Clinical Trial Protocol

Doc. No.: c01618200-19

EudraCT No.:	2009-013157-15
BI Trial No.:	1218.74
BI Investigational Product(s):	Linagliptin
Title:	A multicentre, international, randomised, parallel group, double blind study to evaluate **Car**dio**vas**cular safety of **lina**gliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The **CAROLINA** Trial.
Clinical Phase:	III
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigators:	phone: fax: phone: fax:
Status:	Final Protocol
Version and Date:	Version 7, 20 April 2016

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product Not applicable			
Name of active ingredient: Linagliptin			
Protocol date: 17 August 2010	**Trial number:** 1218.74		**Revision date:** **20 April 2016**
Title of trial:	A multicentre, international, randomised, parallel group, double blind study to evaluate **Car**di**o**vascular safety of **lina**gliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The **CAROLINA** Trial.		
Co-ordinating Investigators:	*and:*		
Trial sites:	Approximately 700 study centres, on average 8 to 10 patients per site		
Clinical phase:	III		
Objectives:	The primary objective is to demonstrate non-inferiority (by means of comparing the upper limit of a two-sided (1-2*alpha)*100**%** confidence interval with the non-inferiority margin of 1.3) of treatment with linagliptin in comparison to glimepiride (as monotherapy or as add-on therapy) with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint (i.e. cardiovascular [CV] death, non-fatal stroke **or** non-fatal myocardial infarction [MI] (excluding silent MI) in patients with type 2 diabetes mellitus [T2DM]. If the non-inferiority hypothesis with margin 1.3 has revealed a significant result, then secondly, the primary composite endpoint will be tested with a superiority hypothesis. If the superiority test has revealed a significant result, then thirdly the first key secondary endpoint will be tested hierarchically with a superiority hypothesis. If the test of the first key secondary hypothesis has revealed a significant result, then fourthly the second key secondary endpoint will be tested hierarchically. If the test of the second key secondary hypothesis has revealed a significant result, then fifthly the third key secondary endpoint will be tested hierarchically. Other objectives are to compare HbA1c change from baseline, the incidence of hypoglycaemia, weight change, treatment sustainability [defined as the proportion of patients that are on study treatment at study end without need for rescue medication, that at Final Visit maintain glycaemic control ($HbA_{1c} \leq 7.0\%$)].		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product Not applicable			
Name of active ingredient: Linagliptin			
Protocol date: 17 August 2010	**Trial number:** 1218.74		**Revision date:** **20 April 2016**

Methodology:	This is a multicentre, multinational, randomised, double blind, parallel group, comparator-controlled study of linagliptin versus glimepiride as monotherapy or as add-on therapy.
No. of patients:	
total entered:	An estimated number of 6000 randomised patients to obtain a minimum of 631 primary endpoints.
each treatment:	An estimated number of 3000 randomised patients per treatment group.
Diagnosis :	T2DM
Inclusion criteria:	Documented diagnosis of T2DM and concurrently insufficient glycaemic control and a high risk of CV events prior to informed consent: • Insufficient glycaemic control (at Visit 1a) defined as: a) HbA_{1c} 6.5 - 8.5% (48 - 69 mmol/mol) while patient is treatment naïve **(**if intolerant or contra-indicated to first line anti-diabetic treatment) or treated with: - metformin monotherapy, or - alpha-glucosidase inhibitor monotherapy (e.g. acarbose, voglibose), or - metformin + alpha-glucosidase inhibitor, or b) HbA_{1c} 6.5 - 7.5% (48 - 58 mmol/mol) while patient is treated with - sulphonylurea (SU) monotherapy, or - glinide monotherapy (e.g. repaglinide, nateglinide), or - metformin + SU (combination maximal up to 5 years), or - metformin + glinide (combination maximal up to 5 years), or - alpha-glucosidase inhibitor + SU (combination maximal up to 5 years), or - alpha-glucosidase inhibitor + glinide (combination maximal up to 5 years)

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product Not applicable			
Name of active ingredient: Linagliptin			
Protocol date: 17 August 2010	**Trial number:** 1218.74		**Revision date:** **20 April 2016**

Inclusion criteria:

- High risk of CV events defined as any one (or more) of A), B), C) or D):

A) Previous Vascular Disease:

- Myocardial infarction (> 6 weeks prior to informed consent)
- Documented coronary artery disease (≥ 50% luminal diameter narrowing of left main coronary artery or ≥50% in at least two major coronary arteries in angiogram)
- Percutaneous Coronary Intervention (PCI) > 6 weeks prior informed consent
- Coronary Artery By-pass Grafting (CABG) > 4 years prior to informed consent or with recurrent angina pectoris following surgery
- Ischemic or hemorrhagic stroke (> 3 months prior to informed consent)
- Peripheral occlusive arterial disease (previous limb bypass surgery, stenting or percutaneous transluminal angioplasty; previous limb or foot amputation due to circulatory insufficiency, angiographic or ultrasound detected significant vessel stenosis (≥ 50%) of major limb arteries (common iliac-, internal iliac-, external iliac-, femoral- and/or popliteal artery), history of intermittent claudication with uni- or bilateral ankle: arm blood pressure ratio < 0.90).

B) Evidence of vascular related end-organ damage:

- Moderately impaired renal function (as defined by modified diet of renal disease (MDRD) formula) with estimated glomerular filtration rate [eGFR]) 30-59 mL/min/1.73 m^2
- Random spot urinary albumin creatinine ratio ≥ 30 µg/mg (≥ 3.4 mg/mmol) in two of three unrelated specimens in previous 12 months prior Visit 1a
- Proliferative retinopathy defined as retinal neovascularisation or previous retinal laser coagulation therapy.

C) Age ≥ 70 years (at Visit 1a)

D) At least two of the following CV risk factors:

- Type 2 diabetes mellitus duration > 10 years at Visit 1a.
- Current* systolic blood pressure (SBP) > 140 mmHg (or on at least one blood pressure lowering treatment at Visit 1a)
- Current daily cigarette smoking
- Current* LDL cholesterol ≥ 135 mg/dL (3.5 mmol/l) (or specific current treatment for this lipid abnormality at Visit 1a)

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product Not applicable			
Name of active ingredient: Linagliptin			
Protocol date: 17 August 2010	**Trial number:** 1218.74		**Revision date:** **20 April 2016**

Inclusion criteria:

* Current = Blood pressure or LDL cholesterol measurement < 6 months prior V1a.

- Body Mass Index (BMI) ≤ 45 kg/m2 at Visit 1b
- Age ≥ 40 and ≤ 85 years at Visit 1a
- Signed and dated written informed consent at the latest by the date of Visit 1a, in accordance with GCP and local legislation
- Stable anti-diabetic background medication (unchanged daily dose) for at least 8 weeks prior V1a and without short term use of insulin. Background medication should be stable during screening/run-in phase to allow randomisation

Treatment compliance in the placebo run-in should be between 80% and 120% to be eligible for randomisation.

Note: To ensure appropriate representation of patients from the different cardiovascular risk categories (A-D), the trial team will monitor the proportion of patients being recruited into these categories (trial level, and by region and/or country). In consultation with the steering committee, 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.

In consultation with the Steering Committee, enrolment of patients currently at least on SU or glinide may be limited.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product Not applicable			
Name of active ingredient: Linagliptin			
Protocol date: 17 August 2010	**Trial number:** 1218.74		**Revision date:** **20 April 2016**

Criteria for exclusion:

- Type 1 diabetes mellitus
- Any history and/or current treatment with other antidiabetic drugs (e.g. rosiglitazone, pioglitazone, GLP-1 analogue/agonists, DPP-IV inhibitors or any insulin) prior to informed consent. Note 1: This also includes clinical trials where these antidiabetic drugs have been provided to the patient. Note 2: Previous short term use of insulin (up to two consecutive weeks) is allowed (e.g. during hospitalisation) if taken at least 8 weeks prior informed consent
- Treatment with anti-obesity drugs within 3 months prior to informed consent
- Uncontrolled hyperglycaemia with a glucose level >240 mg/dl (>13.3 mmol/L) after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day)
- Any previous (or planned within next 12 months) bariatric surgery (open or laparascopic) or intervention (gastric sleeve)
- Current treatment with systemic corticosteroids at time of informed consent or pre-planned initiation of such therapy. Note: inhaled use of steroids (e.g. for asthma/COPD) is no exclusion criterion, as this does not cause systemic steroid action
- Change in dose of thyroid hormones within 6 weeks prior informed consent
- Active liver disease or impaired hepatic function, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at visit 1a
- Pre-planned coronary artery re-vascularisation (PCI, CABG) within next 6 months after V1a or any previous PCI and/or CABG ≤ 6 weeks prior informed consent
- Known hypersensitivity or allergy to the investigational product or its excipients, or glimepiride (or the SU class)
- Inappropriateness of glimepiride treatment for renal safety issues or other issues (e.g. allergy) according to local prescribing information
- Congestive heart failure of NYHA class III or IV
- Acute or chronic metabolic acidosis (present condition in patient history)
- Hereditary galactose intolerance
- Alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation
- Participation in another trial with an investigational drug given within 2 months prior to informed consent

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product Not applicable			
Name of active ingredient: Linagliptin			
Protocol date: 17 August 2010	**Trial number:** 1218.74		**Revision date:** **20 April 2016**

	• 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. • Patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, has a life expectancy less than 5 years for non-CV causes, or has 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 • Acute coronary syndrome ≤ 6 weeks prior to informed consent • Stroke or TIA ≤ 3 months prior to informed consent
Test product:	Linagliptin
dose:	5 mg once daily
mode of admin. :	Tablets per os
Comparator product:	Glimepiride
dose:	1-4 mg once daily
mode of admin. :	Tablets (overencapsulated) per os
Duration of treatment:	2 up to 4 weeks placebo run-in phase followed by up to an estimated 432 weeks treatment period and 30 days follow-up after study drug termination.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product Not applicable			
Name of active ingredient: Linagliptin			
Protocol date: 17 August 2010	**Trial number:** 1218.74		**Revision date:** **20 April 2016**

Criteria for efficacy:	1) Primary endpoint: time to first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal stroke or non-fatal MI (excluding silent MI) 2) First key secondary endpoint: time to first occurrence of any of the following adjudicated components of the composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal stroke, non-fatal MI (excluding silent MI) or hospitalisation for unstable angina pectoris. 3) Second key secondary endpoint: composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c ≤ 7.0%) without need for rescue medication (between end of titration [Visit 6] and Final Visit) and patients without any moderate/severe hypoglycaemic episodes (between Visit 6 and Final Visit) and without > 2% weight gain at Final Visit (between Visit 6 and Final Visit)). 4) Third key secondary endpoint: composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c ≤ 7.0%) without need for rescue medication (between Visit 6 and Final Visit) and patients without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))
Criteria for safety:	1) The occurrence of and time to each of the following adjudicated events: CV death (including fatal stroke and fatal MI), (non)- fatal MI, (non)- fatal stroke, hospitalisation for unstable angina pectoris, TIA, hospitalisation for congestive heart failure, hospitalisation for coronary revascularization procedures (CABG, PCI); and the occurrence of and time to silent myocardial infarction 2) Incidence and intensity of adverse events, physical examination, vital signs, ECG, change from baseline in laboratory parameters 3) Proportion of patients with serious and non-serious hypoglycaemic episodes 4) Change from baseline in weight and proportion of patients with ≤ 2% or > 2% weight gain (with or without rescue medication during maintenance phase) at Final Visit Refer to section 5.2 for a comprehensive list of safety criteria.
Statistical methods:	For the primary analysis a cox proportional hazards regression model of time to the first event with factor treatment will be conducted. The primary analysis will be performed on the full analysis set. The non-inferiority margin will be 1.3 and the hypotheses will be one-sided with an overall significance level of alpha=0.025. The first key secondary endpoint will be analysed with a cox proportional hazards regression model of time to the first event with factor treatment. The second and third key secondary endpoints will be analysed with Chi-Square test.

FLOW CHART

Trial Period	**Screening**	**Placebo run-in**	**Treatment phase (titration)**			
Visit	**1a**	**1b[A]**	**2**	**3**	**4**	**5**
Study week		**-4 / -2**	**0**	**4**	**8**	**12**
Days from randomisation	**-35/ -15**	**-28 / -14**	**0**	**28**	**56**	**84**
Time window (days)[J]				±7	±7	±7
Informed Consent	X					
In-/exclusion criteria	X	X	X[C]			
Medical History/ Concomitant diagnoses	X					
Demographics[o]	X	X				
Physical examination		X[M]				
Vital signs		X[M]	X	X	X	X
Height		X[I]				
Weight		X[I]	X			
Waist circumference		X	X			
12-lead-ECG			X[M]			
Diet and exercise counselling	X		X	X	X	X
Pregnancy Test[F]	X		X			
Fasted Home Blood Glucose Monitoring (HBGM)[G]		X	X[L]	X	X	X
Safety lab Tests (Urine and Blood)[H]	X		X			
Glomerular filtration rate[K]	X		X			

Flow Chart (continued)

Trial Period	**Screening**	**Placebo run-in**	**Treatment phase (titration)**			
Visit	**1a**	**1b[A]**	**2**	**3**	**4**	**5**
Study week		**-4 / -2**	**0**	**4**	**8**	**12**
Days from randomisation	**-35/ -15**	**-28 / -14**	**0**	**28**	**56**	**84**
Time window (days)[J]				**±7**	**±7**	**±7**
Fasting Plasma Glucose[B]		X	X	X	X	X
HbA_{1c}	X		X[C]			
PG sampling [E]			X			
Lipid profile			X			
Adverse events		X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X
Dispense placebo run-in medication (via IXRS)		X				
Randomisation (via IXRS)			X			
Dispense double-blind medication			X	X	X	X
Medication compliance check			X	X	X	X

Flow Chart (continued)

Trial Period	**Treatment phase (maintenance)**												
Visit	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Study week	**16**	**32**	**48**	**64**	**80**	**96**	**112**	**128**	**144**	**160**	**176**	**192**	**208**
Days from randomisation	**112**	**224**	**336**	**448**	**560**	**672**	**784**	**896**	**1008**	**1120**	**1232**	**1344**	**1456**
Time window (days)	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**
Physical examination	X			X			X			X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X			X			X			X			X
12-lead-ECG	X			X			X			X			X
Diet and exercise counselling	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[F]	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasted Home Blood Glucose Monitoring (HBGM)[G]										X[L]			
Safety lab Tests (Urine and Blood)	X	X	X	X	X	X	X	X	X	X	X	X	X
Glomerular filtration rate[K]	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Plasma Glucose[B]	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA_{1c}	X	X	X	X	X	X	X	X	X	X	X	X	X

Flow Chart (continued)

Lipid profile	X			X			X			X			X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense double-blind medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication compliance check	X	X	X	X	X	X	X	X	X	X	X	X	X

Flow Chart (continued)

Trial Period			**Treatment phase (maintenance)**												**F' up**
Visit	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32 EOT[N]**	**33**
Study week	**224**	**240**	**256**	**272**	**288**	**304**	**320**	**336**	**352**	**368**	**384**	**400**	**416**	**432**	**436**
Days from randomisation	**1568**	**1680**	**1792**	**1904**	**2016**	**2128**	**2240**	**2352**	**2464**	**2576**	**2688**	**2800**	**2912**	**3024**	**3054**
Time window (days)	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**+7**
Physical examination			X			X			X			X		X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist circumference			X			X			X			X		X	
12-lead-ECG			X			X			X			X		X	
Diet and exercise counselling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[F]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasted Home Blood Glucose Monitoring (HBGM)[G]														X[L]	
Safety lab Tests (Urine and Blood)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glomerular filtration rate[K]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Plasma Glucose[B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA_{1c}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Flow Chart (continued)

Trial Period			**Treatment phase (maintenance)**												**F' up**
Visit	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32 EOT^{N}**	**33**
Study week	**224**	**240**	**256**	**272**	**288**	**304**	**320**	**336**	**352**	**368**	**384**	**400**	**416**	**432**	**436**
Days from randomisation	**1568**	**1680**	**1792**	**1904**	**2016**	**2128**	**2240**	**2352**	**2464**	**2576**	**2688**	**2800**	**2912**	**3024**	**3054**
Time window (days)	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**+7**
Lipid profile			X			X			X			X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense double-blind medication	X	X	X	X	X	X	X	X	X	X	X	X	X		
Medication compliance check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

A Visit 1b to be performed within 1 week from Visit 1a

B Overnight fasting (10 hours no food and only water)

C HbA_{1c} measured at Visit 1a will be used for inclusion

F 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.

G Home blood glucose monitoring (HBGM) device provided at Visit 1b. The patient should be instructed to bring their HBGM device to the clinic at least at the specified visits for an additional measurement of fasted glucose.

H Visit 1a safety laboratory only includes ALT (SGPT), AST (SGOT), alkaline phosphatase, serum creatinine, urine analysis and urine albumin and creatinine, in addition to HbA1c and does not need to be collected in fasted state.

I Body Mass Index will be calculated automatically.

J Maximal time window between two visits during titration phase is 5 weeks and during maintenance phase 18 weeks.

K Calculated based on MDRD formula (see Section 5.2.3.4). This formula considers the race as an adjustment factor, therefore, the race must be known (and will be collected) for accurate estimation.

M 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 event. If such abnormalities already pre-exist prior study inclusion they should be considered as baseline conditions.

N The End of Treatment Visit (EOT) activities will be performed when a patient discontinues study medication treatment permanently. A follow-up visit will take place 30 days after the EOT visit. Patients who discontinue study drug prematurely should be observed until study end as if they were still receiving blinded study treatment, but no (safety) laboratory sampling (including pregnancy test), ECG or vital signs will be required. 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 and a telephone call at study end (through the patient or alternative person designated by the patient) will be asked for, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit should be recorded.

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. In case the patient is re-instituted on study treatment, the preferred dosage for glimepiride/glimepiride placebo is the dose used before stopping treatment (unless hypoglycaemia was the reason to temporarily stop treatment, see section 4.1.4). In case there is a need for further adjustments after this re-institution the guidance for treatment initiation should be followed.

