will be displayed. The confirmatory test approach is outlined in Section 7.2.

No centre effect will be included into the Cox models, as the centre size is expected to be small. Furthermore, due to the low event rate there would not be a sufficient number of events per centre for the analysis of a centre effect and a centre by treatment interaction.

For the primary and key secondary endpoint~~s~~, sensitivity analyses will be done on the PPS, for the ~~'30 days treatment' set~~ **OS** and as ~~an 'on-treatment'~~ **a 'TS+30'** analysis as described below. These sensitivity analyses will be performed based on the corresponding patient sets for the time patients are on-treatment + 30 days after permanent treatment discontinuation or end of observation, whichever comes first. The ~~'on-treatment analysis'~~ **'TS+30' analysis** will be performed on the ~~FAS~~ **TS** (consisting of all ~~randomized~~ patients who were treated with at least one dose of study drug) with censoring at the time patients are on treatment + 30 days after permanent treatment discontinuation or end of observation, whichever comes first.

For these sensitivity analyses, the randomized study treatment ('as randomized') will be used for treatment assignment.

To check the proportional hazards assumption, Schoenfeld residuals will be plotted for each covariate versus time; in addition, ln(-ln(S(t))) will be plotted vs. time and checked for

parallelism. As a further assessment the interaction of covariates with time will be investigated. In case the proportionality assumption does not hold, a stratified log-rank test will be performed.

7.3.2 Secondary analyses

In addition to the primary analysis (time to first event), crude rates will be displayed for the primary and key secondary endpoints. The interpretation of crude rates has to take into account that the likelihood to observe an event increases with a longer survival and/or observation period; therefore a difference between the treatment groups with regard to the actual observation period will be explored.

The key secondary endpoints are **is** time to the first occurrence of **any of the following by adjudication confirmed components:**

- CV death (including fatal stroke, fatal MI and sudden death), non-fatal MI (excluding silent MI), non-fatal stroke (3-point MACE)
- Composite renal endpoint (renal death, sustained ESRD, sustained decrease of 50 **40**% or more in eGFR)

After non-inferiority has been established for the primary endpoint (4 **3**-point MACE), the same endpoint and the composite renal endpoint (at the final analysis) will be tested for superiority. In case of significant superiority of the 4-point MACE and/or the composite renal endpoint, the 3-point MACE will then be tested for superiority.

For the primary, and key secondary endpoints and, their individual components, **and** the time-to-event analyses will be based on the randomization date; for the other endpoints **time-to-AE analyses** the date of first study drug intake will be used.

Other endpoints:

The key secondary endpoints and the individual components of the primary and key secondary endpoints will be analysed as time to first occurrence. In addition, crude rates will be displayed. Chi-Square tests will be applied for efficacy data; these tests will be interpreted in an exploratory sense, two-sided p-values without alpha-adjustment will be presented. Wilson confidence intervals will be reported for the proportion of patients with primary and key secondary endpoints; in addition logistic regression models will be applied.

7.3.3 Safety analyses

All safety data will be displayed and analysed (Treated Set, 'as randomized') using descriptive statistical methods. No formal inferential analysis is planned for safety comparisons. AEs will be coded using the medical dictionary for drug regulatory activities (MedDRA) coding dictionary. All events with an onset after the first dose of study medication up to a period of seven days after the last dose of study medication will be assigned to the treatment phase for evaluation; in addition, all AEs after the first dose of study medication will be displayed by randomized treatment group. Laboratory values taken after the first dose of randomized treatment up to a period of seven days after the last intake of treatment will be assigned to the treatment phase for evaluation. Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range. Changes from baseline in blood pressure and pulse rate will be summarised by treatment group. For hypoglycaemic events the incidences and the treatment-time adjusted frequencies will be displayed.

7.3.4 Interim analyses

An independent Data Monitoring Committee (DMC) will review safety and efficacy data and make recommendations whether to continue or terminate the study. As described in Section 3.1.1 the DMC analyses and operations will be formally separated from the sponsor, the investigators and the Steering Committee. The details on its procedures and interactions are provided in a separate DMC Charter.

It is planned that there will be one formal interim analysis for CV efficacy after 70% of the expected primary CV events, i.e. after 437 patients have experienced an adjudicated primary CV endpoint. The interim analysis will be performed at the one-sided alpha-level of 1.0%;

~~according to Haybittle-Peto (East version 5.4), this results in a one-sided alpha of 2.12% for the final analysis. The first test will be on non-inferiority of the primary endpoint, in case of significance followed by the superiority tests for the composite CV endpoints outlined in Section 7.2. No confirmatory interim analysis will be performed for the composite renal endpoint, i.e. for the renal endpoint superiority will formally be tested only once after regular or premature study termination, respectively. In case non-inferiority has not yet been demonstrated, the study will be continued as planned unless the interim results indicate major safety concerns. In case of demonstrated superiority of the primary variable at the interim analysis, the DMC may recommend stopping the study; non-inferiority of the primary endpoint may lead to early study termination if the DMC considers it unrealistic to achieve superiority. Further details will be given in the DMC Charter.~~

Prior to the ~~interim~~ **final** analysis, the SC will evaluate available external data with relevance for the superiority test strategy and consequently may suggest to the sponsor adapting the assumptions and study size, respectively.

~~In addition~~ there will be interim analyses for safety, based on all adverse events as recorded, but these interim analyses may not lead to early study termination due to demonstrate non-inferiority or superiority; therefore these interim safety analyses have no negative impact on the alpha-level.

7.3.5 Pharmacokinetic analyses

Not specified in this protocol

7.3.6 Pharmacodynamic analyses

Not specified in this protocol

7.3.7 Pharmacogenomic analyses

No prespecified pharmacogenomic analyses planned.

7.4 HANDLING OF MISSING DATA

Patients with temporary or permanent study treatment termination will be followed up for CV events. Details on how to handle missing data will be outlined in detail in the trial statistical analysis plan (TSAP).

CV safety and other safety endpoints (including renal safety endpoints)

It is not planned to impute missing values.

Diabetes related endpoints

Missing efficacy data for continuous variables for patients who discontinue the study treatment prematurely or miss a visit will be estimated by their last observed data. Missing

data for binary efficacy endpoints for patients who discontinue the study treatment prematurely will be considered as non-responders (worst case-scenario).

Methods to handle any other exceptional cases will be considered before unblinding the data and will be applied in a manner consistent with other trials of this type. The evaluability of patients with deviations from the protocol likely to confound the primary endpoint will be decided prior to unblinding.

The impact of all methods of handling missing data will be analysed using a sensitivity analysis by performing an analysis of the original data (i.e. without any imputation).

7.5 RANDOMIZATION

The sponsor will arrange for the randomization as well as packaging and labelling of study medication. Eligible patients will be randomly assigned to one of the two treatment groups, with equal allocation of treatments. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment sequence will be both reproducible and non-predictable.

The randomization will be performed in blocks. The block size will be reported in the clinical trial report. The allocation process will be performed on visit 2 through IRT. Stratification will be by geographical region. Except for the DMC, access to the code will be restricted to dedicated randomization personnel and any exceptional access to the code (in case of an emergency) will be documented according to the sponsor's standard operating procedures (SOPs).

The study will only be unblinded after all CRF / electronic data have been entered into the trial database, after queries have been resolved and after the database has been locked. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the CTMF.

Practical aspects of the treatment allocation process and methods to carry out blinding are detailed in Sections 4.1.2 and 4.1.5, respectively.

7.6 DETERMINATION OF SAMPLE SIZE

The 1-year event rate for the **initially planned** primary combined endpoint (CV death, non-fatal MI, non-fatal stroke, hospitalisation for unstable angina pectoris) ~~is~~ **was** expected to be 3.5% in the placebo group.