O Race of patients will be collected because T2DM treatment results maybe race sensitive. Furthermore, the renal function will be assessed using the MDRD formula. This formula considers the race as an adjustment factor, therefore, the race must be known for accurate estimation.

TABLE OF CONTENTS

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alaline transaminase (SGPT)
ANCOVA	Analysis of covariance
AST	Aspartate transaminase (SGOT)
AT-II	Angiotensin II
BI	Boehringer Ingelheim
BMI	Body Mass Index (weight divided by height squared)
BP	Blood Pressure
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CEC	Clinical Event Committee
CI	Confidence Interval
CK	Creatinine Kinase
CK-MB	Creatinine Kinase isoenzyme
CML	Clinical Monitor Local
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CT	Computerized Tomography
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CTSU	Clinical Trial Supply Unit
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DPP-IV	Dipeptidyl-peptidase IV
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EASD	European Association for the Study of Diabetes
EOS	End Of Study
EOT	End Of Treatment
eGFR	Estimated Glomerular filtration Rate
EudraCT	European Clinical Trials Database
EU SmPc	European Summary of Product characteristics
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
HAs	Health Authorities
HbA_{1c}	Glycosylated haemoglobin
HBGM	Home Blood Glucose Monitoring
HDL-C	High Density Lipoprotein - Cholesterol
HR	Hazard Ratio
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent To Treat
IUD	IntraUterine Device
IUS	IntraUterine System
IXRS	Interactive Voice and Web-based Response System
LADA	Latent autoimmune diabetes of adults
LDL-C	Low Density Lipoprotein - Cholesterol
LOCF	Last Observational Carried Forward
LTFU	Lost To Follow Up
MACE	Major Adverse Cardiovascular Event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model Repeated Measures
MI	Myocardial infarction
MRI	Magnet Resonance Imaging
NGSP	National Glycohemoglobin Standardization Program
NPH	Neutral Protamine Hagedorn (insulin)
NYHA	New York Heart Association
OAD	Oral Antidiabetic Drug
OPU	Operative Unit
PCI	Percutaneous Coronary Intervention
PG	PharmaGenetic
p.o.	per os (oral)
PPS	Per Protocol Set
PR	Pulse rate
RDC	Remote Data Capture
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Steering Committee
SU	Sulfonylurea
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics

SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Trial Clinical Monitor
T2DM	Type 2 diabetes mellitus
TDMAP	Trial Data Management and Analysis Plan
TG	Triglyceride
TIA	Transient Ischemic Attack
TMT	Trail Making Test
TSAP	Trial Statistical Analysis Plan
UAP	Unstable Angina Pectoris
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper Limit of Normal

1. INTRODUCTION

Linagliptin is an orally available inhibitor of the enzyme dipeptidyl-peptidase IV (DPP-IV) facilitating a decrease of blood glucose levels in 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. The latter is primarily related to increased athero-thrombosis that leads to increased morbidity and premature mortality from cardiovascular (CV) disease [R10-0116, P08-06509]. Studies suggest that 70-75% of all deaths in people with diabetes can be attributed to CV complications [R10-0117]. Since hyperglycaemia in itself probably plays a causal role in this, strategies aiming at improving glycaemic control, could contribute in reducing complications and thereby also societies cost.

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 HbA_{1c} 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 $HbA_{1c} < 7.0\%$ [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 $< 6.5\%$ HbA_{1c} 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 its cautions against use in patients with impaired kidney function [P96-4362] where current product information documents include a 'boxed warning' or contraindication for metformin use if estimated glomerular filtration rate (eGFR) is below 60 mL/min/1.73 m^2 [R10-4375]. Besides this also acute diabetic ketoacidosis, acute conditions with the potential to alter renal function acute or chronic disease which may cause tissue hypoxia, hepatic insufficiency, acute alcohol intoxication and alcoholism, are contraindications against its use. In a UK population study (published in Diabetic Medicine 2001;18:483-488), Emslie-Smith et al found that 6.4% of all patients with T2DM had some of these contraindications against using

this drug. Further limitations of metformin is gastrointestinal (GI) side effects [R10-4375] that e.g. in the A Diabetes Outcome Prevention Trial (ADOPT) affected more than 1/3 of the participants [R09-6400]. However, despite these limitations, this compound is the most widely used and has a good safety profile and also has some degree of support for being cardio protective [R09-6405, R09-6409], or at least 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 T2DM, traditional insulin secretagogues such as the sulfonylureas (SUs) that stimulate to insulin secretion in a non-glucose-dependent manner is widely used; in fact it is the most used second line therapy. However, this treatment carries an increased risk for hypoglycaemia and weight gain [R09-6400] and, as for metformin, is also associated with a lack of sustainable effect [R09-6400]. Therefore, international treatment guidelines have opened for the 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 these drugs have also some side effects that limit their use, e.g. hypoglycaemia, weight gain, GI side effects and peripheral oedema. This could even also have prognostic implications since hypoglycaemia and weight gain was recently postulated as contributors to the adverse outcomes in the "Action to Control Cardiovascular Risk in Diabetes" (ACCORD) [R09-6407] and in the Veterans Affairs Diabetes trial (VADT) serious hypoglycaemia was the 2nd strongest predictor for developing a new myocardial infarction (MI) [R09-6408].

Since CV caveats with drugs to treat T2DM, historically also have been found to arise at relatively late stage; just before, or even after, the compound reached the market, regulating authorities such as the US Food and Drugs Administration (FDA) has issued some guidance to industry in order to rule out potential excessive morbidity and mortality potentially associated with all new drugs for the treatment of T2DM [R09-2151]. Such an assessment could involve dedicated trials. Having seen the potential limitations of drugs that are associated with weight gain and hypoglycaemia it is therefore of interest to explore novel treatment options that offer glycaemic reduction without associated such side effects.

Emerging treatment for T2DM; DPP- IV inhibitors

The incretin effect is a phenomenon where the glucose-dependent insulin secretion is augmented by intestinally derived peptides (i.e. incretins), which 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. Glucagon like peptide 1 (GLP-1) is an important member of the incretin hormone family and accounts, together with glucose-dependent insulinotropic peptide (GIP), for more than 50% of the incretin effect in humans [R09-6409]. These hormones are almost instantaneously inactivated by the enzyme DPP-IV. DPP-IV 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-IV inhibition has been proven as a therapy. Besides its stimulatory effects on insulin secretion, that depend on the actual 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, and, in animal models, to maintain long-term ß-cell function. Especially the maintenance of ß-cell function is of interest, that, if also would be the case in humans, would represent the first modulating therapy of the T2DM. However, no long term studies in human have actually confirmed this yet. An added interesting feature of this therapeutic option is that it seems to be associated with no weight gain and no hypoglycaemia (at least in monotherapy).

Study proposal

In this large-scale intervention trial we will test the impact of treatment with the DPP-IV inhibitor linagliptin head-to-head versus a SU (glimepiride) on CV safety and efficacy. The study will be given the acronym **CAROLINA** (**Car**d**io**vascular safety of **lina**gliptin).

1.2 DRUG PROFILE

The DPP-IV inhibitor compound linagliptin was discovered by Boehringer Ingelheim [BI] Pharma GmBH & Co. KG, Biberach, 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].

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 and relevant efficacy parameters (HbA_{1c}, fasting plasma glucose, treatment sustainability) of treatment with linagliptin in a relevant population of patients with T2DM and compare outcome against one compound of the second most used OAD class, i.e., SU (glimepiride). To date this has not been tested in a long-term trial; as also is the case for other DPP-IV inhibitors. However, there are currently no safety signals that indicate that linagliptin should be inferior to glimepiride in this respect. A recent meta-analysis of the marketed DPP-IV inhibitors on the contrary indicates a potential beneficial CV effect of DPP-IV inhibitors as a class; although this meta-analysis mainly included trials of shorter duration where trial participants were not at a particular high CV risk, leaving the findings as hypothesis generating [R09-6410].

Since most guidelines state that metformin should be first line treatment, this study will in principal be conducted as add-on to metformin background. Since a relatively large proportion of patients with T2DM have some degree of contraindications or intolerance to metformin, or local guidelines may indicate other treatments as first line therapy, the study is also open for inclusion of patients being treatment naïve or on other antidiabetic treatments as specified in Section 3.3.2. In brief, the patients included might be OAD naïve (due to contraindications or intolerant to first line treatment), previously receiving monotherapy with metformin, any SU, any glinide or any alpha-glucosidase inhibitor or previously on dual therapy with metformin + SU, metformin + glinide, metformin + alpha-glucosidase inhibitor, SU + alpha-glucosidase inhibitor or glinide + alpha-glucosidase inhibitor.

Hence, the study has two study arms: linagliptin or glimepiride as monotherapy or as add-on to other allowed treatments. The study design is described in more detail in Section 3.1.

Allowing this will generate a trial population with a short to moderate diabetes duration with a high CV risk (e.g., due to renal impairment, chronic cardiac disease or a recent MI, advanced age) to participate, thereby it will assess the CV safety profile of the drug as compared to one of the most widely used oral antidiabetic drug (OAD) globally (i.e. glimepiride) in a broad and relevant population of patients with T2DM. This study design therefore also concurs with the recent FDA guidelines for target population whom to in particular address CV risk of novel OADs in T2DM [R09-2151] and will also be an integral part of the ongoing CV safety assessment for linagliptin and data will also be used to support regulatory submission.

2.2 TRIAL OBJECTIVES

The primary objective is to demonstrate non-inferiority (by means of comparing the upper limit of a two-sided (1-2*alpha)*100% confidence interval with the non-inferiority margin of 1.3) of treatment with linagliptin in comparison to glimepiride (as monotherapy or as add-on therapy) with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint (i.e. cardiovascular death, non-fatal stroke or non-fatal myocardial infarction (excluding silent MI) in patients with type 2 diabetes mellitus. If the non-inferiority hypothesis with margin 1.3 has revealed a significant result, then secondly, the primary composite endpoint will be tested with a superiority hypothesis. If the superiority test has revealed a significant result, then thirdly the first key secondary endpoint of time to first occurrence of any of the adjudicated components of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction (excluding silent MI) or hospitalisation for unstable angina pectoris will be tested hierarchically with a superiority hypothesis. If the test of the first key secondary hypothesis has revealed a significant result, then fourthly the second key secondary endpoint will be tested hierarchically. If the test of the second key secondary hypothesis has revealed a significant result, then fifthly the third key secondary endpoint will be tested hierarchically.

Other objectives are to compare HbA_{1c} change from baseline, the incidence of hypoglycaemia, weight gain and treatment sustainability defined as the proportion of patients that are on study treatment at study end without need for rescue medication, that at Final Visit maintain glycaemic control (HbA1c $\leq$ 7.0%).

For a description of the endpoints chosen and statistical analyses to assess these objectives, please refer to Section 5 and 7.

2.3 BENEFIT - RISK ASSESSMENT

Potential general benefits for study participants in this trial (irrespective of investigational drug received, i.e. linagliptin or glimepiride) 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 during the study. Further, the participants can contribute to generate a potential future benefit for larger groups of patients with T2DM by participating in this clinical trial if linagliptin fulfils much of its promises as a future treatment of T2DM.

General risk associated with participating is 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

Glimepiride is a drug that has been on the market for a long time, is widely used and therefore is believed to be well characterized in term of risk profile. Patients randomised to glimepiride can nevertheless experience hypoglycaemia as a consequence of its mode of action. However, in a cohort of patients with T2DM of short-to-moderate duration this risk is relatively small as was seen in the UKPDS where yearly rate of severe hypoglycaemia was 1.0% for chlorpropamide (a first generation SU) and 1.4% with glibenclamide (a second generation SU) [R04-2173]. Also, there is a certain risk for patients to gain weight with this treatment; however not all trials with glimepiride has shown a weight increase [R09-6394].

Linagliptin from its clinical phase III testing has shown a "placebo-like" safety profile. It carries a low risk for inducing hypoglycaemia and weight gain. However, linagliptin has by far not the same cumulative exposure compared to glimepiride. 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, the very good tolerability seen 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 when compared to the potential benefits of a successful clinical development of linagliptin for patients with T2DM.

Pioglitazone, metformin, alpha-glucosidase inhibitor or basal insulin could be used in this trial as rescue therapy (see Section 4.2.1). Pioglitazone has been extensively tested and has been associated with CV benefits [R09-6395]. However, some side effects might occur with this drug; i.e. weight gain, peripheral oedema, osteopenia and heart failure. The latter is however relatively infrequent and occurs in those susceptible to this. In combination with SU also hypoglycaemia risk is increased.

Metformin might be used as rescue therapy; however BI expects that the proportion of patients that would be eligible for this would be low due to our inclusion criteria. However, metformin is associated with side effects as gastrointestinal discomfort, nausea and increases also the risk of hypoglycaemia.

An alpha-glucosidase inhibitor may also be used as rescue therapy to maintain glycaemic control; however BI expects that the proportion of patients that would accept this treatment predominantly would be in the Asian study population due to the higher usage of this drug in this region. Side-effect of alpha-glucosidase inhibitors includes gastrointestinal discomfort, diarrea, nausea and increases also the risk of hypoglycaemia, in particular if combined with SU.

Insulin might, as per all international guidelines, be expected required to certain patients as other OADs fail to control blood glucose levels adequately. Basal insulin (i.e. intermediate or long-acting insulin) is all widely used. Side effects of these are weight gain and hypoglycaemia. Some insulins also require need for re-suspension (at least NPH insulin) and they all need to be subcutaneously injected.

Pregnancy

Metformin, alpha-glucosidase inhibitors, glimepiride, pioglitazone, most of the long acting insulin analogues and linagliptin are not approved for use in pregnancy. In the embryofoetal and fertility studies in rats and rabbits with linagliptin, no effects on early embryonic development, mating, male and female fertility, and bearing live young were observed up to and including the high dose group given 240 mg/kg. Therefore, women who are of child-bearing potential will be included in this study provided that they are using adequate contraceptive methods.

Induced liver injury

Based on principal considerations, there is always the possibility that so fare unknown safety issues are upcoming. One of those issues is drug induced liver injury. Albeit there was no risk identified so far, this study will follow a careful protocol to follow-up laboratory alterations of liver parameters in order to safeguard patients' safety and to stay in compliance with international regulatory requirements. Although rare, drug induced liver injury is under constant surveillance by sponsors and regulators. This study requires follow-up and expedited reporting of laboratory alterations of selected liver laboratory parameters to ensure patient safety and to remain compliant with international regulations.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This multicentre, multinational, randomised, double-blind, parallel group, comparator -controlled study compares treatment with linagliptin (5 mg once daily) to treatment with glimepiride (1-4 mg) as monotherapy or as add-on therapy to metformin and/or other antidiabetic treatment as specified in Section 3.3.2.

The trial is event driven and will run with an estimated number of 6000 patients for an estimated treatment time of 432 weeks, beginning with the randomisation of the first patient. In the case the number of events is not or may not be reached within this period the trial duration and/or the number of patients enrolled will be increased until the defined number of adjudicated primary events is reached.

Patients will enter an open-label placebo (add-on) run-in period of 2 up to 4 weeks before randomisation. Patients who successfully complete at least two weeks of the placebo-run (should have a treatment compliance between 80% to 120%) and who still meet the inclusion/exclusion criteria will be randomised to receive either linagliptin or glimepiride. Patients who do not successfully complete at least two weeks of the placebo run-in, may continue the placebo run-in phase up to four weeks to meet the compliance criterion as specified above. Any SU or glinide will be discontinued at randomisation Visit 2 (SU/glinide should not be taken in the morning of Visit 2).

The randomised treatment will be double-blind within the dose groups of linagliptin and glimepiride (i.e. each patient will receive one active treatment and placebo matching the alternative active treatment in a double-dummy design).

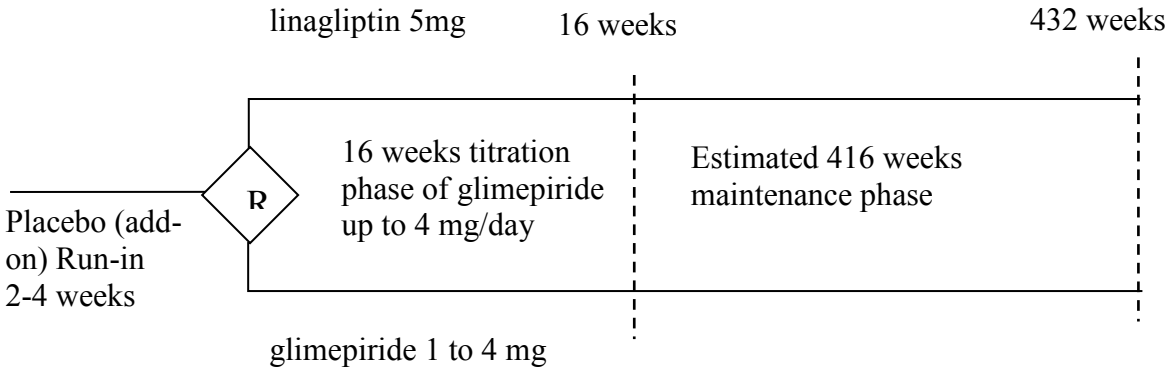

Figure 3.1: 1 Treatment periods and treatment groups in the trial design

For all patients, contacts are scheduled at regular time intervals (see flow chart). The estimated treatment duration for the first randomised patient is 432 weeks. The End of Treatment Visit (EOT) activities will be performed when a patient discontinues study medication permanently. Patients who discontinue study drug prematurely should be observed until study end as if they were still receiving blinded study treatment, but no (safety) laboratory sampling (including pregnancy test), ECG or vital signs will be required. 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 and a telephone call at study end will be asked for (through the patient or alternative person designated by the patient), to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit should be recorded.

All patients will have a follow up visit 30 days following completion of the treatment period. The follow-up visit may be performed as a phone visit for patients who completed the planned treatment period and who do not have any abnormalities at the EOT visit (only adverse events/outcome events and changes in concomitant therapy to be obtained).

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 631, 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 proposed time schedule, communicated via an investigator letter. A follow-up visit will take place 30 days after the EOT visit.

In case early study termination is to be performed (e.g. based on recommendation by the 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. The following committees will participate in the conduct of the trial, their specific functions are summarised below:

Steering Committee

A Steering Committee (SC) will have a scientific and clinical advisory function in the study. The Steering Committee is composed by university and sponsor based scientists with clinical and methodological expertise.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will review safety and efficacy data and make recommendations whether to continue the study, continue the study with modifications, or terminate the study. The DMC analyses and operations will be formally separated from the sponsor, the investigators and the steering committee.

Clinical Event Committees

The study is set up with prospective adjudication of all cardio/cerebrovascular pancreatic 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, a separate independent, blinded, external committee will be set up for adjudication of pancreatic events. The adjudication process for these events will be clarified in a separate CEC charter.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

According to current guidelines of the ADA/EASD, metformin should be initiated concurrently with lifestyle intervention at diagnosis in patients newly diagnosed with T2DM when HbA_{1c} > 7.0% and be titrated to a maximum tolerated dose (up to 2x 1000 mg/day or total 2500 mg/day) [R09-1164]. Therefore, patients enrolling on metformin monotherapy represent an important proportion of patients with T2DM. However, contraindications or intolerance to metformin due to e.g. congestive heart failure or severe renal impairment also constitutes a significant amount of people with T2DM. Further, local guidelines may indicate other first line treatment. Therefore this trial also allows for patients that are treatment naïve or are on other antidiabetic treatments as specified in Section 3.3.2.

Treatment with linagliptin is compared against glimepiride, a drug from the second most widely used antidiabetic class after metformin (i.e. SUs). Treatment goal for HbA_{1c} is in this trial, according to most international guidelines, ≤ 7.0%. During the trial additional therapy ("rescue therapy") is allowed, and encouraged, if HbA_{1c} > 7.5% during maintenance phase. This is considered important as to ensure that an optimal level of standard of care is reached. However, the decision to initiate rescue medication remains with the investigator and the appropriate local treatment guidelines.

The protocol also encourages the investigators to treat all other CV risk factors (lipid levels, blood pressure, micro/macroalbuminuria, unhealthy lifestyle, smoking) according to an optimal level of standard of care. In a high CV risk population this usually implies liberal use (if tolerated or not contraindicated) of statins, ACE-inhibitors, AT-II receptor blockers, aspirin, beta-blockers, calcium channel blockers, etc.). This should be conducted in the context of local or regional guidance for primary or secondary CV prevention.

The treatment period is planned for up to an estimated 432 weeks. The treatment period will be followed by a follow-up period of 30 days.

3.3 SELECTION OF TRIAL POPULATION

Approximately 10000 patients will be screened for the trial in about 45 countries. Approximately 700 trial centres will be participating to randomise the estimated number of 6000 patients.

Participating sites are expected to randomise a least 8 patients. Investigators who fail to randomise 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 recruited.

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 has been randomised to trial treatment. Investigators will be notified when the appropriate number of patients has been screened and screening is complete, and will not be allowed to recruit additional patients for this study. Patients who have completed Visit 1a procedures prior to notification of the termination of recruitment will be allowed to continue in the study, if they meet all entry criteria.

The check for 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. Conditions under therapy are always clinically relevant.

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

Re-screening and/or re-testing (of assessments) is permitted under certain circumstances. Whilst the information provided below is not an exhaustive list, it provides some guidance as to when such re-screening and/or re-testing would be considered appropriate. If a site is in any doubt as to whether re-screening and/or re-testing is appropriate in their particular situation, then clarification should be sought with the CML.

Re-testing:
Re-testing is only to be performed for a lab result which is obviously received beyond stability at the central laboratory or thought to be a spurious result. It is not permitted to perform re-testing (in any time window after V1a sampling) for HbA_{1c} when it does not meet the study criteria only.

Re-screening:
- Re-screening of the same patient is only allowed once.
- The patient should be declared a screening failure in the eCRF/RDC with their original patient number.
- Upon re-screening, the next available (= new) patient number should be selected from RDC.
- The patient must be re-consented using the current approved version of the information sheet and consent form.
- There is no time limit for re-screening – as long as the patient fits the eligibility criteria they could be re-screened whenever the investigator feels they may become eligible.

3.3.1 Main diagnosis for study entry

Patients with documented diagnosis of T2DM with insufficient glycaemic control and at high risk of CV events prior to informed consent can be enrolled in the study. Any antidiabetic background medication at Visit 1a should be on a stable (unchanged) daily dose for at least 8 weeks. There is no short term use of insulin within 8 weeks prior informed consent. Background medication should be stable during screening/run-in phase to allow randomisation.

As local guidelines for management of T2DM will be followed, treatment naive T2DM patients should be offered first line anti-diabetic treatment (e.g. metformin) before allowing them for study inclusion, unless they have specific contra-indications or intolerances to its use (see also Section 2.1).

Prior SU or glinide treatment will be discontinued at Visit 2, whereas if medications such as metformin and alpha-glucosidase inhibitor are being used, these should be continued.

3.3.2 Inclusion criteria

1) Documented diagnosis of T2DM and concurrently 2) insufficient glycaemic control and a high risk of CV events 3) prior to informed consent.

2) Insufficient glycaemic control (at Visit 1a) defined as:

   a) HbA_{1c} 6.5 - 8.5% (48 - 69 mmol/mol) while patient is treatment naïve (if intolerant or contra-indicated to first line anti-diabetic treatment) or treated with:

   - metformin monotherapy, or
   - alpha-glucosidase inhibitor monotherapy (e.g. acarbose, voglibose), or
   - metformin + alpha-glucosidase inhibitor (e.g. acarbose, voglibose), or

   b) HbA_{1c} 6.5 - 7.5% (48 - 58 mmol/mol) while patient is treated with
   - sulphonylurea (SU) monotherapy, or
   - glinide monotherapy (e.g. repaglinide, nateglinide), or
   - metformin + SU (combination maximal up to 5 years), or
   - metformin + glinide (combination maximal up to 5 years), or
   - sulphonylurea + alpha-glucosidase inhibitor (combination maximal up to 5 years), or
   - glinide + alpha-glucosidase inhibitor (combination maximal up to 5 years)

3) High risk of CV events defined as any one (or more) of A), B), C) or D):

   A) Previous Vascular Disease:
   - Myocardial infarction (> 6 weeks prior to informed consent)

- Documented coronary artery disease (≥ 50% luminal diameter narrowing of left main coronary artery or ≥ 50% in at least two major coronary arteries in angiogram) Note: CT or MRI detection of this will not suffice for inclusion; only invasive angiography. The left main coronary artery is often abbreviated to LCA or LCMA. As this is a very important artery that is branched to other major arteries it suffices to have a ≥ 50% stenosis in this artery (any segment) for inclusion. If there are no stenosis in this artery patient could be included if patient has a ≥ 50% stenosis in two, or more, of the other major coronary arteries (any segment): LAD (Left Anterior Descending; also called AIB = Anterior interventricular branch), CX (= art. Circumflex, also called CB=Circumflex branch) or RCA (right coronary artery).
- Percutaneous Coronary Intervention (PCI) > 6 weeks prior informed consent
- Coronary Artery By-pass Grafting (CABG) > 4 years prior to informed consent or with recurrent angina following surgery
- Ischemic or hemorrhagic stroke (> 3 months prior to informed consent)
- Peripheral occlusive arterial disease (previous limb bypass surgery, stenting or percutaneous transluminal angioplasty; previous limb or foot amputation due to circulatory insufficiency, angiographic or ultrasound detected significant vessel stenosis (> 50%) of major limb arteries (common iliac artery, internal iliac artery, external iliac artery, femoral artery, popliteal artery), history of intermittent claudication, with an ankle: arm blood pressure ratio < 0.90 on at least one side).

B) Evidence of vascular related end-organ damage:

- Moderately impaired renal function (as defined by modified diet of renal disease (MDRD) formula) with estimated glomerular filtration rate [eGFRF]) 30-59 mL/min/1.73 m^2
- Random spot urinary albumin: creatinine ratio ≥ 30 µg/mg (≥ 3.4 mg/mmol) in two of three unrelated specimens in previous 12 months prior Visit 1a
- Proliferative retinopathy defined as retinal neovascularisation or previous retinal laser coagulation therapy.

C) Age ≥ 70 years (at Visit 1a)

D) At least two of the following CV risk factors:

- Type 2 diabetes mellitus duration > 10 years at Visit 1a.
- Current* systolic blood pressure (SBP) > 140 mmHg (or on at least one blood pressure lowering treatment at Visit 1a)
- Current daily cigarette smoking
- Current* LDL cholesterol ≥ 135 mg/dL (3.5 mmol/L) (or specific current treatment for this lipid abnormality at Visit 1a).

* Current = Blood pressure or LDL cholesterol measurement < 6 months prior V1a.

Note: To ensure appropriate representation of patients from the different cardiovascular risk categories (A-D), the trial team will monitor the proportion of patients being recruited into these categories (trial level, and by region and/or country). In consultation with the steering committee, 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.

If a patient fulfils more than one CV risk category all CV risk categories will be indicated in the CRF. For CV risk distribution the patient will be allocated to highest CV risk category. CV risk category A is relatively highest category, followed by B, C, D.

Examples: if patient is at age of 71 years and has T2DM > 10 years and is currently smoking, this patient will be allocated to category C.

A patient with vascular end-organ damage and previous stroke will be allocated to category A.

Patients may be included if any criterion A – D is fulfilled as long as it is not in conflict with any other exclusion criteria. Example: a patient at age 73 years may be included [fulfils criterion C] in case CABG was conducted two years ago.

If a patient fulfils CV risk category A, C and/or D and has only one albumin creatinine ratio ≥ 30 µg/mg in previous 12 months prior Visit 1a, and an albumin creatinine ratio ≥ 30 µg/mg at V1a, such patient will also be identified as Cat. B patient in the CRF. The patient will be allocated to highest CV risk group for (A or B).

In consultation with the Steering Committee, enrolment of patients currently at least on SU or glinide may be limited.

4) Body Mass Index (BMI) ≤ 45 kg/m^2 at Visit 1b.

5) Age ≥ 40 and ≤ 85 years at Visit 1a

6) Signed and dated written informed consent at the latest by the date of Visit 1a, in accordance with GCP and local legislation

7) Stable anti-diabetic background medication (unchanged daily dose) for at least 8 weeks prior V1a and without short term use of insulin. Background medication should be stable during screening/run-in phase to allow randomisation.

3.3.3 Exclusion criteria

1) Type 1 diabetes mellitus

2) Any history and/or current treatment with other antidiabetic drugs (e.g. rosiglitazone, pioglitazone, GLP-1 analogue/agonists, DPP-IV inhibitors or any insulin) prior to informed consent.
   Note 1: This also includes clinical trials where these antidiabetic drugs have been provided to the patient. Note 2: Previous short term use of any insulin (up to two consecutive weeks) is allowed (e.g. during hospitalisation) if taken at least 8 weeks prior informed consent

3) Treatment with anti-obesity drugs 3 months prior to informed consent

4) Uncontrolled hyperglycaemia with a glucose level >240 mg/dl (>13.3 mmol/L) after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day).

5) Active liver disease or impaired hepatic function, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at Visit 1a.

6) Any previous (or planned within next 12 months) bariatric surgery (open or laparascopic) or intervention (gastric sleeve)

7) Pre-planned coronary artery re-vascularisation (PCI, CABG) within next 6 months after V1a or any previous PCI and/or CABG ≤ 6 weeks prior informed consent

8) Known hypersensitivity or allergy to the investigational product or its excipients, or glimepiride (or the SU class).

9) Inappropriateness of glimepiride treatment for renal safety issues or other issues (e.g. allergy) according to local prescribing information

10) Congestive heart failure of NYHA class III or IV

11) Acute or chronic metabolic acidosis (present condition in patient history)

12) Hereditary galactose intolerance

13) Alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation

14) Current treatment with systemic corticosteroids at time of informed consent or pre-planned initiation of such therapy. Note: inhaled use of steroids (e.g. for

asthma/COPD) is no exclusion criterion, as this does not cause systemic steroid action.

15) Change in dose of thyroid hormones within 6 weeks prior informed consent

16) Participation in another trial with an investigational drug given within 2 months prior to informed consent

17) 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.

18) Patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, has a life expectancy less than 5 years for non-CV causes, or has 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

19) Acute coronary syndrome ≤ 6 weeks prior to informed consent

20) Stroke or TIA ≤ 3 months prior to informed consent

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 prematurely discontinue study drug should remain in the study and should be observed until study end, preferably at the study time points as pointed out in the Flow Chart.

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 (through the patient or alternative person designated by the patient) will be required, to document the occurrence of outcome events and vital status. If possible, also 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 who prematurely discontinue study medication 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 could 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 determined by investigator as necessary for patient safety, new antidiabetic medication regimen can be started immediately after discontinuation of study treatment and must be recorded in the eCRF (see further details in Section 4.2).

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 otherwise termination of the pregnancy (see further details in Section 5.2.2.2)

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

Patients who drop out during the screening/run-in phase prior to randomisation (Visit 2) will be considered a screening failure. They have to be recorded as screening failure in eCRFs and no further follow-up is required.

Patients who withdraw or discontinue from the study after randomisation will not be replaced.

If a patient needs to take concomitant drugs that interfere with the investigational product (or other study medications) or in the occurrence of hypoglycaemia that may put the patient at risk with continued participation (e.g. repeated hypoglycaemic episodes) the trial medication can be discontinued temporarily, or if needed permanently. Since this is an outcome study, the primary analysis will be performed based on all randomised patients who were treated with at least one dose of study drug. Therefore investigators are encouraged to re-administer study medication to a randomised patient if there are no further safety concerns.

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 must be involved in the discussions with the patient regarding a withdrawal of consent.

If the patient withdrew informed consent the patient should stop taking study medication and should be asked to complete the study ending tests and procedures as described in the Flow Chart for End of Treatment Visit and Visit 33 (Follow up visit). Completing these procedures is strongly recommended for the patient's safety. The

reason for discontinuing treatment will be recorded in the eCRF. The data will be included in the trial database and will be reported.

For patients that have withdrawn informed consent, the patient will be asked to resign an informed consent form, which will allow to enquire at least about the patient's vital status and occurred outcome events through contacts to relatives, acquaintances, family physicians, hospital records, etc.

If patients who discontinue from treatment after randomisation could not be followed-up until the end of study (i.e. at least the vital status could not be collected) those patients will be indicated as Lost To Follow Up (LTFU). The number of LTFU patients should be limited.

The End of Treatment Visit (EOT) activities will be performed when a patient discontinues study treatment permanently.

A follow-up visit will take place 30 days after the EOT visit. Patients who discontinue study drug prematurely should be observed until study end as if they were still receiving blinded study treatment, but no (safety) laboratory sampling (including pregnancy test), ECG or vital signs will be required. 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 and a telephone call at study end will be 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 be recorded.

Patients should keep their antidiabetic medication stable for the course of the trial (except prior SU or glinide treatment which should be stopped at V2. SU/glinide should not be taken in the morning of Visit 2).

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim 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 GCP, the 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 investigational product(s)

The characteristics of the test product are below.

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

The characteristics of the reference product are below.

Substance:	glimepiride 1 mg (Amaryl® 1 mg)
Pharmaceutical form:	tablet (overencapsulated)
Source:	Sanofi-Aventis
Unit Strength:	1 mg
Route of administration:	p.o., once daily

Substance:	glimepiride 2 mg (Amaryl® 2 mg)
Pharmaceutical form:	tablet (overencapsulated)
Source:	Sanofi-Aventis
Unit Strength:	2 mg
Route of administration:	p.o., once daily

Substance:	glimepiride 3 mg (Amaryl® 3 mg)
Pharmaceutical form:	tablet (overencapsulated)
Source:	Sanofi-Aventis
Unit Strength:	3 mg
Route of administration:	p.o., once daily

Substance:	glimepiride 4 mg (Amaryl® 4 mg)
Pharmaceutical form:	tablet (overencapsulated)
Source:	Sanofi-Aventis
Unit Strength:	4 mg
Route of administration:	p.o., once daily

Substance:	Placebo matching glimepiride (Amaryl® 1-4 mg)
Pharmaceutical form:	tablet (overencapsulated)
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

Patients who meet the trial entry criteria at the end of the 2-4 weeks placebo run-in phase will be randomly assigned to linagliptin 5 mg or glimepiride in a balanced ratio (see Section 7.5). Patient assignment to the treatment groups will be determined by a computer generated random sequence using an interactive voice and web-based response system (IXRS). To facilitate the use of IXRS, each study site will receive an information manual describing the steps to randomise a patient, to obtain a medication kit assignment and to acknowledge receipt of study medication.

The assigned medication number will be entered in the eCRF, and the corresponding medication kit should be given to the patient. Using this procedure, the investigator will not know to which treatment group the next patient will belong.

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 (please refer to the actual version of the Investigator's Brochure [U04-1767]) and represents the marketed dose for linagliptin.

4.1.4 Drug assignment and administration of doses for each patient

Following the screening period and the placebo run-in period, patients who qualify will be randomised (Visit 2) to one of the dosage and treatment schedules outlined in Table 4.1.4: 1 below. Medication will be dispensed in a double-blind and double-dummy manner as either 5 mg linagliptin (plus glimepiride placebo) or an initial dose of 1 mg /day of glimepiride (plus linagliptin placebo). IXRS will allocate medication kit numbers at each scheduled in-clinic visit (V2 – 31). At visits 2-5 patients will receive one treatment box, sufficient for 4 weeks treatment (plus 1 week reserve). At visits 6- 31 patients will receive one treatment box, sufficient for 16 weeks (plus two weeks reserve) of treatment.