Assuming a constant hazard over time, the distribution is exponential and the proportion of patients with event can be derived as $F(t)=1-\exp(-\lambda t)$. The 1-year event rate of 3.5% translates into a λ of 0.0356 and this results in an estimated rate of 12.7% patients with ~~primary~~ event after 3.8 years.

Assuming the hazard over time in patients on linagliptin is the same as in patients on placebo (hazard ratio (HR): $\lambda_{linagliptin}/\lambda_{placebo}=1$), ~~625~~ **611** patients with events will deliver an overall power of 90% in a test to demonstrate non-inferiority of linagliptin vs. placebo within the

pre-specified non-inferiority (NI) margin of 1.3 for the HR; at the overall 1-sided α-level of 2.5% ~~and with one interim analysis at α=1.0% after 70% of the events~~ (calculated with East, version 5.4). ~~Assuming a study duration of 3.8 years, recruitment within 3 years and a cumulative lost to follow-up rate of 2.0%, 4150 patients per group are required to achieve 625 patients with a primary endpoint~~. **The change of the primary variable from 4-point MACE to 3-point MACE does not affect the required number of patients with event; the slight reduction from 625 to 611 patients is due to the elimination of the interim analysis. Since the event rate is higher than initially assumed the same power can be achieved within the originally planned timelines with a sample size of approximately 7000 patients.**

~~Out of these, 531 patients are expected to experience CV death, non-fatal MI or non-fatal stroke.~~

If the event distribution is lower than expected, the impact on the study conduct should be carefully considered. The SC would further monitor the recruitment of the trial with regard to baseline data for CV complications and renal impairment. The intent is to obtain a balanced mix of patients with CV complications and albuminuria AND patients with renal impairment. As such the SC may recommend to cap specific patient populations.

If non-inferiority has been demonstrated, then superiority with regard to the primary endpoint will be tested. Assuming ~~625~~ **611** patients with event and a hazard rate on linagliptin at any time 20% less than the risk on placebo ~~(HR: $\lambda_{linagliptin}/\lambda_{placebo}$ = 0.02848/0.0356 = 0.80)~~, then the resulting power to demonstrate superiority at the final analysis is ~~74%~~ **79%** ~~if the~~ **for a** test ~~can be performed~~ at the α-level of ~~1.59%~~ **2.5%** (cf. Section 7.2) ~~and 69% if the test has to be performed at the α-level of 1.06%. If the risk reduction is 21.3% (HR: 0.787) and the test can be performed at the α-level of 1.59%, the power to demonstrate superiority is 80%; the power is 75% if the test has to be performed at the α-level of 1.06%~~.

Assuming 432 patients with a composite renal endpoint, a yearly event rate of 2.5% in the placebo group and a ~~hazard rate~~ **HR** on linagliptin of 0.75, then the resulting power to demonstrate superiority at the final analysis is ~~80%~~ **85%** if the test can be performed at the α-level of ~~1.59% and 75% if the test has to be performed at the α-level of 1.06%~~**2.5%**. **If the HR is 0.70, 210 patients with renal event provide a power of 73%.**

~~If superiority for the primary endpoint and/or the composite renal endpoint has been demonstrated, then superiority with regard to the 3-point MACE (CV death, non-fatal MI, non-fatal stroke) will be tested. Assuming 531 patients with event and a hazard rate on linagliptin at any time 20% less than the risk on placebo (HR: 0.80), then the resulting power to demonstrate superiority at the final analysis is 70% if the test can be performed at the full α-level of 2.12% (if the primary endpoint and the composite renal endpoint are significant) and 50% if the test has to be performed at the α-level of 0.53% (if only one of these endpoints is significant). If the risk reduction is 21.3% (HR: 0.787), then the resulting power to demonstrate superiority at the final analysis is 76% if the test can be performed at the full α-level of 2.12% and 58% if the test has to be performed at the α-level of 0.53%.~~

All calculations are based on an allocation ratio between treatment groups of 1:1 and were derived using **ADDPLAN (version 6.0.4),** East (version 5.4) and nQuery Advisor (version 6.0.1).

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), relevant SOPs of the clinical CRO and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor/CRO immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

<For Japan> and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

~~Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).~~

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by BI in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

The following text is only applicable for Japan:
The investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

The following items need to be included:
1. That the clinical trial is aimed at testing.
2. Objectives of the trial.
3. The name, title, and address of the investigator to contact.
4. Trial procedures.
5. Anticipated benefits of the investigational products and anticipated disadvantages to the patient.
6. Matters concerning other therapeutic measures.
7. Duration of participation in the clinical trial.
8. That the patient may withdraw from the trial at any time.
9. That patient's refusal of or withdrawal from participation in the trial does not cause any disadvantage to him or her.
10. That the monitors, the auditors, and the institutional review board are given access to the relevant source documents on condition that confidentiality of the patient is fully secured.
11. That privacy of the patient is kept.
12. The office of the medical institution to contact in the event of trial-related injury.
13. That necessary treatment is available to the patient in the event of trial-related injury.
14. Matters concerning compensation in the event of any trial-related injury.
15. The type of the IRB which is used for the reviews and deliberations on the matters such as appropriateness of conducting the clinical trial, the matters to be reviewed and deliberated by each IRB, and other matters concerning the IRBs involved in the clinical trial.
16. Other necessary matters concerning the clinical trial.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor/CRO, via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available. All possible attempts should be made to collect source documents for events that trigger adjudication.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

For Japan: "Storage period of records
Trial site(s):The trial site(s) must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and the sponsor's or designated CRO SOP.

Sponsor: The sponsor/CRO must retain the essential documents according to the sponsor's or designated CRO SOPs. When it is no longer necessary for the trial site to retain the source documents and essential documents, the sponsor representative must notify the head of trial site."

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor or CRO evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For linagliptin this is the current version of the Company Core Data Sheet (CCDS). No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities For EU, i.e. the CA.

8.6 COMPLETION OF TRIAL

For Japan, When the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and the sponsor representative of the completion in writing.

For EU member states: The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

8.7 PROTOCOL VIOLATIONS

For Japan: The investigator or sub-investigator should record all CTP violations. The investigator should provide and submit the sponsor representative and the head of the trial site the records of violations infringing the Japanese GCP or violations to eliminate an immediate hazard to trial subjects and for other medically inevitable reasons.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan: In the event of health injury associated with this trial, the sponsor representative is responsible for compensation based on the contract signed by the trial site.

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10. APPENDICES

10.1 INCLUSION OF ILLITERATE PATIENTS

10.1.1 Home blood glucose monitoring

In the event of recruiting an illiterate patient, the following process should be followed with respect to HBGM and documenting the results:

- at visit 1(screening), the person assisting the patient with this process (e.g. the patient's caregiver or relative) will attend the clinic together with the patient

- the site staff should confirm that this individual will be present with the patient, whenever he/she is likely to need to perform HBGM

- the site staff should then train both the patient and above-mentioned individual with respect to the correct use of the HBGM equipment during each period of the trial. This will include the use of the glucose meter itself and the test strips, lancet device and control solution(s). Furthermore, if whole blood referenced test strips are standard in the country(ies) where illiterate patients are being recruited, the site staff must ensure that both the patient and the person assisting the patient with the HBGM, have understood that plasma referenced test strips are used in the trial, and that there may be differences in the results obtained via these two methods. A training letter is available to support this process

- the site staff should also train both the patient and the above-mentioned individual with respect to the completion of the HBGM diary. As for all other patients, the results of all per-protocol HBGM that is performed by/on illiterate patients should be documented on a HBGM diary that will be included in the patients source document file. In the event of hyper or hypoglycaemia, the person assisting the patient should record symptoms on the HBGM diary in accordance with the patients' description

HGBM tests can be performed either by the patient him/herself, or by the person assisting the patient with this aspect of the trial.