After the starting dose of 1 mg/day, glimepiride/ glimepiride placebo has to be uptitrated in 4 week intervals during the first 16 weeks of treatment to the next dose to a potential maximum dose of 4 mg/day, if the fasted HBGM values are > 110 mg/dl (6.1 mmol/l) at the day of visit 3, 4 and 5 (in-clinic HBGM measurement at the day of the visit), unless the investigator considers that it would place the patient at an increased risk for hypoglycaemia. The average HBGM value of previous recent fasting HBGM measurements prior to the day of visit (from the patient's HBGM diary) could also be used to guide uptitration at the discretion of the investigator, if there is a meaningful discrepancy between the single fasted HBGM value at the day of the visit in the clinic and this average HBGM value.

Patients on previous glimepiride may continue on their previous glimepiride dose up to Visit 2 (SU/glinide should not be taken in the morning of Visit 2). These patients will start the glimepiride/glimepiride placebo at their pre-trial glimepiride dose. If prior glimepiride dose was ≥ 4 mg/day, the patient will start the glimepiride/ glimepiride placebo in the randomisation phase at a dose of 4 mg/day combined with 5 mg /day linagliptin/ linagliptin placebo. Patients on a previous SU, that is not glimepiride, or glinide should start glimepiride /glimepiride placebo at Visit 2 at a starting dose of 1 mg/day combined with 5 mg/day linagliptin/ linagliptin placebo.

The patients will be instructed to bring their HBGM devices to a visit for an additional measurement of fasted glucose during the titration phase, and if required, during maintenance phase (see flow chart).

HBGM measurements at visits during Titration Phase are mandatory to efficaciously uptitrate dosing of the glimepiride/glimepiride placebo.

Uptitration of glimepiride/glimepiride placebo may occur at (un)scheduled visits during the maintenance phase in case of deterioration of glucose control to the next dose to a potential maximum of 4 mg/day (glimepiride or placebo) combined with 5 mg/day linagliptin/ linagliptin placebo (with at least a dose interval of 4 weeks), provided fasted and confirmed HBGM values are > 110 mg/dl (6.1 mmol/L).

At any time during the study, the glimepiride/glimepiride placebo can be down titrated to prevent recurrent hypoglycaemic events.

Glimepiride/glimepiride placebo may be uptitrated again to the next dose (in case it was down titrated due to hypoglycaemia) to the potential maximum dose of 4 mg/day with 5 mg/day linagliptin/ linagliptin placebo.

Table 4.1.4: 1 Linagliptin and glimepiride oral administration per dose group and day

Dose group	Tablet	**Capsule (overencapsulated tablet)**
(For run-in phase only) Placebo	Placebo tablet matching to linagliptin	Placebo capsule matching to glimepiride
(For treatment phase only) linagliptin 5 mg	5 mg tablet	Placebo capsule matching to glimepiride
glimepiride 1 mg	Placebo matching to linagliptin 5 mg tablet	1 mg capsule
glimepiride 2 mg	Placebo matching to linagliptin 5 mg tablet	2 mg capsule
glimepiride 3 mg	Placebo matching to linagliptin 5 mg tablet	3 mg capsule
glimepiride 4 mg	Placebo matching to linagliptin 5 mg tablet	4 mg capsule

If applicable, patients will continue with their standard metformin therapy (preferably ≥ 1500 mg daily) 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 discontinued according to local guidelines (see also Section 4.2.2.1). The above principle also applies for patients being included on a background of alpha-glucosidase inhibitor.

During the maintenance phase it is investigator's judgement to change the glimepiride/glimepiride placebo and/or background medication dose. Rescue medication could also be initiated provided protocol criteria are met (see section 4.2.1)

Administration of the study medication is once daily. Patients should be instructed to take their trial medication once daily with 150 mL of 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 should be taken shortly before or during a meal.

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. In case the patient is re-instituted on study treatment, the preferred dosage for glimepiride/glimepiride placebo is the dose used before stopping treatment (unless hypoglycaemia was the reason to temporarily stop treatment). In case there is a need for further adjustments after this re-institution the guidance for treatment initiation should be followed.

Patients should be instructed 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, ideally on the following day. Background and/or rescue medication will be taken as prescribed including visit days.

Patient visits should be routinely scheduled in the morning (preferably between 7:00 AM and 11:00 AM), 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.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

After randomisation at Visit 2, neither the patients nor the investigators or sponsor will be aware of the treatment allocation.

Patients assigned to one of the double-blind treatments will take 1 tablet and 1 capsule daily, either:

- One 5 mg tablet of linagliptin plus one inactive placebo capsule (overcapsulated tablet) matching glimepiride

- One 1 mg or 2 mg or 3 mg or 4 mg glimepiride capsule (overencapsulated tablet) plus one inactive placebo tablet matching linagliptin.

The placebo tablets and capsules will be identical in appearance to the respective active treatments.

At any time during the study, glimepiride/glimepiride placebo can be down titrated to prevent recurrent hypoglycaemic events. Glimepiride/ glimepiride placebo dose adjustments can be done through IXRS in a blinded manner.

4.1.5.2 Procedures for emergency unblinding

In the event of a medical emergency which requires identification of an individual patient's treatment, investigators will be able to access this information via IXRS. The local Clinical 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. A 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, Biberach, Germany. All study medication will be contained in medication boxes identified with the trial number and medication number. Each medication box will contain an appropriate amount of BI linagliptin tablets or glimepiride capsules, plus some reserve, for dosing until the next scheduled visit.

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

Examples of the labels will be available in the Investigator's Site File (ISF)

4.1.7 Storage conditions

All trial medication should be stored at room temperature (not above 25 ºC) in the original containers. Patients should be instructed not to remove the trial medication from the blisters/wallets 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 site. If the storage conditions are found to be outside the specified range, the CML, IXRS and the BI 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 and/or appointed CRO, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Throughout the trial, drug receipt, usage, and return must be documented by the site and verified by the CRA, any discrepancies in drug supplies will be noted and explained. All unused medication including blisters/wallets and patient boxes (empty or filled) must be returned to the sponsor.

The investigator, pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor 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 IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the 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
- if applicable availability of the proof of a medical licence for the principal investigator
- *for USA only: availability of the 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 and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor and/or appointed CRO, 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.

This text is only applicable to Japan:

The Investigator / pharmacist / investigational drug storage manager should return the unused and collected investigational drugs (including the empty containers) 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 container (excluding empty containers) 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 and other relevant trial staff members remain blinded to the patient's name on the package (container or label) of the investigational drugs.

Upon completion of the trial, the Investigator / pharmacist / investigational drug storage manager will submit to the Sponsor 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 and other relevant trial staff members remain blind to the patient's name.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

The use of rescue medication will be permitted in this trial, and will be limited to pioglitazone, metformin, alpha-glucosidase inhibitor or basal insulin (i.e. intermediate or long-acting insulin such as insulin glargine, insulin determir, neutral protamine hagedorn [NPH] insulin) including during the FU period.

In specific situations (e.g. during hospitalisation) short-acting insulin may be given as rescue medication for up to two weeks in combination with the study medication.

The dose of rescue medication will be according to local labelling at the investigator's discretion. Rescue medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations. Particular rescue medication may not be available in countries (e.g. pioglitazone).

The use of rescue medication in case of hyperglycaemia will be permitted during the randomised treatment period of the trial only and only if one or more of the following criteria have met:

- During the titration phase (Visit 2 to Visit 6): The patient has a glucose level >240 mg/dl (>13.3 mmol/L) after an overnight fast.
- During the maintenance phase (Visit 6 to Final Visit): The patient has a glucose level >180 mg/dl (>10.0 mmol/L) after an overnight fast
- During the maintenance phase (Visit 6 to Final Visit): the patient has an HbA_{1c} > 7.5% (58 mmol/mol)

The above results for fasting plasma glucose, which could be obtained from the HBGM device, should be confirmed, meaning that there is a minimum of two measurements, at least one of which should be performed after an overnight fast at the investigational site, and on a different day to the initial measurement.

In the case of repeated symptomatic hypoglycaemia or severe hypoglycaemia (criteria see Section 5.2.2.1.); appropriate adjustment of oral antidiabetic therapy like dose reduction of metformin, alpha-glucosidase inhibitor, rescue therapy or study medication should be initiated.

The use of rescue medication 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 rescue medication than the protocol defined rescue therapy should discontinue study treatment when the combined use of the study treatment and this rescue medication is contraindicated, but will remain in the trial.

Any additional treatment, that does not qualify as a rescue medication, 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.

All concomitant (additional) and/or rescue medication 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 antidiabetic agents (next to background therapy and any rescue therapy) such as other oral agents, short-acting insulin* or injectable GLP-1 analogue/agonists will be prohibited during the course of the study.

*Short acting insulin may be given as rescue medication for up to two weeks (e.g. during hospitalisation).

Additionally treatment with anti-obesity drugs is prohibited.

In case metformin is used as background therapy and participants are in need for intravascular administration of iodine containing contrast agents: metformin is allowed to be discontinued according to local practice; usually before administration and 48 hours afterwards.

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 dose can be reduced, or the study medication can be discontinued temporarily, or if needed permanently (see also Section 3.3.4.1).

4.2.2.2 Restrictions on diet and life style

No restrictions given; all patients should be provided healthy lifestyle advice at baseline and also have this reinforced during the trial. Available educational material (e.g. from national diabetes associations or national health authorities) relevant for the country/region could be supplied by the site.

4.3 TREATMENT COMPLIANCE

Patients will be asked to bring all trial medication (with or without any remaining tablets/capsules) with them to each trial Visit. The tablets/capsules will be counted by the investigator or his/her designate and compliance will be calculated. Compliance will be calculated according to the formula:

$$\text{Compliance } (\%) = \frac{\text{Nr. of tablets/capsules actually taken since last tablet/capsule count}}{\text{Nr. of tablets/caps. which should have been taken in the same period}} \times 100\,\%$$

Compliance during the open-label placebo run-in phase should be between 80% and 120%. If compliance is outside this range, the patient should be carefully interviewed and, if necessary, re-informed about the purpose and the conduct of the trial. Investigator may extend the placebo-run phase up to four weeks to meet this compliance requirement. Unreliable patients should be withdrawn from the study before randomisation at the discretion of the investigator.

Compliance during the randomised treatment phase should also be between 80% and 120%. Severe violation of treatment compliance is defined as an important protocol violation and will lead to the exclusion from the per protocol set (PPS).

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 adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) or non-fatal stroke

The key secondary efficacy endpoints are:

- time to the first occurrence of any of the following adjudicated components of CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris
- composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control ($HbA_{1c} \leq 7.0\%$) without need for rescue medication (between end of titration [Visit 6] and Final Visit) and patients without any moderate/severe hypoglycaemic episodes (between Visit 6 and Final Visit) and without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))
- composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control ($HbA_{1c} \leq 7.0\%$) without need for rescue medication (between Visit 6 and Final Visit) and patients without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))

Whereas moderate/severe hypoglycaemic episodes are defined as:

- Moderate hypoglycaemic event: documented symptomatic hypoglycaemia with plasma glucose concentration ≤ 70 mg/dL. Event accompanied by typical symptoms of hypoglycaemia but no need for external assistance

- Severe hypoglycaemic event: documented hypoglycaemic episode requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions need for external assistance

Additionally secondary efficacy endpoints are the change from baseline of HbA_{1c}, FPG, proportion of patients that at Final Visit maintain glycaemic control without need for rescue medication (between end of titration [Visit 6] and Final Visit) to obtain $HbA_{1c} \leq 7.0\%$ or that obtain $HbA_{1c} \leq 7.0\%$ overall (see Section 7.1).

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 Investigator's Site File (Lab manual).

FPG:

Blood samples for the determination of FPG will be taken according to the Flow Chart after an overnight fast (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 at a central laboratory using validated assays. Further details about sample handling and shipment can be found in the Investigator Site File (Lab manual).

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Secondary and tertiary CV endpoints are described in Section 7.

In addition, 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, cardiovascular outcome events that occur after randomisation and represent a 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.

Cardiovascular outcome events are defined as the following components of the primary, secondary and tertiary cardiovascular endpoints:

- cardiovascular death
- non fatal myocardial infarction
- silent myocardial infarction
- non fatal stroke (ischemic/hemorrhagic/etiology unknown)
- hospitalisation for unstable angina
- heart failure requiring hospitalisation
- transient ischemic attack (TIA)
- coronary revascularisation procedures (PCI and CABG)

For definitions of the cardiovascular outcome events see Appendix 10.2.

The investigator must document immediately (within 24 hours or the next business day whichever is shorter) the outcome events on the appropriate eCRF page in the RDC.

In case of a stroke the disability or dependence in the daily activities will be collected with the grade of modified Rankin Scale (mRS) at day 7 or at hospital discharge (if duration of hospitalization is < 7 days) and 3-6 months after stroke onset.

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 unfavorable 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.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which 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 which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

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) which 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 a 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 linagliptin, active comparator glimepiride and placebo.

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 including blood pressure, pulse rate, ECG*, physical examination, and laboratory tests results will be recorded as (S)AEs in the eCRF if they are judged clinically relevant by the investigator.

* Changes in the ECG indicating silent MI should be reported as cardiovascular outcome event (see also Section 10.5).

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 study inclusion they should be considered as baseline conditions.

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 ≤ 70 mg/dl (3.9 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 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 (or less than 54 mg/dL) and all asymptomatic hypoglycaemic

events that are considered as adverse events by the investigator have to be recorded as an adverse event.

Adverse Events of Special Interest (AESI)

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 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 ISF)
- Pancreatic cancer

Hepatic injury is defined by the following alterations of liver parameters: for patients with normal liver function at baseline: 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 draw sample. Patients showing these lab abnormalities need to be followed up according to Section 10.6 of this clinical trial protocol and the "DILI checklist" provided in ISF.

Hepatic events:
If AST and/or ALT are increased ≥ 3 x ULN, follow-up laboratory tests of ALT, AST, total bilirubin (with differentiation of bilirubin in direct and indirect if total bilirubin is elevated) and additionally alkaline phosphates (ALP), CK (CK-MB if CK is elevated), amylase, lipase and INR must be initiated as soon as possible (ideally within 48 to 72 hours of the pathologic test result). Further follow-up investigations shall be initiated depending on the clinical course until the patient is recovered and/or a diagnosis was made. See for further details Section 10.6.2.

Laboratory Criteria for "Potential Hy's Law case":

1. AST and/or ALT > 3 x ULN and
2. Total bilirubin > 2 x ULN and
3. ALP < 2 x ULN

Renal events:
If creatinine shows a ≥ 2-fold increase from baseline, the investigator should make arrangements for follow-up blood samples(s) to be collected for repeat analysis of creatinine.

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.

Skin lesions:

If skin lesions (such as exfoliative rash, skin necrosis, or bullous dermatitis - see further detailed list in ISF): 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.

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 such a suspected or diagnosed protocol specific AESI. AESIs once identified by the investigator must be reported on a SAE form in an expedited manner similar to SAEs, even if they do not meet any of the SAE seriousness criteria.

These additional searches (summarised 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/Remote Data Capture (RDC) system and changes will be communicated to all investigators.

5.2.2.2 Adverse event and serious adverse event reporting

Reporting will be done according to the specific definitions and instructions detailed in the ‘Adverse Event Reporting’ section of the Investigator Site File (ISF).

All adverse events, serious and non-serious and all AESIs, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the residual effect period (REP) until the individual patient’s end of trial) will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs pages.

The REP (timeframe after last dose of study medication when measurable drug levels or pharmacodynamic effects are still likely to be present) is defined as 7 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see section 7.3.3. Events which occurred after the REP will be considered as post treatment events.

After the individual patient's end of trial the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.

However, if in an individual patient only vital status information is collected after premature discontinuation, from then on and until the individual patient's end of trial, the investigator does not need to actively monitor the patient for AEs but should only report fatal AEs, relevant SAEs and relevant AESIs of which the investigator may become aware of.

Immediate documentation of events:
The investigator must report immediately (within 24 hours of awareness the following events on the SAE form to the sponsor's unique entry point as specified in the ISF:

- All SAEs
- All serious and non-serious AESIs
- Non-serious AEs relevant for a reported SAE(s) and/or AESI(s)
- Potential Hy's Law cases (see Section 5.2.2.1)
- Cardiovascular outcome events if they represent a SAE and occur during the screening/run-in phase

The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

AEs considered "Always Serious"
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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.

BI has established 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 a SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found via the RDC-system.

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

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication, and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP).

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

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 protocol-specified AESIs 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. Drug exposure during pregnancy has to be reported immediately (within 24 hours of awareness to the defined unique entry point for SAE forms of the respective BI OPU (country-specific 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), or whether diabetes is a marker of 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, detailed information will be requested and should be provided. 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
- Pancreas
- Endometrium

- Colon and rectum
- Breast
- Bladder
- Thyroid
- Prostate

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

5.2.3.1 Haematology

- Haematocrit
- Haemoglobin
- Erythrocyte count
- Platelet count
- Total and automates differential leukocyte counts (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes) in absolute counts

5.2.3.2 Clinical chemistry

- Amylase
- Lipase
- AST** (aspartate transaminase, SGOT)
- ALT** (alanine transaminase, SGPT)
- γ-GT (gamma-glutamyl-transferase)
- Alkaline phosphatase
- Lactic dehydrogenase (LDH)
- Total bilirubin**
- Direct and indirect bilirubin if total bilirubin is elevated
- Total Protein
- Albumin
- Creatine kinase (CK)
- CK-MB, if CK is elevated
- Potassium
- Sodium
- Creatinine
- Urea
- Calcium
- Inorganic phosphorous
- Urid acid
- Cholesterol (total)***
- HDL cholesterol***
- LDL cholesterol***
- Triglycerides***
- Troponin

**AST, ALT and Total bilirubin are combined in any lab assessment, with exception of Visit 1a.
*** Lipid profile, only obtained at Visits 2, 6, 9, 12, 15, 18, 21, 24, 27, ~~and~~ 30 and **32**.

5.2.3.3 Urinalysis

- Albumin, Creatinine (spot urine – quantitative measurement)
- Protein
- Ketone
- Leucocytes

Visit 1a safety laboratory only includes ALT (SGPT), AST (SGOT), alkaline phosphatase, serum creatinine, urine analysis and urine albumin and creatinine, in addition to HbA1c and does not need to be collected in fasted state.

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

Albumin/creatinine ratio will be calculated at the central lab.

Pregnancy testing (urine dipstick method) will be performed in female patients of child-bearing potential according to the Flow Chart. Testing will be performed locally, using pregnancy test kits provided by the central laboratory.

Immediately after the result of a pregnancy test is known, the pregnancy test kit will be discarded at the site. The result of the test must therefore be documented in the source documents available at site for future verification by the on-site monitor.

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.

5.2.3.4 Renal function impairment

Renal function impairment will be assessed by the central lab based on the plasma creatinine value measured according to the Flow Chart.

Estimated Creatinine clearance will be calculated from serum creatinine using the following MDRD formula as specified in the Statistical Analysis Plan.

This formula considers the race as an adjustment factor, therefore, the race must be known (and will be collected) for accurate estimation.

Renal impairment will be classified in the following way:

- No renal function impairment: eGFR ≥ 90 mL/min/1.73m^2;
- Mild renal function impairment: eGFR 60-89 mL/min/1.73m^2;
- Moderate renal function impairment: eGFR 30-59 mL/min/1.73m^2;
- Severe renal function impairment: eGFR 15-29 mL/min/1.73m^2;
- Kidney failure: eGFR < 15 mL/min/1.73m^2.

5.2.4 Electrocardiogram (ECG)

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 and stored by third party. Investigators will receive evaluated ECGs within 3 working days by third party, unless there are unresolved discrepancies. 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, if necessary, the patient will be removed from the trial and medically treated.

5.2.5 Assessment of other safety parameters

Vital signs and height

Systolic and diastolic blood pressure 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 blood pressure recording instrument (i.e., approved sphygmomanometer or an approved blood pressure meter utilizing liquid mercury) 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 1a.

Weight and Waist circumference

Weight measurements (kilogram, kg) should always be done using 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, 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 horizontal to the floor and applied with sufficient tension to conform to the measurement surface [R07-4080].

Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest [R07-4080].

Physical examination

A complete physical examination 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 Home Blood Glucose Monitoring (HBGM) equipment and supplies for use at home during the 2 up to 4 week run-in phase. HBGM testing should be performed at least once a week after an overnight fast during the placebo run-in phase of the trial and when patient experiences signs/symptoms of hypo- or hyperglycaemia. Once the patient is randomised, weekly testing is no longer required for study purposes and may be discontinued, however the patients will be instructed to bring their HBGM devices to a visit for an additional measurement of fasted glucose if required (see flow chart). HBGM measurements at visits during the titration phase are mandatory to efficaciously uptitrate dosing of the glimepiride/ glimepiride placebo arm.

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 Testing Log 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 <=3.9mmol/L (>=54 and <=70 mg/dL), if not considered as adverse event, the single HBGM values will be recorded in the CRF.

If the results of a HBGM test reveal blood plasma glucose value of > 240 mg/dL (>13.3 mmol/L) after an overnight fast during the titration phase or > 180 mg/dL (>10.0 mmol/L) after an overnight fast during the maintenance phase 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 (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 something containing carbohydrate.

HBGM (i.e. fasting glucose) will be measured in the morning of the visit prior the cognitive function testing (see Flow Chart).

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

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, standard 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.

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 on the morning of a visit before attending the clinic (excluding visits starting before randomisation) or comes in non-fasted where a fasting condition is required (all visits except Visit 1a), 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 randomisation Visit 2). The trial medication packs contain sufficient medication to allow for these time windows.

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 and Placebo run-in period

After informed consent process is complete and written informed consent is obtained, the patients will be assessed for study eligibility (Visit 1a) including central laboratory assessments: ALT (SGPT), AST (SGOT), alkaline phosphatase, serum creatinine, urinalysis and urine albumin and creatinine, in addition to HbA_{1c}. Visit 1b should occur within one week after Visit 1a once it has been confirmed that the patient is eligible to continue to Visit 1b.

Those patients who qualify at screening (as determined at Visit 1a and Visit 1b), will undergo a 2 up to 4 week placebo run-in phase (Visit 1b to Visit 2). During the run-in phase the patients will continue receiving their background therapy and they will be given a Home Blood Glucose Monitor and all the necessary supplies to use it. The HBGM will be used according to Section 5.2.5. Patients requiring rescue therapy during the screening and/or placebo run-in phase will not be eligible.

Patients must satisfy all inclusion and exclusion criteria prior to randomisation (see Sections 3.3.2 and 3.3.3). In addition, if during the run-in phase there is any indication that the patient is not stable enough, in terms of their type 2 diabetes, to complete the study or that the patient will be non-compliant with the study medication or restrictions, then these patients should not be randomised. The placebo-run phase could be extended up to 4 weeks to satisfy patients' successful completion of run-in phase.

6.2.2 Treatment phase

Randomisation will occur at Visit 2 using IXRS.

The patients will return to the clinic for regularly scheduled visits 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. Between Visit 2 and Visit 6 glimepiride/glimepiride placebo will be uptitrated up to maximal 4 mg/day **(**refer to section 4.1.4).

At each visit trial medication compliance will be calculated and new supplies from a new medication kit assigned via IXRS will be dispensed.

This is an outcome study. 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). 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 (through the patient or alternative person designated by the patient) will be required, to document the occurrence of outcome events and vital status. If possible, also 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 who prematurely discontinued study medication during the Maintenance Phase are allowed to restart the study medication at any time. Every attempt should be made by the investigator to have the patient restart study medication, even if the dose must be ~~down~~ titrated.

6.2.3 End of trial and Follow-up period

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 must be involved in the discussions with the patient regarding a withdrawal of consent.

If the patient withdrew informed consent the patient should stop taking study medication and should be asked to complete the study ending tests and procedures as described in the Flow Chart for End of Treatment Visit and Visit 33 (Follow up visit). Completing these procedures is strongly recommended for the patient's safety.

For patients that have withdrawn informed consent, the patient will be asked to resign an informed consent form, which will allow to enquire at least about the patient's vital status and occurred outcome events through contacts to relatives, acquaintances, family physicians, hospital records, etc.

End of Treatment Visit (EOT) activities will be performed when a patient discontinues study medication treatment permanently. A follow-up visit will take place 30 days after the EOT visit.

The follow-up visit may be performed as a phone visit for patients who completed the planned treatment period (only adverse events/outcome events and changes in concomitant therapy, details on trial completion and vital status to be obtained).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Design

This is a multicentre, multinational, randomised, double blind, parallel group, comparator-controlled safety study of linagliptin versus glimepiride. The trial is event driven and will run with an estimated number of 6000 patients for approximately 432 weeks beginning with the randomisation of the first patient. In the case the numbers of events is not or may not be reached within this period the trial duration and/or the number of patients enrolled will be increased until the defined number of adjudicated primary events is reached. We plan a 2 to 4 weeks run-in phase.

Objectives

The study objectives are described in Section 2.2.

For the primary objective the upper bound of the two-sided (1-2*alpha)*100% confidence interval which equals the upper bound of the one-sided (1-alpha)*100% confidence interval will be used to investigate non- inferiority of linagliptin versus glimepiride regarding 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 significance level is 2.5%. The alpha for each analysis depends on the alpha-spending function and the schedule of interim analyses.

Primary endpoint

The primary endpoint used in the primary analysis is time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) or non-fatal stroke.

If patients do not experience a primary endpoint event, they will be considered censored at their last documented study visit. If a patient died and has no primary outcome event, the patient will be censored at the date of death.

Key Secondary endpoints

As key secondary endpoints will be analysed:

1) time to the first occurrence of any of the following adjudicated components of the composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris.

2) composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c ≤ 7.0%) without need for rescue medication* (between end of titration [Visit 6] and Final Visit) and patients without any moderate/severe hypoglycaemic episodes (between Visit 6 and Final Visit) and without > 2% weight gain at Final Visit (between Visit 6 and Final Visit)).

3) composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c ≤ 7.0%) without need for rescue medication* (between Visit 6 and Final Visit) and patients without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))

* Any dose increase of anti-diabetic background medication or introduction of new anti-diabetic treatment during study medication treatment will be counted as rescue medication. Short term use of any insulin- up to two weeks - (e.g. during hospitalisation) won't count as rescue medication in the definition of treatment sustainability.

Secondary cardiovascular endpoints

In additional analyses the occurrence of the primary and first key secondary endpoint will be evaluated, resulting in the number of patients with at least one of the events above and the relative frequency with respect to the number of patients in the full analysis set (FAS).

Further secondary CV-endpoints are the occurrence of and time to:

- Composite endpoint of all CEC confirmed adjudicated events (see tertiary cardiovascular endpoints)

Secondary diabetes related endpoints

Secondary diabetes related endpoints include change from baseline to Final Visit in the following laboratory parameters:

- HbA_{1c}
- fasting plasma glucose
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Creatinine
- eGFR (MDRD formula)
- Urinary albumin

In addition any transition in albuminuria classes will be investigated.

7.2 NULL AND ALTERNATIVE HYPOTHESES

For the primary objective, first a non-inferiority hypothesis is tested with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint.

$H_{0(NonInf)}$: $HR_{linagliptin\ vs.\ glimepiride} \geq \delta$

($H_{0(NonInf)}$: Linagliptin is inferior to glimepiride by at least δ regarding the risk of the primary composite endpoint of cardiovascular events.)

vs.

$H_{1(NonInf)}$: $HR_{Linagliptin\ vs.\ glimepiride} < \delta$

($H_{1(NonInf)}$: Linagliptin is non-inferior to glimepiride by the margin δ regarding the risk of the primary composite endpoint of cardiovascular events.)

The non-inferiority margin δ is chosen to be 1.3 [R09-2151]

If the non-inferiority hypothesis with margin 1.3 has revealed a significant result, then secondly, a superiority hypothesis is tested with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint.

$H_{0(Superiority)}$: $HR_{linagliptin\ vs.\ glimepiride} \geq 1$ vs.

($H_{0(Superiority)}$: Linagliptin is inferior to glimepiride regarding the risk of the composite primary endpoint of cardiovascular events.)

vs.

$H_{1(Superiority)}$: $HR_{linagliptin\ vs.\ glimepiride} < 1$

($H_{1(Superiority)}$: Linagliptin is superior to glimepiride regarding the risk of the composite primary endpoint of cardiovascular events.)

If the superiority hypothesis has revealed a significant result, then thirdly, a superiority hypothesis is tested with respect to the first key secondary endpoint

$H_{0(Superiority)}$: $HR_{linagliptin\ vs.\ glimepiride} \geq 1$ vs.

($H_{0(Superiority)}$: Linagliptin is inferior to glimepiride regarding the risk of the first key secondary endpoint.)

vs.

$H_{1(Superiority)}$: $HR_{linagliptin\ vs.\ glimepiride} < 1$

($H_{1(Superiority)}$: Linagliptin is superior to glimepiride regarding the risk of the first key secondary endpoint.)

If the superiority hypothesis has revealed a significant result, then fourthly the second key secondary endpoint will be analysed hierarchically. The second key secondary endpoint (see Section 7.1) will be tested regarding the following hypothesis (p: probability for composite endpoint)

$H_{0(\text{key secondary 2})}$: $p_{\text{linagliptin}} - p_{\text{glimepiride}} = 0$ vs.

($H_{0(\text{key secondary2 })}$: Linagliptin is equal to glimepiride regarding the occurrence of the second key secondary endpoint.)

$H_{1(\text{key secondary 2})}$: $p_{\text{linagliptin}} - p_{\text{glimepiride}} \neq 0$

($H_{1(\text{key secondary 2})}$: Linagliptin is unequal to glimepiride regarding the occurrence of the second key secondary endpoint.)

If this hypothesis has revealed a significant result, then fifthly the third key secondary endpoint will be tested hierarchically regarding the following hypothesis:

$H_{0(\text{key secondary 3})}$: $p_{\text{linagliptin}} - p_{\text{glimepiride}} = 0$ vs.

($H_{0(\text{key secondary 3})}$: Linagliptin is equal to glimepiride regarding the occurrence of the third key secondary endpoint.)

$H_{1(\text{key secondary 3})}$: $p_{\text{linagliptin}} - p_{\text{glimepiride}} \neq 0$

($H_{1(\text{key secondary 3})}$: Linagliptin is unequal to glimepiride regarding the occurrence of the third key secondary endpoint.)

Any confirmatory hypothesis test will be performed on the full analysis set.

7.3 PLANNED ANALYSES

The primary analysis will be performed on the full analysis set (FAS). The FAS will consist of all randomised 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’ will be done. That means that:

- the patient set consists of the FAS,
- the allocated study treatment at randomisation will be used for the FAS of patients for analysis (‘as randomised’)
- all events which occurs 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 who have important protocol violations will be excluded from the PPS. A protocol violation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint and/or first key secondary endpoints.

Important protocol violations include:

- Randomised study drug: incorrect active study drug taken.
- Severe violation of treatment compliance (defined as less than 50% of visits from Visit 3 on (excluding placebo run-in phase) with treatment compliance outside 80-120% range.
- Non-adherence to other specifications of the protocol that could bias the primary endpoint

Additionally 30-days-treatment set of patients will be created for sensitivity analysis. The 30-days-treatment set will include all randomised patients with a 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.

7.3.1 Primary analyses

The one-sided overall significance level will be alpha=2.5%. For the primary analysis a 'classical ITT-analysis on the FAS will be performed as described above.
For the primary analysis a cox proportional hazards regression model of time to the first event with factor treatment will be conducted. The non-inferiority margin will be 1.3.
As described in Section 7.3.4 the DMC will perform formal interim analyses. The overall significance level of 2.5% will be allocated to the DMC-interim analyses and the final analysis according to the O'Brien & Fleming alpha-spending function.
The O'Brien & Fleming alpha-spending function defined the significance level for the first interim analysis on 4P-MACE.

Due to the change of the primary endpoint after the first DMC interim analysis a Bonferroni adjustment will be applied in addition, to control the overall alpha-level. That means, the alpha spent at the first DMC interim analysis (performed for 4P-MACE and based on the O'Brien & Fleming alpha-spending function) is subtracted from the initial overall alpha. The O'Brien & Fleming alpha-spending function based on the new overall alpha (after additional Bonferroni adjustment) defines the allocation of the still available overall significance level for the second interim analysis and the final analysis.

The significance levels for the analyses are denoted by α_i, i=1,…,3. The total number of analyses is three, including 2 interim analyses.
In the i-th analysis, i=1,…,3, the upper limit of the two sided $(1-2*\alpha_i)*100\%$-confidence interval of the hazard ratio will be compared with the non-inferiority margin. Also the one-sided p-value of the non-inferiority test based on the Wald chi-squared statistic will be given. If the non-inferiority test satisfies the non-inferiority margin, a superiority test (Wald chi-squared statistic) will be performed. If the superiority test has revealed a significant result, a superiority test on the first key secondary endpoint will be performed on the same significance level as for the primary endpoint. If the superiority test has revealed a significant result, the second and third key secondary endpoints will be tested hierarchically (see Section 7.2.). The second and third key secondary endpoints will be analysed with Chi-Square test on the same significance level $(2*\alpha_i)*100\%$ as the primary endpoint.

No centre effect is included into the model, 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 endpoint sensitivity analyses will be done on the PPS, the 30-days-treatment set and as an 'on-treatment analysis' as described below. For the first key secondary endpoint sensitivity analyses will be done on the PPS and as an 'on-treatment 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' will be performed on the FAS (consisting of all randomised 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 all these sensitivity analyses the allocated study treatment at randomisation will be used for treatment assignment.

For the second and third key secondary endpoints sensitivity analyses will be done on the PPS and the 30-days-treatment set. For the sensitivity analysis on the 30-days-treatment set patients who prematurely discontinue study treatment will not be counted as non-responders as in the primary analysis for the second and third key secondary endpoints. The measurement of Final Visit will be used. For the sensitivity analysis on the PPS patients who prematurely discontinue study treatment will be counted as non-responders as in the primary analysis. For both sensitivity analyses the allocated study treatment at randomisation will be used for treatment assignment.

7.3.2 Secondary analyses

All other secondary analyses are of exploratory nature, no correction for multiple hypotheses testing will be made. All statistical tests and confidence intervals are two-sided with a significance level of alpha=0.05 and will include the factor treatment, unless stated otherwise.

For all cardiovascular endpoints that include time-to-event data the same models and testing procedures as the primary analysis will be applied to compare the two treatment groups.

For continuous secondary diabetes related endpoints with several on-treatment measurements change from baseline will be evaluated with a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach with fixed, categorical effects of treatment, week, treatment-by-week interaction, with the continuous covariates of baseline and baseline-by-week interaction. For those continuous secondary diabetes related endpoints with only one measurement on treatment an analysis of covariance (ANCOVA) model with the factor treatment and the baseline value of the respective variable as covariate will be performed. For qualitative secondary diabetes related endpoints, a Chi-Square test is used to compare the two treatment groups.

7.3.3 Safety analyses

All safety data will be displayed and analysed using descriptive statistical methods. No formal inferential analysis is planned for safety comparison. AEs will be coded using the 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. Other AEs will be assigned either to the screening or follow-up phase as appropriate. Laboratory values taken after the first dose of randomised 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.

7.3.4 Interim analyses

An independent Data Monitoring Committee (DMC) will review safety and efficacy data and make recommendations whether to continue the study, continue the study with modifications, 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 DMC will perform formal interim analyses of the primary endpoint for non-inferiority and superiority. The trial team and Steering Committee stay blinded for these interim analyses. The sponsor will perform the final analysis. To prevent an inflation of the significance level a group sequential design according to the alpha-spending approach [R97-0643] is chosen. The O'Brien & Fleming alpha-spending function defines the allocation of the overall significance level to the analyses.

The O'Brien & Fleming alpha-spending function defined the significance level for the first interim analysis on 4P-MACE. Due to the change of the primary endpoint after the first DMC interim analysis a Bonferroni adjustment will be applied in addition, to control the overall alpha-level. That means, the alpha spent at the first DMC interim analysis (performed for 4P-MACE and based on the O'Brien & Fleming alpha-spending function) is subtracted from the initial overall alpha. The O'Brien & Fleming alpha-spending function based on the new overall alpha (after additional Bonferroni adjustment) defines the allocation of the still available overall significance level for the second interim analysis and the final analysis.