10.1.2 Patient information and informed consent

In the event of recruiting an illiterate patient, the following process should be followed with respect to patient information and informed consent:

- The designated site personnel performing the informed consent process will read the trial-approved patient information sheet and informed consent form to the patient, and explain the details of the trial, all in the presence of an impartial witness

- This impartial witness must be literate, and can be the patient's relative or caregiver, or a member of staff employed by the clinic but not part of the immediate trial team. In addition, if there are any further local regulations with respect to the consent of illiterate patients, these should also be followed

- The requirements of the trial will be explained thoroughly and the patient will be given ample time to ask questions and consider his/her participation. If he/she wishes, the patient can take the patient information sheet and informed consent form home for further consideration

- If patient agrees to take part in the trial, he/she would then return to the clinic for the consent process to be completed. The site designated personnel responsible for this process will confirm that the patient has no further questions in the presence of the same impartial witness (if the patient returns on another day). If a different impartial witness is present, the entire informed consent process must be repeated

- Participating patients will provide a thumb impression or make a mark (or signature if the patient is able to sign him/herself) on the signature section of the informed consent form

- The date of the patient's signature will be left blank as the patient is illiterate. However, if the patient is able, he/she will date the mark/signature personally

- The impartial witness or the site designated personnel may write the name of the patient on the informed consent form

- The impartial witness should enter his/her name, sign and personally date the witness section of the informed consent form. In countries where local data protection regulation permits it, the address or identification number of the impartial witness should also be entered. The signature then attests that the content of the patient information sheet and informed consent form was accurately explained to the patient, who apparently understood and freely gave consent to participate in the trial

- The designated site personnel also signs and personally dates the informed consent form

10.2 DEFINITIONS OF ENDPOINT EVENTS

Definitions of the adjudicated endpoint events and the principles of standardised data collection in the centralised CEC adjudication process are outlined in the CEC charters and process guidelines.

10.3 BLOOD PRESSURE MEASUREMENT PROCEDURE

Initially, blood pressure should be taken three times in both arms. The arm with the higher pressure (either systolic –if needed to decide- or diastolic) should be used for subsequent measurements.

Blood pressure measurements can be performed with either a standard mercury sphygmomanometer or a fully automated blood pressure device, depending on the standard practice at each study site - Note: BI will not provide electronic devices to sites that use the standard manual sphygmomanometers. The fully automated blood pressure devices should be validated by website: dableducational.org. Other devices are not acceptable.

Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The same method must be used throughout the trial, for a given patient, i.e. if a patient receives the first blood pressure measurement for example with an electronic device, the same method and a similar type of device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patients variability is acceptable, i.e. a study site is allowed to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient.

After patients have rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken approximately two minutes apart. The seated pulse rate will be taken during the two-minute interval between the second and third blood pressure reading. If an electronic blood pressure device is used the pulse rate at time of the second blood pressure reading ~~may~~ **should** be used.

Blood pressure measurements should be recorded to the nearest 0 or 5 mmHg only when measured with a manual sphygmomanometer; when digital devices are used the value from the device should be rounded to the nearest 1 mmHg. For calculation of mean values, decimal places should be rounded to integers (e.g. a DBP of 94.5 would be rounded to 95 mmHg and a DBP of 109.4 would be rounded to 109 mmHg or 110 mmHg in case of a manual sphygmomanometer). **The mean value should be recorded in the eCRF.**

10.4 SILENT MYOCARDIAL INFARCTION

~~Incidence and impact of silent MI will be assessed in this study. Its definition is based on the global MI guidelines currently described as the presence in the ECG of:~~

Definition of relevant ECG abnormalities related to silent MI is the presence of:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

An MI will only be classified as silent if 1) the ECG criteria's are fulfilled, 2) the ECG changes were absent from baseline or previous ECGs ~~and~~ 3) no preceding clinical history of MI **(including stent thrombosis and other coronary events)** during study follow-up occurred **and 4) investigator reporting of silent MI.**

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of CTP modification		1
Date of CTP modification		24 October 2013
EudraCT number		2011-004148-23
BI Trial number		1218.22
BI Investigational Product(s)		Linagliptin (BI 1356)
Title of protocol		A multicenter, international, randomized, parallel group, double-blind, placebo-controlled **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		**Clinical trial protocol synopsis (objectives)**
Description of change		....sustained loss in estimated global filtration rate (eGFR) ≥ 50% from baseline… *Was changed into*: ....sustained decrease in estimated global filtration rate (eGFR) ≥ 50% from baseline …
Rationale for change		To use consistent terminology
Section to be changed		**Clinical trial protocol synopsis (criteria for efficacy)**
Description of change		Change 1:

Description of change		
		Change 2: For clarification. Change 3: To use consistent terminology. Change 4: To clarify that endpoint event definitions are outlined in the CEC charters.
Section to be changed		**Clinical trial protocol synopsis (statistical methods)**
Description of change		b) the composite renal endpoint (i.e. renal death, sustained ESRD, sustained loss in estimated GFR ≥ 50% from baseline) *was changed into:*

		b) the composite renal endpoint (i.e. renal death, sustained ESRD, sustained decrease in estimated GFR ≥ 50% from baseline
Rationale for change		To use consistent terminology.
Section to be changed		**Flowchart**
Description of change		Change 1: Adding pharmacogenetic sampling. Change 2: Footnote C: …end of trial (EOT visit) *was changed into*: end of treatment (EOT visit). Change 3: Footnote C: Patients who discontinue study drug prematurely should continue study visits until study end, but no physical examination, vital signs, (safety) laboratory sampling (including pregnancy test, lipid panel HbA_{1c} **,** UACR and eGFR) or ECG will be required. *Was changed into*: Footnote C: Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of , collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR. Change 4: The following text under footnote G was deleted:

		Change 5: Footnote K: At visit 1 safety laboratory includes ALT, AST, alkaline phosphatase and creatinine to check for eligibility in addition to urine albumin, urine creatinine and HbA_{1c} as specified in the flow chart. *Was changed into:* At visit 1 safety laboratory includes ALT, AST, alkaline phosphatase and creatinine to check for eligibility in addition to lipase, urine albumin, urine creatinine and HbA_{1c} as specified in the flow chart. Change 6: Footnote L: …In case of an eGFR loss of ≥ 50% since baseline (visit 2) an additional visit 4 weeks after detection should be scheduled to collect a blood sample for repeat analysis of creatinine (eGFR)…. *Was changed into:* …In case of an eGFR decrease of ≥ 40% since baseline (visit 2) and again in case of an eGFR decrease of ≥ 50% since baseline (visit 2) an additional visit 4 weeks after detection should be scheduled to collect a blood sample for repeat analysis of creatinine (eGFR)…. Change 7: Footnote N: ….. (plus 2 week reserve) *was changed into:* …(2 weeks reserve). Change 8: Footnote O: Returned study medication may be re-dispensed if the time window around the patient visit schedule requires this. *Was changed into:* Footnote O: The protocol allows a time window of +/- 7 days for visit 3 and +/- 14 days for all scheduled visits in the treatment period after visit 3. To ensure sufficient medication, visits after visit 3 should be scheduled within 182 days and visit 3 should take place no later than 91 days after visit 2. Change 9: Footnote P was added: To allow possible retrospective pharmacogenetic analyses, all patients eligible for randomization will be asked for a blood sample with a separate informed consent. The pharmacogenetic sample should preferably be taken at visit 2, but could also be taken at any later visit, depending on availability of the respective informed consent. Pharmacogenetic sampling is voluntary and is not a prerequisite for participation in the study.