The second interim analysis will be performed based on approximately 411 primary endpoint events. The final analysis will take place after the observation of a minimum of 631 primary endpoint events.

The trial will be terminated after a formal DMC-interim analysis, if superiority for linagliptin can be shown with respect to cardiovascular safety, with particular emphasis on CV mortality. The trial should be terminated after DMC interim analysis for futility, if superiority of glimepiride with respect to the primary endpoint can be shown prematurely or if a futility assessment shows that the 1.3 non-inferiority margin likely will not be met.
The criteria for stopping the trial after a DMC-interim analysis in favour for the alternative hypothesis are given by the alpha-spending function according to O'Brien and Fleming and an additional Bonferroni adjustment applied after the first DMC interim analysis for 4P-MACE and the following analyses regarding 3P-MACE to control the overall alpha-level, with the possibility to stop the trial in favour for the alternative. The bounds of the group sequential design (α_i, i=1,..3) result from an overall α=2.5%, number of events for final analysis= 631 and the chosen alpha-

spending function [R10-2517] and the additional Bonferroni adjustment for the second interim and final analysis.

The first formal DMC-interim analysis of the primary endpoint should be based on a minimum number of 80 adjudicated primary outcome events and a minimum duration of 1.5 years after the randomisation of the first patient. The Power of such an interim analysis would be > 80%, if the true HR is extraordinary low.

The DMC will perform periodic safety reviews with an emphasis on cardiovascular and neurological events and CV mortality. The frequency of these reviews is detailed in the DMC charter, but additional looks may be scheduled as needed by the DMC. In addition, the Steering Committee may also request the DMC to meet for a safety review.

7.4 HANDLING OF MISSING DATA

Patients with temporary or permanent study treatment termination will be followed up for cardiovascular events.

Cardiovascular safety and other safety endpoints

With respect to safety evaluations, it is not planned to impute missing values.

Diabetes related endpoints

The REML based MMRM analysis will handle missing data for continuous diabetes related endpoints for patients who discontinue the study treatment prematurely or miss a visit. This approach is valid, if missing observations are missing at random. 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 last observation carried forward (LOCF) approach will be performed in a sensitivity analysis on diabetes related endpoints.

7.5 RANDOMISATION

The sponsor will arrange for the randomisation 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 randomisation 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 randomisation will be performed in blocks. The block size will be reported in the CTR. Stratification by centre will be achieved by allocating complete blocks for each site. The allocation process will be performed on Visit 2 through an interactive voice and web-based response system (IXRS).
Except for the DMC, access to the code will be restricted to dedicated randomisation personnel and any exceptional access to the code (in case of an emergency) will be documented according to the sponsor's 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

A group sequential design with according to the alpha-spending approach [R97-0643] was chosen. The critical values and the test characteristics of the group sequential test design are calculated according to the O'Brien & Fleming alpha-spending function with an additional Bonferroni adjustment applied after the first DMC interim analysis for 4P-MACE and the following analyses based on 3P-MACE.
The overall Power depends on the number and time points of interim analyses. Therefore the overall Power cannot be calculated explicitly. Therefore the Power will be given for a one-stage design without any interim analyses.
In a one-stage trial, for specified α= 2.5%, and assuming equal risk between the two treatments (HR = 1.0~~)~~ the Power for showing non inferiority (non-inferiority margin=1.3) will be 90.9% if the log rank test is performed at 631 number of accumulated events.
The computation assumes an allocation ratio of 1:1.
Assuming 1-year event rates of 0.018 for the glimepiride group and 0.018 for the linagliptin group and an accrual time of 2 years and a follow-up time of 5.4 years and a 1-year loss to follow-up rate of 1.5% a total of 6000 patients is expected to yield the necessary number of events.

In a one-stage trial, with 1-year event rates of 0.018 for the glimepiride group and 0.0144 for the linagliptin group (HR = 0.8) the Power for showing superiority will be 80% if the log rank test is performed at 631 number of accumulated events.
Assuming an accrual time of 2 years and a follow-up time of 6.2 years and a 1-year loss to follow-up rate of 1.5% a total of 6000 patients is expected to yield the necessary number of events.

The sample size calculations were calculated with Addplan 4.0.3 [R10-2517].

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) and relevant BI Standard Operating Procedures (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 immediately of any urgent safety measures taken to protect the study patients 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 (for Japan: trial site) and of the sponsor with regard to publication of the results of this trial are described in the investigator contract (for Japan: trial site). 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).

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 Institutional Review Board (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.

For Japan: The investigator must give a full explanation to trial patients by using 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 respective procedure for illiterate patients is described in the Appendix 10.1.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim 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 (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

In order to achieve a high level of standardised processes, data collection of efficacy and safety endpoints is coordinated centrally:

- Central lab analysis of efficacy endpoints and safety lab
- Central ECG collection
- Central IXRS for randomisation and kit allocation at each visit
- Central Outcome event adjudication process

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in CTMF.

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

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or 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.

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 sponsor's 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 SOP.

Sponsor:

The sponsor must retain the essential documents according to the Sponsor's SOP.

When it is no longer necessary for the trial site to retain source documents and essential documents, the sponsor must notify the head of the 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 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 Investigator's Brochure [U04-1767]. For glimepiride this is the EU SPC (Amaryl). The current versions of these reference documents are to be provided in the ISF. 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. Cardiovascular outcome events that occur after randomisation and represent a SAE, are exempted from expedited reporting to health authorities. 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 sponsor 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/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

8.7 PROTOCOL VIOLATIONS

The investigator should document any deviations from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

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

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P08-01788 Ryden L, Standl E, Bartnik M, Berghe G van den, Betteridge J, Boer MJ de, Cosentino F, Jonsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: full text: the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD).Eur Heart J 9 (Suppl C), C3 - C74 (2007)

R10-0116 Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G, Stamler J, Multiple Risk Factor Intervention Trial (MRFIT) Research Group. Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the Multiple Risk Factor Intervention Trial. Arch Intern Med 164, 1438 - 1443 (2004)

R10-0117 Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971 - 1993. Diabetes Care 21 (7), 1138 – 1145 (1998)

R07-1076 International Diabetes Federation, Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels: International Diabetes Federation (2005)

R09-6397 Asian-Pacific Type 2 Diabetes Policy Group. Type 2 diabetes: practical targets and treatments. 4th ed. Melbourne, Singapore: International Diabetes Institute, In Vivo Communications (Asia) (2005)

R08-1310 AACE Diabetes Mellitus Clinical Practice Guidelines Task Force American association of clinical endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 13 (Suppl 1), 3 - 68 (2007)

R10-4077 National Institute for Health and Clinical Excellence. Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes (this short clinical guideline partially updates NICE clinical guideline 66. The recommendations have been combined with unchanged recommendations from CG66 in NICE clinical guideline 87 (NICE short clinical guideline 87, issue date: May 2009). weblink: nice.org.uk ; London: National Institute for Health and Clinical Excellence (2009)

P08-06509 Johansen OE. Cardiovascular disease and type 2 diabetes mellitus: a multifaceted symbiosis. Scand J Clin Lab Invest 2007;67(8):786-800.

R10-2212 Williams R, Van Gaal L, Lucioni C, Advisory Board. Assessing the impact of complications on the costs of Type II diabetes. Diabetologia 2002;45:S13-7

P10-00533 Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 32(suppl 1), S1-S201. 2008

R09-1164 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:193-203.

R10-0133 Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? Diabetes Care 2008;31:81-86

R10-0134 Liebl A, Mata M, Eschwege E, Advisory Board. Evaluation of risk factors for development of complications in Type II diabetes in Europe. Diabetologia 2002;45:S23-8

R10-0657 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999;281:2005-12.

R09-6400 Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355:2427-43

R09-6405 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-65

R09-6409 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89

R09-6407 Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. N Engl J Med 2008; 358(24): 2545-2559

R09-6408 Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-139

R10-2210 Nissen SE, Wolski K, Topol EJ.Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA. 2005;294:2581-6.

R10-2211 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457-71

R09-2151 Guidance for industry: diabetes mellitus - evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (December 2008). Silver Spring: U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2008

R09-6409 Meier JJ, Nauck MA. Glucagon-like peptide 1 (GLP-1) in biology and pathology. Diabetes Metab Res Rev 2005;21:91–117

R09-6410 Monami M, Iacomelli I, Marchionni N, Mannucci E. Dipeptydil peptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutrition, Metabolism and Cardiovascular Diseases, article in press, doi: 10.1016/j.numecd.2009.03.015 Nutr Metab Cardiovasc Dis 2009

R04-2173 Turner RC, Holman RR, Cull CA, Stratton IM, Matthews DR, Frighi V, Manley SE, Neil A, McElroy H, Wright D, Kohner E, Fox C, Hadden D, UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-853.

R09-6394 Bell DSH. Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy. Clin Ther 2004;26(11):1714-1727.

R09-6395 Dormandy JA, et al, PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-1289.

R09-6396 American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycaemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28(5):1245-1249.

R10-2517 ADDPLAN, 2007. Software for Adaptive Designs and Analyses: Release 4. ADDPLAN GmbH, Cologne, Germany.

R97-0643 Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70(3):659-663.

P96-4362 Harrower ADB. Pharmacokinetics of oral antihyperglycaemic agents in patients with renal insufficiency. Clin Pharmacokinet 31 (2), 111 - 119 (1996)

R10-4375 Glucophage (metformin hydrochloride tablets), Glucophage XR (metformin hydrochloride extended-release tablets) (Bristol-Myers Squibb Company) (NDA 20-357/S-031, NDA 21-202/S-016, version: 08/27/2008).

R07-4080 Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL et al. Waist circumference and cardiometabolic risk: a consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Am J Clin Nutr 2007;85:1197-202.

R10-6494 Vigneri P, FF, Sciacca L, PG, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103-1123.

R10-6495 Hemminki K, Li X, Sundquist J, Sundquist K. Risk of cancer following hospitalization for type 2 diabetes. Oncologist 2010;15:548-555.

R10-6496 Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007;132(6):2208-2225.

R10-6497 Smith U, Gale EAM. Does diabetes therapy influence the risk of cancer? Diabetologia 2009;52:1699-1708.

R10-6498 Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr 2007;86(Suppl):823S 835S.

R10-6536 Hjartaker A, Langseth H, Weiderpass E. Obesity and diabetes epidemics: cancer repercussions. In: Berstein LM, Santen RJ, editors.Innovative endocrinology of cancer.Austin: Landes Bioscience 2008:72-93.

R10-6638 Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. Diabetes Care 33 (7), 1674 - 1685 (2010).

P15-02848 Marx N, Rosenstock J, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, Espeland MA, Bluhmki E, Mattheus M, Ryckaert B, Patel S, Johansen OE, Woerle HJ Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA). Diabetes Vasc Dis Res 12 (3), 164-174 (2015).

P13-02826 Rosenstock J, Marx N, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, Bluhmki E, Patel S, Johansen OE, Woerle HJ Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. Diabetes Vasc Dis Res 10 (4), 289-301 (2013).

P16-04169 Pocock SJ. Design of major randomized trials: part 3 of a 4-part series on statistics for clinical trials. J Am Coll Cardiol 2015. 66(24):2757.

R13-3903 Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, WiviottSD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mozenson O, McGuire DK, Ray KK, Leiter LA, Raz I, SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus.N Engl J Med 369, 1317 - 1326 (2013).

R13-3902 White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F, EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes.N Engl J Med 369 (14), 1327 - 1335 (2013).

R16-1123 Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJV, Probstfield JL, Riddle MC, Solomon SD, Tardif JC, ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome.N Engl J Med 373 (23), 2247 - 2257 (2015).

R15-3017 Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Werf F van de, Peterson ED, Holman RR, TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes.N Engl J Med, (2015)

R09-2151 Guidance for industry: diabetes mellitus - evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (December 2008). Silver Spring: U.S. Department of Health and Human Services,

Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (2008)

R12-3960 European Medicines Agency (EMA) Committee for Medicinal Products For Human Use (CHMP): guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (14 May 2012,CPMP/EWP/ 1080/00 Rev. 1).

9.2 UNPUBLISHED REFERENCES

U04-1767 Linagliptin Investigator's Brochure. Current Version.

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 1b, 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 testing log. 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 testing log 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 testing log 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 endpoints events and the principles of standardised data collection in the centralised CEC adjudication process are outlined in the current CEC Charter and process guideline.

10.3 BLOOD PRESSURE MEASUREMENT PROCEDURE AND TREATMENT RECOMMENDATIONS

Initially, blood pressure should be taken three times in both arms. The arm with the mean 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 an electronic device, i.e. either electronic or manual measurements of blood pressure are acceptable, depending on the standard practice at each study site - Note: Boehringer Ingelheim will not provide electronic devices to sites that use the standard manual sphygmomanometers.

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 or third blood pressure reading may be used.

Blood pressure measurements should be recorded to the nearest 2 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).

It has been clearly established that the co-existence of hypertension and diabetes increases the risk of developing renal and other organ damage, leading to a much greater incidence of stroke, coronary heart disease, congestive heart failure, peripheral artery disease and cardiovascular mortality. Reduction of high blood pressure could decrease the risk of stroke, heart disease and reduce the likelihood of dementia, heart failure, and death.

Treatment recommendations of hypertension in diabetic patients are described in several guidelines, e.g. the current “Guidelines on Diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes” [P08-01788], also accessible at weblink: escardio.org.

10.4 TREATMENT RECOMMENDATIONS FOR DYSLIPIDAEMIA

Increased cardiovascular risk in T2DM patients is independently associated with their hyperglycemia together with high blood pressure (BP) and dyslipidaemia, the last typically the high-density lipoprotein cholesterol (HDL-C) and raised triglyceride (TG) levels found as components of the metabolic syndrome. Although low-density lipoprotein cholesterol (LDL-C) levels are not particularly higher in T2DM patients,

the opportunity to reduce cardiovascular risk is currently greatest through lipid lowering management by reducing LDL-C. There is almost a linear relationship between the absolute risk reduction in LDL-C and the proportional reductions in the incidence of cardiovascular events.

Treatment recommendations of dyslipidaemia in diabetic patients are described in several guidelines, e.g. the current "Guidelines on Diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes" [P08-01788], also accessible at weblink: escardio.org.

10.5 SILENT MYOCARDIAL INFARCTION

Incidence and impact of silent MI will be assessed in this study.

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.

10.6 CLINICAL EVALUATION OF LIVER INJURY

10.6.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (protocol specific adverse events of special interest) are to be further evaluated using the following procedures:

10.6.2 Procedures

Repeat the following lab tests: ALT, AST, total bilirubin (with differentiation of bilirubin in direct and indirect) and additionally alkaline phosphates (ALP), CK (CK-MB, if CK is elevated), amylase, lipase, INR - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, total bilirubin (with differentiation of bilirubin in direct and indirect) and additionally alkaline phosphates (ALP), CK (CK-MB, if CK is elevated), amylase, lipase, INR will be evaluated by local laboratory and results are made available to the investigator

and to BI as soon as possible. If in such a case ALT and/or AST ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

In addition,

- initiate close observation of subjects by repeat testing of ALT, AST, alkaline phosphates (ALP), CK (CK-MB, if CK is elevated), total bilirubin (with differentiation of bilirubin in direct and indirect), amylase, lipase, INR with repeated testing of these parameters at least weekly until ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

- initiate examination for alternative reasons for elevation of liver parameters:

    - obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "DILI checklist" provided in the ISF

    - obtain history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF

    - obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF

  and report these via the CRF.

    - obtain further lab tests to evaluate for alternative causes (need to be done once):
        - Hepatitis-Serology:
            - Anti-HAV-IgM,
            - HBsAg, HBcAg, anti-HBs (for documentation of probably non-acute infection) (if any are positive then HBV DNA by PCR),
            - Anti-HCV (if positive then HCV RNA by PCR);
            - Anti-HDV IgM;
            - Anti-HEV (if positive then Anti-HEV IgM or HEV-RNA by PCR);
            - Epstein-Barr-Virus: VCA-IgG, VCA-IgM, or early antigen
            - Cytomegalovirus (anti CMV-IgG and anti CMV-IgM)
            - Herpes Simples virus (IgG, IgM)

- Parvovirus (IgG, IgM)
- Toxoplasmosis (IgG, IgM)

- Screen for autoimmune hepatitis (ANA, SMA, AMA, anti-LKM)
- Metabolic screen (glucose, cholesterol, triglycerides)
- Coeruloplasmin, alpha-a antitrypsin,

– obtain further information on medical history and additional data as far as possible, use the 'DILI' checklist in the ISF for collecting the information.

– Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.

10.6.3 Decision to Stop Drug Administration

Based on the potential risk for a patient, it can be necessary to discontinue study drug treatment. This decision should be made in close cooperation between the investigator and Boehringer Ingelheim.

11. SUMMARY OF CLINICAL TRIAL PROTOCOL MODIFICATIONS

Summary of Clinical Trial Protocol Modifications Sheet (SOMS)

Number of CTP modification		1
Date of CTP modification		21 July 2011
EudraCT number		2009-013157-15
BI Trial number		1218.74
BI Investigational Product(s)		Linaglitin
Title of protocol		A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The CAROLINA Trial.
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		**Protocol synopsis (objectives)**
Description of change		Description of treatment sustainability
Rationale for change		To correct definition of treatment sustainability
Section to be changed		**Protocol synopsis (inclusion criteria)**

Description of change		Change 1: Inclusion of patients with background medication of - sulphonylurea + alpha-glucosidase inhibitor or - glinide + alpha-glucosidase inhibitor Change 2: Documented coronary artery disease (≥50% luminal diameter narrowing of left main coronary artery or ≥ 50% in at least two major coronary arteries in angiogram). Change 3: Peripheral occlusive arterial disease will include stenting as inclusion criterion. Change 4: Since blood pressure and LDL are not measured at V1a, these values should be known prior study enrolment if used for inclusion (values < 6 months old prior V1a). Change 5: BMI ≤ 45 kg/m^2 at Visit 1b Change 6: Addition of inclusion criterion: stable anti-diabetic background medication (unchanged daily dose) for at least 8 weeks prior V1a and without short term use of insulin. Background medication should be stable during screening/run-in phase to allow randomisation Change 7: Limitation of recruitment of patients of Category C and D.
Rationale for change		Change 1: Combination therapy of sulphonylurea/glinide + alpha-glucosidase inhibitor is a suitable combination therapy for the protocol target population Change 2: To clarify that ≥ 50% luminal diameter narrowing is documented in at least two

		major coronary arteries. Including note for further clarification. Change 3: To allow stenting cardiovascular risk Change 4 :(inclusion criterion 3) To clarify current blood pressure and LDL measurements if used for inclusion. Change 5: BMI will be measured at V1b Change 6: Medication should be stable 8 weeks prior V1a to allow enrolment) and during screening/run-in phase (to allow randomisation) Change 7: Since the cardiovascular risk is relatively lower for patients of category C and D compared to category A and B, recruitment of patients of category C will be limited to approximately 25% and recruitment of patients of category D will be limited to approximately 25% of total amount of randomised patients. This will be arranged on regional/country level.
Section to be changed		**Protocol synopsis (duration of treatment)**
Description of change		Observational study duration is clarified
Rationale for change		To clarify observational study duration
Section to be changed		**Protocol synopsis (Criteria for efficacy)**
Description of change		Description of primary efficacy endpoint
Rationale for change		To be in line with section 5.1.1.
Section to be changed		**Protocol synopsis (main exclusion criteria)**
Description of change		Change 1: Treatment with other diabetic drugs (as specified in inclusion criteria) prior informed consent is excluded. This included also clinical trials where these antidiabetic drugs have been provided to patients. Change 2: Sibutramine and orlistat were removed as specifically named anti-obesity drugs

		Change 3: Pre-planned coronary artery re-vascularisation (PCI, CABG) within next 6 months after V1a or any previous PCI ≤ 6 months prior informed consent or any previous CABG < 3 months prior informed consent Change 4: (new exclusion criterion) Exclusion of acute coronary syndrome ≤ 6 weeks prior to informed consent Change 5: (new exclusion criterion) Exclusion of stroke or TIA ≤ 3 months prior to informed consent
Rationale for change		Change 1: To ensure other antidiabetic drugs are also excluded if prescribed in another clinical trial. Change 2: To remove specific anti-obesity medication and prevent need for future revisions when available products of this class may chance. Change 3: To exclude recent PCI and CABG Change 4: (new exclusion criterion) To ensure that patients with acute coronary syndrome ≤ 6 weeks prior to informed consent are not included. Change 5: (new exclusion criterion) To ensure that patients with stroke or TIA ≤ 3 months prior to informed consent are not included.
Section to be changed		**Flow Chart**
Description of change		Change 1: Interactive Voice and Web-based Response System will be used, so called IXRS Change 2: At Visit 15 and Visit 30 (EOT/EOS) cognition testing will be performed. As a

		result at these visit also HBGM will be done prior testing. Change 3: (footnote L) The FPG range is more specified for cognitive testing. Change 4: (footnote J) Between V1a and V1b AEs should also be collected in screen failures prior V1b. Change 5: (new footnote J) Maximal time window between visits is specified. Change 6: (footnote M) 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. Change 7: (footnote O)
Rationale for change		Change 1: To clarify that Interactive Voice and Web-based Response System will be used, so called IXRS Change 2: To ensure FPG levels are within range to measure cognition data. Change 3: (footnote L) The HBGM results at certain FPG concentrations may allow repeated HBGM after at least one hour. Change 4: (footnote J) To ensure all AEs will be captured, also in screen failures prior V1b. Change 5: (new footnote J) To ensure patient will not run-out of study medication Change 6: (footnote M)

		To ensure that clinically relevant abnormalities will be reported as adverse events if not pre-existing prior signing of informed consent. Change 7: (footnote O)
Section to be changed		**2.1**
Description of change		Inclusion of patients with background medication of - sulphonylurea + alpha-glucosidase inhibitor or - glinide + alpha-glucosidase inhibitor
Rationale for change		Combination therapy of sulphonylurea/glinide + alpha-glucosidase inhibitor is a suitable combination therapy for the protocol target population
Section to be changed		**2.2**
Description of change		Change 1: Description of primary objectives Change 2: Description of treatment sustainability
Rationale for change		Change 1: Description of primary objectives was missing in this Section Change 2: To correct the definition of treatment sustainability.
Section to be changed		**2.3**
Description of change		Reference to linagliptin's phase III program.
Rationale for change		Linagliptin's phase III program has been completed for registration.
Section to be changed		**3.1.1**
Description of change		Change 1: Steering Committee (SC) and Data Monitoring (DMC) Charters won't be provided in ISF Change 2: Description of inclusion of treatment naïve T2DM patients.
Rationale for change		Change 1: SC and DMC procedures are not required for sites. If required, the Charter(s) will be

		submitted to IEC/IRB or Health Authority for notification. Change 2: To clarify that treatment naive T2DM patients should be offered first line therapy (e.g. metformin) before allowing them for study inclusion, unless they have specific contra-indications to its use.
Section to be changed		**3.2**
Description of change		Treatment goal for HbA1c is <7% and rescue medication is encouraged if HbA1c is >7.5%. However, the decision to initiate rescue medication remains with the investigator and the appropriate local treatment guidelines.
Rationale for change		To provide clarification of treatment goal and use of rescue medication to be in line with section 4.2.1
Section to be changed		**3.3**
Description of change		Permission to randomise more than 30 patients will only be allowed after a careful review of enrolment status, resources and data quality of the site.
Rationale for change		Site should have sufficient resources and data quality to allow randomisation of more than 30 patients.
Section to be changed		**3.3.1**
Description of change		Change 1: Background medication should also be stable during screening/run-phase to allow randomisation. Change 2: Deletion of sentence.
Rationale for change		Change 1: To clarify that background medication should also be stable during screening/run-in phase to allow randomisation. Change 2: Background medication is already highlighted in section 4.1.4.
Section to be changed		**3.3.2**
Description of change		Change 1:

		Order of inclusion criteria has changed, i.e. T2DM is now a specific inclusion criterion number 1. <u>Change 2: (inclusion criterion 2)</u> Inclusion of patients with background medication of - sulphonylurea + alpha-glucosidase inhibitor or - glinide + alpha-glucosidase inhibitor <u>Change 3: (inclusion criterion 2)</u> Documented coronary artery disease (≥50% luminal diameter narrowing of left main coronary artery or ≥ 50% in at least two major coronary arteries in angiogram). <u>Change 4: (inclusion criterion 3)</u> Peripheral occlusive arterial disease will include stenting as inclusion criterion. <u>Change 5</u>: Since blood pressure and LDL are not measured at V1a, these values should be known prior study enrolment if used for inclusion (values < 6 months old prior V1a). <u>Change 6: (inclusion criterion 5)</u> BMI ≤ 45 kg/m^2 at Visit 1b <u>Change 7: (new inclusion criterion 7)</u> Stable anti-diabetic background medication (unchanged daily dose) for at least 8 weeks prior V1a and without short term use of insulin. Background medication should be stable during screening/run-in phase to allow randomisation <u>Change 8</u>: Limitation of recruitment of patients of Category C and D.
Rationale for change		<u>Change 1:</u> To clearly identify T2DM as inclusion criterion and to be in line with CRF. <u>Change 2: (inclusion criterion 2)</u> Combination therapy of sulphonylurea/glinide + alpha-glucosidase

		inhibitor is a suitable combination therapy for the protocol target population Change 3: (inclusion criterion 3) To clarify that ≥ 50% luminal diameter narrowing is documented in at least two major coronary arteries. Including note for further clarification. Change 4: (inclusion criterion 3) To allow stenting cardiovascular risk Change 5 :(inclusion criterion 3) To clarify current blood pressure and LDL measurements if used for inclusion. Change 6: (inclusion criterion 5) BMI will be measured at V1b Change 7: (new inclusion criterion) Medication should be stable 8 weeks prior V1a to allow enrolment) and during screening/run-in phase (to allow randomisation) Change 8: Since the cardiovascular risk is relatively lower for patients of category C and D compared to category A and B, recruitment of patients of category C will be limited to approximately 25% and recruitment of patients of category D will be limited to approximately 25% of total amount of randomised patients. This will be arranged on regional/country level.
Section to be changed		**3.3.3**
Description of change		Change 1: (exclusion criterion 2) Treatment with other diabetic drugs (as specified in inclusion criteria) prior informed consent is excluded. This included also clinical trials where these antidiabetic drugs have been provided to patients. Change 2: (exclusion criterion 3) Sibutramine and orlistat were removed as specifically named anti-obesity drugs Change 3: (exclusion criterion 7)

		Pre-planned coronary artery re-vascularisation (PCI, CABG) within next 6 months after V1a or any previous PCI ≤ 6 months prior informed consent or any previous CABG < 3 months prior informed consent Change 4: (exclusion criterion 17) Sexual abstinence (if allowed by local authorities) and double barrier added to list of acceptable method of birth control Change 5: (new exclusion criterion 19) Exclusion of acute coronary syndrome ≤ 6 weeks prior to informed consent Change 6: (new exclusion criterion 20) Exclusion of stroke or TIA ≤ 3 months prior to informed consent
Rationale for change		Change 1: (exclusion criterion 2) To ensure other antidiabetic drugs are also excluded if prescribed in another clinical trial. Change 2: (exclusion criterion 3) To remove specific anti-obesity medication and prevent need for future revisions when available products of this class may chance. Change 3: (exclusion criterion 7) To exclude recent PCI and CABG Change 4: (exclusion criterion 17) In certain countries sexual abstinence is allowed by local authorities as acceptable method of birth control. Double barrier is an acceptable method of birth control. Change 5: (new exclusion criterion 19) To ensure that patients with acute coronary syndrome ≤ 6 weeks prior to informed consent are not included. Change 6: (new exclusion criterion 20)

		To ensure that patients with stroke or TIA ≤ 3 months prior to informed consent are not included.
Section to be changed		**3.3.4.1**
Description of change		Change 1: Updated procedures for patients who withdraw informed consent. Change 2: Indicating that all study procedures, e.g. lab measurements should be done in patients who discontinued study medication prematurely. Change 3: Addition of minimal requirements for patients who discontinued study treatment. Change 4: Background medication should be kept stable for the course of the trial unless medical emergencies, or other plausible reasons (e.g. hyper -or hypoglycaemia) necessitate changes at the discretion of the investigator
Rationale for change		Change 1: To clarify procedures for patients who withdraw informed consent Change 2: To clarify that study procedures should be done as much as possible in patients who discontinued study medication prematurely. Change 3: To capture minimal data (i.e. primary endpoint events and vital status) of patients who discontinued study treatment. Change 4: To allow treatment flexibility for background medication in this long term trial, as you may expect that diabetes will progress over time.
Section to be changed		**4.1.3**
Description of change		Linagliptin marketed dose is 5mg
Rationale for change		Linagliptin 5mg is marketed in countries
Section to be changed		**4.1.4**

Description of change		Change 1: Background medication should be kept stable for the course of the trial unless medical emergencies, or other plausible reasons (e.g. hyper -or hypoglycaemia) necessitate changes at the discretion of the investigator. Change 2: Rephrase of uptitration. Change 3: Patients on previous glimepiride will start the randomisation phase at same glimepiride dose. Change 4: Uptitration of glimepiride becomes more flexible and will be allowed at (un) scheduled visits during maintenance phase. Change 5: During the maintenance phase it is investigator judgement to change the study and/or background medication dose. Rescue medication could also be initiated provided protocol criteria are met. Change 6: Study medication should be taken shortly before or during a meal (except on visit days) Change 7: Background and/or rescue medication will be taken as prescribed including visit days.
Rationale for change		Change 1: To allow treatment flexibility for background medication in this long term trial, as you may expect that diabetes will progress over time. Change 2: To clarify that during titration phase uptitration is mandatory at certain FPG levels, provided there is no risk for hypoglycaemia (investigator's judgement).

		Change 3: To clarify those patients on previous glimepiride will start study medication on same glimepiride dose. Change 4: To increase flexibility of study medication. Instructions for uptitration of glimepiride are indicated. Change 5: To clarify that it is investigator judgement to change study and/or background medication dose or to initiate rescue medication. Change 6: According to prescription guidelines glimepiride should be taken shortly before or during a meal. Change 7: To clarify that background and/or rescue medication will be taken as usual on visit days.
Section to be changed		**4.1.5.2**
Description of change		A patient could continue with study medication after site or global unblinding.
Rationale for change		To clarify that patient could continue on study medication after site or global unblinding.
Section to be changed		**4.2.1**
Description of change		Change 1: Alpha-glucosidase inhibitors will be allowed as rescue medication Change 2: Adding sentence regarding rescue medication
Rationale for change		Change 1: To increase potential rescue medication in countries where alpha-glucosidase inhibitors are prescribed. Change 2: Particular rescue medication may not be available in countries (e.g. pioglitazone).

Section to be changed		**4.2.2.1**
Description of change		If any restricted medication are given to the patient, the study medication **can** be discontinued temporarily, or if needed permanently.
Rationale for change		Discontinuation of study medication is medical judgement by investigator. To ensure this paragraph is in line with section 3.3.4.1
Section to be changed		**4.2.2.2**
Description of change		All patients should be provided with healthy advice and relevant educational material to be used for this purpose will be supplied
Rationale for change		To ensure patients will receive advice and educational material regarding healthy advice.
Section to be changed		**5.2.1.1**
Description of change		Exemption of cardiovascular outcome events (heartfailure requiring hospitalisation, TIA. PCI and CABG) from expedited and unblinded SUSAR reporting.
Rationale for change		To avoid unblinding of these cardiovascular outcome events to maintain the integrity of the trial.
Section to be changed		**5.2.2.1 (hepatic events)**
Description of change		Section has been updated regarding procedures for follow-up of lab parameters.
Rationale for change		To be in line with section 10.6.2.
Section to be changed		**5.2.2.2**
Description of change		<u>Change 1</u>: 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. <u>Change 2</u>: Cardiovascular outcome events if they represent an SAE should be reported as SAE if occurred during screening/run-in phase. <u>Change 3</u>: Cardiovascular outcome events should be reported as outcome event if occurred after randomisation.

Rationale for change		Change 1: To ensure that clinically relevant abnormalities will be reported as adverse events if not pre-existing prior signing of informed consent. Change 2: To ensure prior randomisation cardiovascular outcome events will be reported as SAE. Change 3: To ensure the integrity of the trial, cardiovascular outcome events should be reported as outcome event if occurred after randomisation, i.e. no unblinding will occur.
Section to be changed		**5.2.2.3**
Description of change		New paragraph regarding oncology adverse events is added
Rationale for change		In order to assess patients with oncology adverse events in detail, detailed information will be requested and has to be provided.
Section to be changed		**5.2.3.2**
Description of change		Change 1: Change 2: AST, ALT and Total bilirubin are combined in any lab assessment
Rationale for change		Change 1: Change 2: To fulfil the FDA Drug Induce Liver Injury guideline
Section to be changed		**5.2.5**
Description of change		Change 1: Section vital signs and height has been updated. Reference to section 10.3 Change 2: Weight should be measured on same type of scale Change 3: Further instructions for use of HBGM diary.

Rationale for change		Change 1: To be in line with Flow Chart and to highlight section 10.3 Change 2: To allow flexibility for weight measurements. Change 3: To clarify instructions of HBGM diary

Section to be changed		**6.2.2**
Description of change		Addition of minimal requirements for patients who discontinued study treatment.
Rationale for change		To capture minimal data (i.e. primary endpoint events and vital status) of patients who discontinued study treatment.
Section to be changed		**6.2.3**
Description of change		Deletion of sentence regarding discontinued patients.
Rationale for change		Information is already indicated in section 3.3.4.1 and 6.2.2
Section to be changed		**7.1 (tertiary diabetes related endpoints)**
Description of change		Change 1: Change of endpoint: proportion of patients with moderate/severe hypoglycaemic episodes. Change 2: Change of endpoint: Proportion of patients with treatment sustainability (defined as the proportion of patients that are on study treatment at study end without rescue medication) with $\leq$ 2% weight gain at Final Visit (with or without rescue medication during maintenance phase) (between Visit 6 and Final Visit)) Change 3: Short term use of basal insulin- up to two weeks - (e.g. during hospitalisation) won't count as rescue medication in the definition of treatment sustainability.
Rationale for change		Change 1: Definitions of hypoglycaemic episodes in line with section 5.1.1. Change 2: To ensure weight endpoint will be based on population with treatment sustainability Change 3: Short term use of basal insulin is a common treatment option when dual oral therapy failed. Per definition it will be seen as (new)

		rescue treatment if given more than two weeks.
Section to be changed		**7.1 (other endpoints)**
Description of change		Incidence of particular adverse events will be analysed as "other endpoint".
Rationale for change		To fulfil safety requirements of health authorities.
Section to be changed		**7.3.4.**
Description of change		Change 1: The DMC will perform formal interim analyses of the primary endpoint for non-inferiority and superiority Change 2: Sentence deleted, regarding stopping rule for futility.
Rationale for change		Change 1: To clarify formal interim analyses by DMC. Change 2: Stopping rules for futility are already indicated in same paragraph.
Section to be changed		**8.4.2**
Description of change		Cardiovascular outcome events should be reported as outcome event if occurred after randomisation
Rationale for change		To ensure the integrity of the trial.
Section to be changed		**9.1**
Description of change		References added
Rationale for change		References added regarding oncology adverse events and new standardised definitions for endpoint events in cardiovascular trials (October 2010)
Section to be changed		**10.2 (and sub-sections)**
Description of change		Sub-sections in 10.2 are updated according to new standardised definitions for endpoint

		events in cardiovascular trials (October 2010)
Rationale for change		To provide the definitions of the cardiovascular outcome events based on the current "Standardised Definitions for endpoint events in cardiovascular trials, Final recommendations (2010).
Section to be changed		**10.3**
Description of change		Clarification on blood pressure measurements
Rationale for change		Clarification on blood pressure measurements
Section to be changed		Several sections throughout the protocol
Description/rational of change		Typo's, minor errors has been corrected throughout the protocol
Section to be changed		**10.6.3**
Description of change		No check-list will be provided in the ISF supporting the collecting of further information.
Rationale for change		Patients who discontinued study medication should be followed as much as possible.