		Change 10: Footnote Q was added: Urine Albumin Creatinine Ratio (UACR) will be calculated at the central lab, and should be measured on a first morning void specimen wherever possible.
Rationale for change		Change 1: To allow possible retrospective pharmacogenetic analyses. Change 2: For clarification. Change 3: For clarification and to add creatinine for calculation of eGFR to the assessments for patients who pre-maturely discontinue study medication, but are willing to return to the pre-defined study visits (ITT principle, primary renal endpoint). Change 5: To add lipase to the laboratory assessment schedule. Change 7: Correction of typographical error. Change 8: To clarify the allowed time window between study visits in relation to the available study medication dispensed. Change 9: To add an explanatory footnote for the pharmacogenetic sampling added to the flowchart. Change 10: For clarification in line with section 5.2.3 of the clinical trial protocol.
Section to be changed		**Abbreviations**
Description of change		The following abbreviation was added: DNA – Deoxyribonucleic Acid In addition: EOT - End of Trial *was changed into*: EOT – End of Treatment.
Rationale for change		Change 1: Abbreviation added.

		Change 2: For clarification.
Section to be changed		**1.1 Medical background**
Description of change		In this large-scale intervention trial we will test the impact of treatment with the DPP-4 inhibitor linagliptin head-to-head versus placebo on long-term CV safety. *Was changed into:* In this large-scale intervention trial we will test the impact of treatment with the DPP-4 inhibitor linagliptin head-to-head versus placebo on long-term CV safety as well as the potential preventive impact on CV and renal complications.
Rationale for change		To underscore the importance of the renal aspects in the study.
Section to be changed		**2.1 Rationale for performing the trial**
Description of change		Paragraph 5: …predefined urin albumin …was changed into ….predefined urine albumin.
Rationale for change		Correction of typographical error.
Section to be changed		**3.1 Overall trial design and plan**
Description of change		Change 1: End of Trial….. *was changed into:* End of Treatment…. Change 2: ….Patients who discontinue study drug prematurely should continue study visits until study end, but no physical examination, vital signs, (safety) laboratory sampling (including pregnancy test, lipid panel HbA_{1c} , UACR and eGFR) or ECG will be required. *Was changed into*: Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.
Rationale for change		Change 1: For clarification. Change 2: For clarification and to add creatinine for calculation of eGFR to the assessments for patients who pre-maturely discontinue study medication, but are willing to return to the pre-defined study visits (ITT principle, primary renal endpoint).

Section to be changed		**3.1.1 Administrative structure of the trial**
Description of change		Additionally, a separate independent, blinded, external committee will be set up for adjudication of renal events. The adjudication process for renal events will be clarified separately in a CEC charter. *Was changed into:* Additionally, separate independent, blinded, external committees will be set up for adjudication of renal events and pancreatic events. The adjudication process for renal events and pancreatic events will be clarified in a separate CEC charter.
Rationale for change		To add independent adjudication of pancreatic events.
Section to be changed		**3.3.2 inclusion criteria**
Description of change		Change 1: Inclusion criterion number 8: the definition of albuminuria ≥ 30 mg/l (milligram albumin per litre of urine) was removed. Change 2: Inclusion criterion number 8: Impaired renal function (as defined by MDRD formula) with an eGFR: 15- 45 mL/min/1.73 m^2 at Visit 1 (screening) with any UACR. *Was changed into:* Impaired renal function (as defined by MDRD formula) with an eGFR: 15- <45 mL/min/1.73 m^2 at Visit 1 (screening) with any UACR. Change 3: Inclusion criterion number 8: the definition of UACR ≥ 200 mg/l (milligram albumin per litre of urine) was removed. Change 4: Inclusion criterion number 8: MRI angiography was added as clinical test and clinical tests were added to the second bullet under inclusion criterion 8b and 8c.
Rationale for change		Change 1: To reflect the definition KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Change 2: For clarification. Change 3: To reflect the definition KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Change 4: To add MRI angiography as clinical test and to clarify

		allowed clinical testing for inclusion criterion 8b and 8c.
Section to be changed		**3.3.3 exclusion criteria**
Description of change		Exclusion criterion number 5: ..(open or laparascopic) ..was changed into… (open or laparoscopic)…
Rationale for change		Correction of typographical error.
Section to be changed		**3.3.4.1 Removal of individual patient**
Description of change		….Patients who discontinue study drug prematurely should continue study visits until study end, but no physical examination, vital signs, (safety) laboratory sampling (including pregnancy test, lipid panel HbA_{1c} , UACR and eGFR) or ECG will be required. *Was changed into*: Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of , collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.
Rationale for change		For clarification and to add creatinine for calculation of eGFR to the assessments for patients who pre-maturely discontinue study medication, but are willing to return to the pre-defined study visits (ITT principle, primary renal endpoint).
Section to be changed		**4.1.4 Drug assignment and administration of doses for each patient**
Description of change		<u>Change 1:</u> Paragraph 4: …..Returned study medication may be re-dispensed if the time window around the patient visit schedule requires this. *Was changed into:* The protocol allows a time window of +/- 7 days for visit 3 and +/- 14 days for all scheduled visits in the treatment period after visit 3. To ensure sufficient medication, visits after visit 3 should be scheduled within 182 days and visit 3 should take place no later than 91 days after visit 2. <u>Change 2:</u> Paragraph 4….. (plus 2 week reserve) *was changed into:* …(2 weeks reserve).
Rationale for change		<u>Change 1:</u> To clarify the allowed time window between study visits in relation to the available study medication dispensed. <u>Change 2:</u> To correct a typographical error

Section to be changed		**5.1.1 Endpoint(s) of efficacy**
Description of change		Change 2: Albuminuria change over time *was changed into:* UACR change over time. Change 3: Sustained loss of 50% or more in eGFR *was changed into:* Sustained decrease of 50% or more in eGFR. In addition: Composite microvascular outcome (50% loss of eGFR, albuminuria progression, requirement for renal replacement therapy or death due to renal failure, use of retinal photocoagulation or intravitreal injections of an anti-VEGF therapy for diabetic retinopathy). *was changed into:* Composite microvascular outcome (50% decrease or more in eGFR, albuminuria progression, requirement for renal replacement therapy or death due to renal failure, use of retinal photocoagulation or intravitreal injections of an anti-VEGF therapy for diabetic retinopathy). Change 4: The following text was added: Definitions of the adjudicated endpoint events are outlined in the CEC charters.
Rationale for change		Change 2: For clarification. Change 3: To use consistent terminology. Change 4: To clarify that endpoint event definitions are outlined in the CEC charters.

Section to be changed		**5.2.2.1 Definitions of adverse events**
Description of change		Change 1: A list of terms that must be documented as AESI for each topic is provided in the ISF. Renal events will be adjudicated by an independent adjudication committee. *Was changed into:* A list of terms that must be documented as AESI for each topic is provided in the ISF. Renal events and pancreatic events will be adjudicated by independent adjudication committees. Change 2: Patients showing an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample need to be followed up locally. *Was changed into:* Patients showing an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample need to be followed up locally according to the "DILI checklist" provided in ISF. Change 3: In case of an eGFR loss of ≥ 50% since baseline (Visit 2) an additional visit 4 weeks after detection should be scheduled (unless detected at the EOT visit at study end) to collect a blood sample for repeat analysis of creatinine for calculation of the eGFR. *Was changed into:* In case of an eGFR decrease of ≥ 40% since baseline (visit 2) and again in case of an eGFR decrease of ≥ 50% since baseline (visit 2) an additional visit 4 weeks after detection should be scheduled (unless detected at the EOT visit at study end) to collect a blood sample for repeat analysis of creatinine for calculation of the eGFR.
Rationale for change		Change 1: Adjudication of pancreatic events added. Change 2: To provide additional guidance for follow-up of patient showing an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN. Change 3: To add an additional trigger for repeat analysis of eGFR in line with the newly added tertiary endpoints.

Section to be changed		**5.2.2.2 Adverse event and serious adverse event reporting**
Description of change		Change 1: All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through 1 week residual effect period) will be collected, documented and reported to the sponsor/CRO by the investigator on the appropriate CRF(s) / eCRFs/ SAE reporting forms. The investigator should report any SAEs which occurred to a subject after the residual effect period/follow-up period. *Was changed into*: All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the last per protocol visit) will be collected, documented and reported to the sponsor/CRO by the investigator on the appropriate CRF(s) / eCRFs/ SAE reporting forms. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the last per protocol visit, it should be reported by the investigator to the sponsor if considered relevant by the investigator. Change 2: If not stipulated differently in the ISF, the investigator must report the following events, using the CRO electronic submission process immediately (within 24 hours or the next business day whichever is shorter) to the sponsor/CRO: SAEs, AESI and non-serious AEs relevant for the reported SAE or AESI. The investigator must document immediately (within 24 hours or the next business day whichever is shorter)……. *Was changed into:* The investigator must report the following events, immediately (within 24 hours of awareness) to the sponsor/CRO: SAEs, AESI and non-serious AEs relevant for the reported SAE or AESI. The investigator must document immediately (within 24 hours of awareness)…. Change 3: ….. or by using the electronic submission process was deleted. Change 4: Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter)…

		Was changed into: Drug exposure during pregnancy has to be reported immediately (within 24 hours of awareness)….
Rationale for change		Change 1: To clarify that AEs are collected even after the residual effect period for patients who pre-maturely discontinue study medication and to clarify that SAEs which occurred to a subject after the last per protocol should be reported if considered relevant by the investigator. Change 2: To reflect the paper based reporting process and to update the definition of immediately. Change 3: To reflect the paper based reporting process and to update the definition of immediately. Change 4: To update the definition of immediately.
Section to be changed		**5.2.3 Assessment of safety laboratory parameters**
Description of change		Lipase added to visit 1 and visit 2 In addition: *Visit 3 – EOT* • Clinical chemistry: creatinine • Urine analysis: albumin and creatinine (Visit 4, Visit 6 and thereafter yearly). • Clinical chemistry: cholesterol (total), HDL cholesterol, LDL cholesterol and triglycerides (Visit 4, Visit 6 and thereafter yearly) HbA_{1c} will be determined at all scheduled visits. *Was changed into:* *Visit 3 – EOT - FU* • Clinical chemistry: creatinine and lipase • Urine analysis: albumin and creatinine (Visit 4, Visit 6 and thereafter yearly). • Clinical chemistry: cholesterol (total), HDL cholesterol, LDL cholesterol and triglycerides (Visit 4, Visit 6 and thereafter yearly) HbA_{1c} will be determined at all scheduled visits, with exception of the FU visit.
Rationale for change		For clarification and to add lipase to the laboratory assessment schedule.

Section to be changed		**5.2.5 Assessment of other safety parameters**
Description of change		……If not stipulated differently in the ISF, patient … was deleted.
Rationale for change		Following confirmation that a paper diary is used.
Section to be changed		
Rationale for change		Change 1: To reflect recruitment planning per country following completion of feasibility. Change 2: For clarification.
Section to be changed		**5.3.3 Pharmacogenomic evaluation**
Description of change		Section 5.3.3 was added.
Rationale for change		To allow possible retrospective pharmacogenetic analyses.

Section to be changed		**6.2.3 End of trial and follow-up period**
Description of change		Sub header was changed into end of treatment and follow-up. *In addition:* Patients who discontinue study drug prematurely should continue study visits until study end, but no physical examination, vital signs, (safety) laboratory sampling (including pregnancy test, lipid panel HbA_{1c} **,** UACR and eGFR) or ECG will be required. *Was changed into*: Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.
Rationale for change		For clarification and to add creatinine for calculation of eGFR to the assessments for patients who pre-maturely discontinue study medication, but are willing to return to the pre-defined study visits (ITT principles, primary renal endpoint).
Section to be changed		**7.1 Statistical design –model**
Description of change		If a patient dies without a primary outcome event, the patient will be censored at the date of death. *Was changed into:* If any measurement of laboratory data or ECG is available after the last visit of a patient, the date of the respective measurement will be used for censoring of the CV endpoint. If any measurement of eGFR is available after the last visit of a patient, the date of the respective measurement will be used for censoring of the renal endpoint. For all endpoints including the component CV (renal) death, adjudicated CV (renal) death will be counted even if occurred thereafter.
Rationale for change		To add more specific information regarding censoring of the CV and renal endpoint, respectively.
Section to be changed		**7.3 Planned analyses**
Description of change		Additional analyses will be explored in specific subgroups, e.g. depending on characteristics at baseline with respect to the primary and secondary endpoints. Covariates that will be explored include: • Region (North America, Europe, Asia etc.) • Age (<65, ≥ 65 years) • Systolic and diastolic blood pressure (≤ 160/100 mmHg , > 160/100 mmHg, other) • Gender (male, female)

		• Prior anti-diabetic treatment (none, monotherapy, combination therapy) *was changed to*: Additional analyses will be explored in specific subgroups, e.g. depending on characteristics at baseline with respect to the primary and key secondary endpoints. Covariates that will be explored include: • Region (North America, Europe, Asia etc.) • Age (<65, ≥ 65 years) • Systolic and diastolic blood pressure (≤ 160 and ≤ 100 mmHg , > 160 or > 100 mmHg) • Gender (male, female) • Prior anti-diabetic treatment (none, monotherapy, combination therapy) • eGFR < 60 mL/min/1.73 m^2 at baseline
Rational for change		To reflect definitions regarding systolic and diastolic blood pressure subgroups in other outcome studies and to add a subgroup analysis reflecting the renal status.
Section to be changed		**7.3.2 Secondary analyses**
Description of change		<u>Change 1:</u> Composite renal endpoint (i.e. renal death, sustained ESRD, sustained loss of 50% or more in eGFR) *was changed into:* Composite renal endpoint (i.e. renal death, sustained ESRD, sustained decrease of 50% or more in eGFR) <u>Change 3:</u> Albuminuria change over time *was changed into:* UACR change over time. <u>Change 4:</u> Sustained loss of 50% or more in eGFR *was changed into:* Sustained decrease of 50% or more in eGFR. <u>In addition:</u> Composite microvascular outcome (50% loss of eGFR, albuminuria progression, requirement for renal replacement therapy or death due to renal failure, use of retinal photocoagulation or intravitreal injections of an anti-VEGF therapy for diabetic retinopathy).

		was changed into: Composite microvascular outcome (50% decrease or more in eGFR, albuminuria progression, requirement for renal replacement therapy or death due to renal failure, use of retinal photocoagulation or intravitreal injections of an anti-VEGF therapy for diabetic retinopathy). Change 5: Clopper and Pearson confidence intervals *was changed into:* Wilson confidence intervals. Change 6: The following text was deleted: Patients without occurrence of a specific endpoint will be considered censored at the end of study or lost to follow-up, whichever comes first. Change 7: Last paragraph: secondary *was changed into:* key secondary.
Rationale for change		Change 1: To use consistent terminology. Change 3: For clarification. Change 4: To use consistent terminology. Change 5: Wilson confidence intervals are less conservative. Change 6: Censoring has been addressed more specifically in section 7.1. Change7: For clarification/consistency
Section to be changed		**7.3.7 Pharmacogenomic analyses**
Description of change		Not specified in this protocol *was changed into*: No pre-specified pharmacogenomics analyses planned.
Rationale for change		To allow possible retrospective pharmacogenetic analyses.
Section to be changed		**8.3.1 Source documents**
Description of change		The following text was added: All possible attempts should be made to collect source documents for events that trigger adjudication.
Rationale for change		To emphasise the importance of source documents for adjudication of events.

Number of CTP modification		2
Date of CTP modification		22 November 2016
EudraCT number		2011-004148-23
BI Trial number		1218.22
BI Investigational Product(s)		Linagliptin (BI 1356)
Title of protocol		A multicenter, international, randomized, parallel group, double-blind, placebo-controlled **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		**Title page**
Description of change		added as TCM
Rationale for change		added as TCM
Section to be changed		**Clinical trial protocol synopsis**
Description of change		Change 1: The primary endpoint changed from 4-point MACE to 3-point MACE. The key secondary endpoints were changed from 3-point MACE and composite renal endpoint (renal death, sustained ESRD, sustained decrease of 50% or more in eGFR) to composite renal endpoint (renal death, sustained ESRD, sustained decrease of 40% or more in eGFR). Change 2: If non-inferiority has been demonstrated, then the primary composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to the composite renal endpoint (i.e. renal

		death, sustained end-stage renal disease (ESRD), sustained decrease in estimated global filtration rate (eGFR) ≥ 50% from baseline), will be investigated separately with a test on superiority. *Was changed into:* If non-inferiority has been demonstrated, then the primary composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to the composite renal endpoint (i.e. renal death, sustained end-stage renal disease (ESRD), sustained decrease in estimated glomerular filtration rate (eGFR) ≥ 40% from baseline), will be investigated separately with a test on superiority Change 3: Number of randomized patients decreased from 8300 to 7000 and number of patients per treatment group decreased from 4150 to 3500. Change 4: Number of patients with primary endpoint events decreased from 625 to 611 and estimated treatment period increased from 48 to 54 months. Change 5: The primary endpoint (4-point MACE) will be tested for non-inferiority. Thereafter the 4-point MACE and the combined composite renal endpoint will be tested separately (= in parallel) for superiority. In case the 4-point MACE and/or the composite renal endpoint is significantly superior, the 3-point MACE will be tested for superiority. *Was changed into:* The primary endpoint (3-point MACE) will be tested for non-inferiority. Thereafter if non-inferiority has been demonstrated the 3-point MACE and the combined composite renal endpoint will be tested separately for superiority.

		Change 8: Statistical methods: The primary analyses will be performed on the full analysis set… *Was changed into:* The primary analyses will be performed on the Treated Set… Change 9: Statistical methods: … then two separate hypothesis tests for • the primary composite endpoint • the composite renal endpoint (i.e. renal death, sustained ESRD, sustained decrease in estimated GFR ≥ 50% from baseline) will be tested for superiority in parallel, each with the Cox proportional hazards regression model for time to first event. *Was changed into:* Statistical methods: … then two separate hypothesis tests for • the primary composite endpoint • the composite renal endpoint (i.e. renal death, sustained ESRD, sustained decrease in estimated GFR ≥ 40% from baseline) will be tested for superiority, each with the Cox proportional hazards regression model for time to first event. And the following text was added: To adjust for multiplicity a sequentially rejective multiple test procedure will be applied.
Rationale for change		Change 1: Based on review of recently published cardiovascular outcome trials, changing the protocol definitions of the primary and secondary endpoints, essentially substituting 4-Point MACE (Cardiovascular (CV) Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction and Hospitalization for Unstable Angina) with 3-Point MACE (CV Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction). Change 2: eGFR cut off changed in response to the NIH/FDA scientific workshop on GFR decline as an endpoint for

		clinical trials in CKD and the current clinical landscape on decline in estimated glomerular filtration rate and subsequent risk of end stage renal disease and mortality. Change 3: Overall MACE event rates are higher than initially expected and this allows reducing the sample size without major impact on study duration. Change 4: Since the interim analysis for efficacy was deleted, the required number of patients with primary endpoint to achieve a power of 90% for non-inferiority is reduced from 625 to 611. The estimated trial duration increased slightly due to the change of the primary endpoint while ensuring a sufficiently long drug exposure for the last recruited patients. Change 5: Since the primary endpoint was changed to 3-point MACE it is no longer listed as key secondary endpoint. Change 8: For clarification Change 9: For clarification
Section to be changed		**Flow chart**
Description of change		Change 1: Change in follow-up period from 7 to 30 days Change 2: Guidance revised on the timing of the EOT visit after study stop announcement after 611 endpoint events are reached In addition • ...changes since last visit might be recorded *Was changed into* • ...changes since last visit should be recorded

		Change 3: Footnote L: estimated creatinine clearance *Was changed into:* Estimated glomerular filtration rate
Rationale for change		Change 1: To allow for outcome event data collection up to 30 days after EOT Change 2: To clarify the respective actions to stop the trial when 611 endpoint events are reached Change 3: For clarification
Section to be changed		**Abbreviations**
Description of change		CHC – Congestive Heart Failure and VEGF - Vascular endothelial growth factor deleted OS - On-treatment Set and TS – Treated Set were added
Rationale for change		Due to change in the text.
Section to be changed		**1.2 Drug profile**
Description of change		Drug profile section updated
Rationale for change		For clarification per current version of the investigator brochure.
Section to be changed		**2.2 trial objectives**
Description of change		Change 1: The primary endpoint changed from 4-point MACE to 3-point MACE. The key secondary endpoints were changed from 3-point MACE and composite renal endpoint (renal death, sustained ESRD, sustained decrease of 50% or more in eGFR) to composite renal endpoint (renal death, sustained ESRD, sustained decrease of 40% or more in eGFR). Change 2: If non-inferiority has been demonstrated, then the primary composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to the composite renal endpoint (i.e. renal death, sustained ESRD, sustained loss in estimated glomerular filtration rate (eGFR) ≥ 50% from baseline), will be investigated with a test on superiority. The CV and renal superiority tests will be performed separately, with no upfront imbalance regarding the assigned alpha-levels. If linagliptin is superior with regard to the primary endpoint and/or the composite renal endpoint, a further

		test will evaluate the superiority of linagliptin with regard to the 3-component Major Adverse Cardiovascular Events (MACE) endpoint (CV death [including fatal stroke, fatal MI and sudden death], non-fatal stroke, non-fatal MI [excluding silent MI]). *Was changed into*: If non-inferiority has been demonstrated, then the primary composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to the composite renal endpoint (i.e. renal death, sustained ESRD, sustained loss in estimated glomerular filtration rate (eGFR) ≥ 40% from baseline), will be investigated with a test on superiority. The CV and renal superiority tests will be performed separately, with an upfront imbalance regarding the assigned alpha-levels.
Rationale for change		Change 1: Based on review of recently published cardiovascular outcome trials, changing the protocol definitions of the primary and secondary endpoints, essentially substituting 4-point MACE (Cardiovascular (CV) Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction and Hospitalization for Unstable Angina) with 3-point MACE (CV Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction). eGFR cut off changed in response to the NIH/FDA scientific workshop on GFR decline as an endpoint for clinical trials in CKD and the current clinical landscape on decline in estimated glomerular filtration rate and subsequent risk of end stage renal disease and mortality. Change 2: A higher alpha-level will be assigned to the composite renal endpoint, the endpoint with the expected higher power for superiority. Nevertheless, this strategy allows testing both, 3-point MACE and the renal endpoint for superiority, independently of each other.
Section to be changed		**3.1 Overall trial design and plan**
Description of change		Change 1: Number of randomized patients decreased from 8300 to 7000 and number of patients per treatment group decreased from 4150 to 3500. Change 2: Number of endpoint events decreased from 625 to 611 and estimated treatment period increased from 48 to 54 months. Change 3: Guidance revised on the timing of the EOT visit after

		study stop announcement after 611 endpoint events are reached. Change 4: Change in follow-up period from 7 to 30 days Change 5: …in a separate CEC charter *Was changed into:* …in the CEC charter
Rationale for change		Change 1: Overall MACE event rates are higher than initially expected and this allows reducing the sample size without major impact on study duration. Change 2: Since the interim analysis for efficacy was deleted, the required number of patients with primary endpoint to achieve a power of 90% for non-inferiority is reduced from 625 to 611. The estimated trial duration increased slightly due to the change of the primary endpoint while ensuring a sufficiently long drug exposure for the last recruited patients. Change 3: To clarify the respective actions to stop the trial when 611 endpoint events are reached. Change 4: To allow for outcome event data collection up to 30 days after EOT Change 5: For clarification
Section to be changed		**3.3 Selection of trial population**
Description of change		Number of randomized patients decreased from 8300 to 7000 and number of patients per treatment group decreased from 4150 to 3500.
Rationale for change		Overall MACE event rates are higher than initially expected and this allows reducing the sample size without major impact on study duration
Section to be changed		**3.3.3 Exclusion criteria**
Description of change		Exclusion criterion 4: corrections of eGFR unit.
Rationale for change		For clarification
Section to be changed		**3.3.4.1 Removal of individual patients**
Description of change		Patient retention language revised
Rationale for change		To optimize retention language
Section to be changed		**4.1.1 identity of BI investigational product and comparator product(s)**
Description of change		Film-coated added to tablets under pharmaceutical form

		and sponsor entity omitted.
Rationale for change		For clarification
Section to be changed		**4.1.5.1.**
Description of change		Change 1: Text related to code breaking in case of SUSARs added. Change 2: Text related to code breaking added for Japan
Rationale for change		Change 1 and change 2: For clarification
Section to be changed		**4.1.7 storage condition**
Description of change		All trial medication should be stored according to the storage conditions as specified on the label and in the original package. *Was changed into:* The study medication must be kept in its original packaging under the recommended storage conditions indicated on the label.
Rationale for change		For clarification
Section to be changed		**4.2.2.**
Description of change		DDP4 was changed to DPP4.
Rational for change		Correction of typographical error
Section to be changed		**4.3 treatment compliance**
Description of change		Capsules were changed into tablets
Rationale for change		Correction of error
Section to be changed		**5.1.1 endpoints of efficacy**
Description of change		<u>Change 1:</u> The primary endpoint changed from 4-point MACE to 3-point MACE. The key secondary endpoints were changed from 3-point MACE and composite renal endpoint (renal death, sustained ESRD, sustained decrease of 50% or more in eGFR) to composite renal endpoint (renal death, sustained ESRD, sustained decrease of 40% or more in eGFR). In addition: The primary endpoint in this trial is time to the first occurrence of any of the following adjudicated components of the primary composite endpoint… *Was changed into* The primary endpoint in this trial is time to the first occurrence of any of the following by adjudication confirmed components of the primary composite endpoint….. <u>Change 2:</u> At the final analysis the primary endpoint (4-point MACE) will be tested for non-inferiority. Thereafter the

		4-point MACE and the combined composite renal endpoint will be tested separately (= in parallel) for superiority. In case the 4-point MACE and/or composite renal endpoint is significantly superior, the 3-point MACE will then be tested for superiority. *Was changed into:* The primary endpoint (3-point MACE) will be tested for non-inferiority. Thereafter, if non-inferiority has been demonstrated, the 3-point MACE and the combined composite renal endpoint will be tested separately for superiority.

		In addition: Definition of MI added.

		Change 5: Definition of albuminuria progression updated.
Rationale for change		Change 1: Based on review of recently published cardiovascular outcome trials, changing the protocol definitions of the primary and secondary endpoints, essentially substituting 4-Point MACE (Cardiovascular (CV) Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction and Hospitalization for Unstable Angina) with 3-Point MACE (CV Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction). eGFR cut off changed in response to the NIH/FDA scientific workshop on GFR decline as an endpoint for clinical trials in CKD and the current clinical landscape on decline in estimated glomerular filtration rate and subsequent risk of end stage renal disease and mortality. Change 4: For clarification Change 5: For clarification/correction of error.
Section to be changed		**5.2.1.1 reporting waiver for cardiovascular-outcome events**
Description of change		….. secondary *was changed into* key secondary…
Rationale for change		For clarification
Section to be changed		**5.2.2.1 definition of adverse events**
Description of change		Change 1: The definition of AEs was updated and AESI language was revised reflecting the newly released process by drug safety for reporting of AESIs.

		Change 2: Estimated creatinine clearance *Was changed into:* Estimated glomerular filtration rate
Rationale for change		Change 1: To reflect the current standard AEs text and revised AESI process Change 2: For clarification
Section to be changed		**5.2.2.2 Adverse event and serious adverse event reporting**
Description of change		Section was updated
Rationale of change		For clarification per current standard text.
Section to be changed		**5.2.2.3 Oncological adverse events**
Description of change		Added a reference to the oncology committee assessment charter
Rationale for change		For clarification
Section to be changed		**5.2.3.1**
Description of change		No renal impairment with evidence of kidney damage (UACR ≥30mg/ g creatinine) Was changed into: No renal impairment with evidence of kidney damage (eGFR ≥ 90 mL/min/1.73m^2 and UACR ≥30mg/ g creatinine) In addition definition of prevalent kidney disease added.
Rationale for change		For clarification
Section to be changed		**6.2.2 treatment period & 6.2.3 end of treatment and follow-up**
Description of change		Change 1: Patient retention language revised Change 2: Change in follow-up period from 7 to 30 days
Rationale for change		Change 1: To optimize retention language Change 2: To allow for outcome event data collection up to 30 days after EOT
Section to be changed		**7.1 Statistical design - model**
Description of change		Change 1: Number of randomized patients decreased from 8300 to 7000 and number of patients per treatment group decreased from 4150 to 3500.

		Change 2: Number of endpoint events decreased from 625 to 611. Change 3: The primary endpoint was changed from 4-point MACE to 3-point MACE
Rationale for change		Change 1: Overall MACE event rates are higher than initially expected and this allows reducing the sample size without major impact on study duration. The required number of patients with event is not affected by the lower number of randomised patients in this event-driven study Change 2: Since the planned interim analysis for efficacy will not be performed, a slightly lower number of patients with event is required for the same power (90% for non-inferiority) Change 3: Based on review of recently published cardiovascular outcome trials, changing the protocol definitions of the primary and secondary endpoints, essentially substituting 4-Point MACE (Cardiovascular (CV) Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction and Hospitalization for Unstable Angina) with 3-Point MACE (CV Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction).
Section to be changed		**7.2 Null and alternative hypothesis**
Description of change		Relevant changes are summarised as follows: Change 1: An interim analysis will be performed at the one-sided alpha-level of 1.0%, the final analysis at the one-sided alpha-level of 2.12%. At the interim analysis MACE endpoints will be tested in a pre-specified order, at the final analysis also the composite renal endpoint will be tested for superiority *Was changed into:* No confirmatory interim analysis for efficacy endpoints will be performed Change 2: The experimentwise (multiple) level alpha is controlled with the following three step gatekeeping hierarchy within the interim and final analysis, respectively. For the final analysis, the first hypothesis (non-inferiority of the primary endpoint) will be tested at the one-sided alpha-level of 2.12%. In case of significance, the null hypothesis is rejected in a confirmatory sense and the next set of hypotheses (two separate hypothesis tests) will be tested: a) test of the primary endpoint for superiority and b) test of the composite renal

		endpoint for superiority. To adjust for multiplicity the truncated Hochberg multiple test procedure will be applied with a selected gamma of 0.5. Both one-sided hypotheses H0(Sup1) and H0(Sup2) will be tested separately. If both tests are significant at the one-sided alpha-level of 1.59% each, superiority of both endpoints (4-point MACE and composite renal endpoint) has been demonstrated. If not, superiority can only be claimed for the endpoint significant at the alpha-level of 1.06%. If superiority of both, the 4-point MACE and the composite renal endpoint has been demonstrated at the one-sided alpha-level of 1.59% each, then superiority of the 3-point MACE can be tested at the alpha-level of 2.12%. If superiority of only one of these endpoints (4-point MACE or composite renal endpoint) has been demonstrated at the one-sided alpha-level of 1.06%, then superiority of the 3-point MACE can be tested at the alpha-level of 0.53%. *Was changed into:* For the final analysis, the first hypothesis (non-inferiority of the primary endpoint) will be tested at the one-sided alpha-level of 2.5%. In case of significance, the null hypothesis is rejected in a confirmatory sense and the next set of hypotheses (two separate hypothesis tests) will be tested: a) test of the primary endpoint for superiority and b) test of the composite renal endpoint for superiority. To adjust for multiplicity a sequentially rejective multiple test procedure will be applied. Both one-sided hypotheses H0(Sup1) and H0(Sup2) will be tested separately, at the initial alpha-levels of 0.2*alpha for 3-point MACE and 0.8*alpha for the composite renal endpoint, respectively. If both null hypotheses cannot be rejected at these initial alpha-levels, the procedure stops and for none of these endpoints superiority can be declared. After having shown superiority for one of these endpoints, the used alpha can be shuffled to the other test: If H0(Sup2) is rejected at the alpha-level of 0.8*alpha, then H0(Sup1) can be tested at the full alpha-level of 2.5% (one-sided). If H0(Sup1) is rejected at the alpha-level of 0.2*alpha, then H0(Sup1) can be tested at the full alpha-level of 2.5% (one-sided).
Rationale for change		A higher alpha-level will be assigned to the composite renal endpoint, the endpoint with the expected higher power for superiority. Nevertheless, this strategy allows testing both, 3-point MACE and the renal endpoint for superiority, independently of each other.
Section to be changed		**7.3 planned analysis**
Description of change		Change 1: Hospitalisation for unstable angina pectoris deleted from Important protocol violations.

		Change 2: Systolic and diastolic blood pressure (≤160 and ≤ 100 mmHg , > 160 or > 100 mmHg) *Was changed into:* Systolic and diastolic blood pressure (<140 and < 90 mmHg , ≥ 140 or ≥ 90 mmHg) Change 3: Prior anti-diabetic treatment (none, monotherapy, combination therapy) *Was changed into:* Prior anti-diabetic treatment (insulin, no insulin) Change 4: The following subgroup has been added: Prevalent kidney disease defined as eGFR < 60 mL/min/1.73 m^2 at baseline and/or UACR > 300mg/g creatinine at baseline Change 5: 'In case only randomized patients take study drug, this set is identical to the FAS…' was deleted Change 6: Analysis sets have been redefined in 7.3 and 7.3.1 as follows: The full analysis set (FAS) consisting of all randomized patients who were treated with at least one dose of study drug *Was changed into:* The Treated Set consisting of all patients who were treated with at least one dose of study drug In addition: The '30-day treatment' set of patients including all patients with minimum treatment duration of 30-days *Was changed into:* The 'on-treatment' set (OS) including all patients with minimum treatment duration of 30-days In addition:

		The 'on-treatment analysis' on the FAS (consisting of all randomized patients who were treated with at least one dose of study drug) with censoring at the time patients are on treatment + 30 days after permanent treatment discontinuation or end of observation *Was changed into:* The 'TS+30 analysis' on the TS (consisting of all patients who were treated with at least one dose of study drug) with censoring at the time patients are on treatment + 30 days after permanent treatment discontinuation or end of observation
Rationale for change		Change 1: Deleted due to the change of the primary endpoint. Change 2: BP limit changed to 140/90 mmHg, to reflect BP treatment standards for the CARMELINA population. Change 3: Insulin treatment (with or without oral anti-diabetics) is considered the most important differentiator of anti-diabetic treatment, while e.g. combination therapy of anti-diabetic drugs per se is not associated with a different risk for outcome events as compared to monotherapy (including insulin). Change 4: To investigate the potential impact of impaired renal function on outcome events and renal endpoints Change 5: Only randomized patients took study drug and therefore this statement is no longer required Change 6: Since only randomized patients took study drug, the TS is identical to the FAS and thus there is no impact on derived analysis sets. Labels were changed in order to align with recently published outcome studies and notations used by FDA.
Section to be changed		**7.3.2 Secondary analyses**
Description of change		Change 1: The key secondary endpoints were changed from 3-point MACE and composite renal endpoint (renal death, sustained ESRD, sustained decrease of 50% or more in eGFR) to composite renal endpoint (renal death, sustained ESRD, sustained decrease of 40% or more in eGFR). In addition: After non-inferiority has been established for the primary

		endpoint (4-point MACE), the same endpoint and the composite renal endpoint (at the final analysis) will be tested for superiority. In case of significant superiority of the 4-point MACE and/or the composite renal endpoint, the 3-point MACE will then be tested for superiority. *Was changed into:* After non-inferiority has been established for the primary endpoint (3-point MACE), the same endpoint and the composite renal endpoint will be tested for superiority.

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Rationale for change		Change 1: Based on review of recently published cardiovascular outcome trials, changing the protocol definitions of the primary and secondary endpoints, essentially substituting 4-Point MACE (Cardiovascular (CV) Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction and Hospitalization for Unstable Angina) with 3-Point MACE (CV Death, Non-Fatal Stoke, Non-fatal Myocardial Infarction). eGFR cut off changed in response to the NIH/FDA scientific workshop on GFR decline as an endpoint for clinical trials in CKD and the current clinical landscape on decline in estimated glomerular filtration rate and subsequent risk of end stage renal disease and mortality. Change 3: For clarification
Section to be changed		**7.3.4 Interim analyses**
Description of the change		Interim analyses removed
Rationale for change		Based on observed event rates, the time interval between interim and final analyses is estimated to be around nine months. This time interval is too short to make meaningful differences to trial conduct, especially as the overall objective is to ensure adequate exposure to study drugs to characterise cardiovascular, renal and overall safety profile
Section to be changed		**7.6 Determination of sample size**
Description of change		Assuming the hazard over time in patients on linagliptin is the same as in patients on placebo (hazard ratio (HR): λ linagliptin/λ placebo =1), 625 patients with events will deliver an overall power of 90% in a test to demonstrate

		non-inferiority of linagliptin vs. placebo within the pre-specified non-inferiority (NI) margin of 1.3 for the HR; at the overall 1-sided α-level of 2.5% and with one interim analysis at α=1.0% after 70% of the events (calculated with East, version 5.4). Assuming a study duration of 3.8 years, recruitment within 3 years and a cumulative lost to follow-up rate of 2.0%, 4150 patients per group are required to achieve 625 patients with a primary endpoint *Was changed into:* Assuming the hazard over time in patients on linagliptin is the same as in patients on placebo (hazard ratio (HR): λ linagliptin/λ placebo =1), 611patients with events will deliver an overall power of 90% in a test to demonstrate non-inferiority of linagliptin vs. placebo within the pre-specified non-inferiority (NI) margin of 1.3 for the HR; at the overall 1-sided α-level of 2.5% (calculated with East, version 5.4)
Rationale for change		The change of the primary variable does not affect the required number of patients with event; the slight reduction from 625 to 611 patients is due to the elimination of the interim analysis. Since the event rate is higher than initially assumed the same power can be achieved within the originally planned timelines with a sample size of approximately 7000 patients.
Section to be changed		**8. Informed consent, data protection, trial records**
Description of change		Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File). *Was changed into:* The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.
Section to be changed		**9.2.Unpublished references**
Decsription of change		Author of IB omitted
Rationale for change		Change in authorship
Rationale for change		For clarification
Section to be changed		**10.3 Blood pressure measurement procedure**
Description of change		Change 1: …..If an electronic blood pressure device is used the pulse rate at time of the second blood pressure reading may be used. *Was changed into:* …..If an electronic blood pressure device is used the pulse rate at time of the second blood pressure reading

		should be used. In addition the following wording was added in the last paragraph: the mean value should be recorded in the eCRF.
Rationale for change		Change 1: For clarification
Section to be changed		**10.4 silent myocardial infarction**
Description of change		Definition of silent MI requires no preceding clinical history of MI (including stent thrombosis and other coronary events) and investigator reporting of silent MI
Rationale for change		Clarification added

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		23 Nov 2016 13:09 CET
Approval-Therapeutic Area		23 Nov 2016 13:24 CET
Approval-Team Member Medicine		23 Nov 2016 13:51 CET
Author-Trial Statistician		23 Nov 2016 14:14 CET
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