Number of CTP modification		2
Date of CTP modification		6 March 2012
EudraCT number		2009-013157-15
BI Trial number		1218.74
BI Investigational Product(s)		Linaglitin
Title of protocol		A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The CAROLINA Trial.
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		☐
Section to be changed		**Protocol synopsis (objectives)**
Description of change		Change 1: Exclusion of silent MI from primary endpoint Change 2: Correction of confidence interval
Rationale for change		Change 1: Silent MI will be reported as tertiary cardiovascular endpoint Change 2: Confidence interval is determined based on the alpha from the alpha-spending function.
Section to be changed		**Protocol synopsis (criteria for safety)**
Description of change		Change 1: Summarization of non-fatal and fatal MI, as well as non-fatal and fatal stroke for evaluation of time to and occurrence of adjudicated events. Change 2:

		Deletion of stable angina pectoris as study endpoint.
Rationale for change		Change 1: To allow for an analysis of single components with inclusion of death resulting from such a component. Change 2: Stable angina pectoris will not be adjudicated as tertiary cardiovascular endpoint.
Section to be changed		**Protocol synopsis (inclusion criteria)**
Description of change		Change 1: Addition of the statement in the inclusion criteria that anti-diabetic treatment naïve patients are only eligible for study enrolment if they are intolerant or contra-indicated to first line anti-diabetic treatment. Change 2: In consultation with the Steering Committee, enrolment of patients currently at least on SU or glinide may be limited.
Rationale for change		Change 1: To clarify this criterion for naïve patients in the inclusion criteria as stated in protocol section 3.3.1. Change 2: To ensure an early/moderate disease population with short to moderate diabetes duration. To allow assessment of the CV safety profile of linagliptin versus glimepiride.
Section to be changed		**Protocol synopsis (main criteria for exclusion)**
Description of change		Change 1: The wording any history and/or current treatment with other antidiabetic drugs added to inclusion criteria Change 2: Current treatment with systemic corticosteroids will exclude a patient of study enrolment Change 3:

		Inappropriateness of glimepiride treatment for other issues (e.g. allergy) according to local prescribing information.
Rationale for change		Change 1: To clarify that any history and/or current treatment of anti-diabetic drugs as specified in the inclusion criteria will exclude a patient from study enrolment Change 2: Clinical relevant drug-drug interaction of the study medication is limited to corticosteroids Change 3: To avoid patients being enrolled with allergies to the SU class
Section to be changed		**Flowchart**
Description of change		Change 1: Addition of maximal/minimal days from randomisation for screening to be performed. Change 2: Visit time window of visit 6 is +/- 7 days
Rationale for change		Change 1: To clarify that maximal 42 days and minimal 15 days should be between screening and randomisation Change 2: Since patient received at visit 5 medication up to maximal 5 weeks, the time window for visit 6 is limited to +/- 1 week.
Section to be changed		**1.1 (medical background)**
Description of change		Change of reference number
Rationale for change		Incorrect reference number
Section to be changed		**1.2 (drug profile)**
Description of change		Updated drug profile
Rationale for change		To add new clinical trial data
Section to be changed		**2.1 (rationale for performing the trial)**
Description of change		Addition of the statement that anti-diabetic treatment naïve patients are only eligible for study enrolment if they are intolerant or contra-indicated to first line anti-diabetic treatment.

Rationale for change		To clarify this criterion for naïve patients as stated in protocol section 3.3.1.
Section to be changed		**2.2 (trial objectives)**
Description of change		Correction of confidence interval
Rationale for change		Confidence interval is determined based on the alpha from the alpha-spending function.
Section to be changed		**2.3 (benefit – Risk assessment)**
Description of change		Change 1: Add description of alpha-glucosidase inhibitor as possible rescue medication (as indicated in section 4.2.1) Change 2: Updated list of anti-diabetic drugs (given as study medication or allowed as rescue medication) which are not approved for use in pregnancy.
Rationale for change		Change 1: To provide background of alpha-glucosidase inhibitor as possible rescue medication Change 2: To update list of antidiabetic drugs (given as study medication or allowed as rescue medication) which are not approved for use in pregnancy.
Section to be changed		**3.3 (selection of trial population)**
Description of change		Change 1: Change 2: Addition of procedures for re-screening and re-testing
Rationale for change		Change 1: Change 2:

		Procedures for re-screening and re-testing are permitted under certain circumstances
Section to be changed		**3.3.1 (main diagnosis for study entry)**
Description of change		Change 1: Change of wording "therapy" into "anti-diabetic treatment" Change 2: Adding of wording "intolerances" Change 3: Adding wording "whereas if medications such as metformin and alpha-glucosidase inhibitor are being used, these should be continued".
Rationale for change		Change 1: To clarify that treatment naïve T2DM patients should be offered first line anti-diabetic treatment before patients are eligible for study inclusion Change 2: To clarify that anti-diabetic treatment naïve patients are only eligible for study enrolment if they are intolerant or contra-indicated to first line anti-diabetic treatment. Change 3: To clarify that background anti-diabetic medication such as metformin and alpha-glucosidase inhibitor should be continued at Visit 2.
Section to be changed		**3.3.2 (inclusion criteria)**
Description of change		Change 1: Addition of the statement in the inclusion criteria that anti-diabetic treatment naïve patients are only eligible for study enrolment if they are intolerant or contra-indicated to first line anti-diabetic treatment. Change 2: In consultation with the Steering Committee, enrolment of patients currently at least on SU or glinide may be limited.
Rationale for change		Change 1:

		To clarify this criterion for naïve patients in the inclusion criteria as stated in protocol section 3.3.1. Change 2: To ensure an early/moderate disease population with short to moderate diabetes duration. To allow assessment of the CV safety profile of linagliptin versus glimepiride.
Section to be changed		**3.3.3 (exclusion criteria)**
Description of change		Change 1: The wording any history and/or current treatment with other antidiabetic drugs added to exclusion criteria Change 2: Adding wording "any" insulin. Change 3: Clinical relevant drug-drug interaction of the study medication is limited to corticosteroids Change 4: Add wording "SU class "to exclusion criterion 8.
Rationale for change		Change 1: To clarify that any history and/or current treatment of anti-diabetic drugs as specified in the exclusion criteria will exclude a patient from study enrolment Change 2: To clarify that short term us of any insulin (up to two weeks) is allowed. Change 3: Clinical relevant drug-drug interaction of the study medication is limited to corticosteroids Change 4: To clarify that also known allergy to SU treatment will exclude the patient for study enrolment.
Section to be changed		**3.3.4 (removal of patients from therapy or assessments)**

Description of change		Change 1: Addition of the definition of Lost-To-Follow-Up Change 2: Study medication can be discontinued temporarily. Investigators are encouraged to re-administer study medication to a randomised patient if there are no further safety concerns.
Rationale for change		Change 1: Clarification which patients are considered Lost-To-Follow-Up Change 2: Since this is an outcome study, the primary analysis will be performed based on all randomised patients who were treated with at least one dose of study drug. Therefore investigators are encouraged to re-administer study medication to a randomised patient if there are no further safety concerns.
Section to be changed		**4.1.4 (drug assignment and administration of doses for each patient)**
Description of change		Change 1: The average HBGM value of previous recent fasting HBGM measurements prior to the day of visit (from the patient's HBGM diary) could also be used to guide uptitration at the discretion of the investigator, if there is a meaningful discrepancy between the single fasted HBGM value at the day of the visit in the clinic and this average HBGM value. Change 2: The titration process of the study medication has been further clarified/described Change 3: To add wording that "The above principle also applies for patients being included on a background of alpha-glucosidase inhibitor.
Rationale for change		Change 1:

		To allow to use additional HBGM values if there is a meaningful discrepancy between the HBGM value at the day of visit in the clinic and the HBGM values in patient's HBGM diary Change 2: To clarify the titration phase in more detail to ensure titration process will be followed. Change 3: To clarify that the principle also applies for patients being included on a background of alpha-glucosidase inhibitor.
Section to be changed		**4.2.1 (rescue medication, emergency procedures, and additional treatment(s))**
Description of change		Change 1: Short-acting insulin may be given as rescue medication for up to two weeks in combination with the study medication (e.g. during hospitalisation). Change 2: The results for fasting plasma glucose to initiate rescue medication could be obtained from the HBGM device. Change 3: Add alpha-glucosidase inhibitor Change 4: Adding wording "the protocol defined rescue therapy"
Rationale for change		Change 1: In practice short-acting insulin is given as rescue medication to T2DM patients (e.g. during hospitalization). Such treatment may be given in combination with the study medication for up to two weeks. Change 2: To clarify that the results for fasting plasma glucose to initiate rescue medication could be obtained from the HBGM device. Change 3: To be consistent since alpha-glucosidase inhibitor could be described as anti-diabetic background medication

		Change 4: To clarify that there is specific protocol defined rescue medication
Section to be changed		**4.2.2.1 (restrictions)**
Description of change		Change 1: Short acting insulin may be given as rescue medication up to two weeks (e.g. during hospitalisation) Change 2: If any restricted treatments or any other concomitant drugs interfering with the study medication, the study medication dose can be reduced.
Rationale for change		Change 1: In practice short-acting insulin is given as rescue medication to T2DM patients (e.g. during hospitalization). Such treatment may be given in combination with the study medication for up to two weeks. Change 2: To clarify that study medication dose can be changed if concomitant drugs interfere with the study medication.
Section to be changed		**5.1.1 (endpoint(s) of efficay)**
Description of change		Exclusion of silent MI from primary endpoint
Rationale for change		To clarify that silent MI will be reported as tertiary cardiovascular endpoint
Section to be changed		**5.2.1.1 (reporting waver for cardiovascular events)**
Description of change		Silent MI is added to list of cardiovascular outcome events
Rationale for change		To avoid unblinding of patient with silent MI to ensure the integrity of the trial.
Section to be changed		**5.2.2 (assessment of adverse events)**
Description of change		Change 1: Change of adverse event reporting in case of worsening of the underlying disease or other pre-existing conditions Change 2: Change of adverse event reporting in case of changes in vital signs, ECG, physical examinations, and laboratory test results

		Change 3: Updated reporting of clinical evaluation of hepatic injury
Rationale for change		Change 1: To clarify the criteria for (S)AE reporting. Change 2: To expand the criteria for (S)AE reporting. Change 3: To incorporate clinical evaluation of hepatic injury according to BI standards
Section to be changed		**5.2.2.2 (adverse event and serious adverse event reporting)**
Description of change		Change 1: The observational phase ends 30 days after the patient has completed the study. Change 2: The following paragraph has been added to the protocol: "BI has established 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 via the RDC-system."
Rationale for change		Change 1: To clarify that the he observational phase ends 30 days after the patient has completed the study (with or without study medication). Change 2: To expand the definition of SAEs.
Section to be changed		**5.2.5 (assessment of other safety parameters)**
Description of change		To add wording "something containing"
Rationale for change		For further clarification

Description of change		
Rationale for change		
Section to be changed		**7.1 (objectives)**
Description of change		Addition of "*100" to reflect percentage
Rationale for change		Typo correction
Section to be changed		**7.1 (primary endpoint)**
Description of change		Exclusion of silent MI from primary endpoint
Rationale for change		Silent MI will be reported as tertiary cardiovascular endpoint.
Section to be changed		**7.1 (key secondary endpoints)**
Description of change		Change 1: Definition of rescue medication for evaluation of key secondary endpoints was added. Change 2: Both short acting and basal insulin may be used as rescue medication. Short acting insulin only up to two weeks (e.g. during hospitalisation). Therefore the word "basal" was deleted.
Rationale for change		Change 1: To clarify definition of rescue therapy for evaluation of key secondary endpoints. Change 2: Short-acting insulin may also be used as rescue medication up to two weeks. Use of insulin up to two weeks will not count as rescue medication in the definition of treatment sustainability.
Section to be changed		**7.1 (secondary cardiovascular endpoints)**
Description of change		Change 1: Replace treated patients by patients in the full analysis set. Change 2: Exclusion of silent MI from primary endpoint
Rationale for change		Change 1:

		According to Section 7.3 the primary analysis is performed on the patients in the FAS. Change 2: Silent MI will be reported as tertiary cardiovascular endpoint.
Section to be changed		**7.1 (tertiary cardiovascular endpoints)**
Description of change		Change 1: Summarization of non-fatal and fatal MI, as well as non-fatal and fatal stroke for evaluation of time to and occurrence of tertiary cardiovascular endpoints. Change 2: Refine wording of tertiary cardiovascular endpoint. Change 3: Addition of silent MI as tertiary cardiovascular endpoint.
Rationale for change		Change 1: To allow for an analysis of single components with inclusion of death resulting from such a component. Change 2: Improve wording Change 3: To clarify that silent MI will be analysed as tertiary cardiovascular endpoint.
Section to be changed		**7.1 (secondary diabetes related endpoints)**
Description of change		Addition of any transitions in albuminuria classes and change from baseline in albuminuria as secondary diabetes related endpoints.
Rationale for change		Albuminuria and change of albuminuria are important diabetes related endpoints, which results may be different between the two treatment arms. These endpoints are added to allow any publication of the results.
Section to be changed		**7.1 (tertiary diabetes related endpoints)**
Description of change		Change 1: Addition of time to rescue medication intake as tertiary diabetes related endpoint.

		Change 2: Addition of proportion of patients with rescue therapy intake as tertiary diabetes related endpoint. Change 3: Definition of rescue medication for evaluation of tertiary endpoints was added. Change 4: Deletion of stable angina pectoris as study endpoint.
Rationale for change		Change 1: Definition of new endpoints Change 2: Definition of new endpoints Change 3: To clarify definition of rescue therapy for evaluation of tertiary diabetes related endpoints. Change 4: Stable angina pectoris will not be adjudicated as tertiary cardiovascular endpoint.
Section to be changed		**7.1 (other endpoints)**
Description of change		Change 1: Add proportion of patients with hypoglycaemia and time to first hypoglycaemia as other endpoint. Change 2: Delete all-cause mortality from other endpoints.
Rationale for change		Change 1: Definition of new endpoints Change 2: All-cause mortality is already included in tertiary cardiovascular endpoints.
Section to be changed		**7.2 (null and alternative hypotheses)**
Description of change		Adopt hypotheses for key secondary endpoints.

Rationale for change		As Fisher's exact test will be replaced by Chi-Square test, the two-sided p-value will be reported and hence hypotheses needed to be changed.
Section to be changed		**7.3 (planned analyses)**
Description of change		Change 1: Definition of severe violation of treatment compliance refined. Change 2: The definition of the on-treatment set was refined to be more precise.
Rationale for change		Change 1: Refine definition of violation of compliance Change 2: Clarify the definition of the on-treatment set in detail.
Section to be changed		**7.3.1 (primary analyses)**
Description of change		Change 1: Addition of "*100" to reflect percentage Change 2: Change of the test for evaluation of key secondary endpoints to Chi-Square test, on the same significance level $(2*\alpha_i)*100\%$ as the primary endpoint.
Rationale for change		Change 1: Typo correction. Change 2: Use of Chi-Square test instead of Fisher's exact test as this test is more powerful. Use of two-sided p-values.
Section to be changed		**7.3.2 (secondary analyses)**
Description of change		Change 1: For all cardiovascular endpoints that include occurrence of an event, Chi-Square test is used to compare the two treatment groups. Change 2: A logistic regression with factor treatment is performed for cardiovascular endpoints.

		Change 3: There will not be any one-sided tests (test for superiority of linagliptin versus glimepiride, alpha= 0.025) be performed for diabetes related endpoints. Change 4: For continuous secondary diabetes related endpoints with several on-treatment measurements change from baseline will be evaluated with a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach. For those continuous secondary diabetes related endpoints with only one measurement on treatment an analysis of covariance (ANCOVA) model with the factor treatment and the baseline value of the respective variable as covariate will be performed. Change 5: For qualitative secondary diabetes related endpoints, Chi-Square test is used to compare the two treatment groups.
Rationale for change		Change 1: Use of Chi-Square test instead of Fisher's exact test as this test is more powerful. Change 2: The logistic regression will be performed additionally to report odds ratios. Change 3: In order to provide a consistent picture, all binary and continuous diabetes related endpoints will be investigated in the same way, respectively. Change 4: The MMRM approach will be performed to allow dealing with missing values and to account for correlations between repeated measurements. Change 5:

		Use of Chi-Square test instead of Fisher's exact test as this test is more powerful.
Section to be changed		**7.3.4 (interim analyses)**
Description of change		Deleted filing of DMC charter in ISF.
Rationale for change		The DMC charter will not be filed in the ISF.
Section to be changed		**7.4 (handling of missing data)**
Description of change		Change 1: The REML based MMRM analysis will handle missing data for continuous diabetes related endpoints. Change 2: The last observation carried forward (LOCF) approach will be performed in a sensitivity analysis on diabetes related endpoints.
Rationale for change		Change 1: This analysis will deal with missing values. Change 2: As the MMRM approach will be used to deal with missing observations of continuous diabetes related endpoints, LOCF will be performed in a sensitivity analysis.
Section to be changed		**8 and 8.1 (study approval, patient information, and informed consent)**
Description of change		Additional wording/paragraph for Japan
Rationale for change		To fulfil Japanese requirements
Section to be changed		**8.2 (data quality assurance)**
Description of change		Additional paragraph regarding data quality assurance
Rationale for change		To clarify data quality assurance
Section to be changed		**8.4.1 (listedness and expedited reporting of adverse events)**
Description of change		Change of required SPC references
Rationale for change		Unique reference documents for metformin and pioglitazone are no longer required, since rescue medication is not pre-specified. Per protocol there are several options for rescue medication (investigator's judgement).

Section to be changed		**8.7 (protocol violations)**
Description of change		Addition of paragraph regarding reporting of protocol violations
Rationale for change		To clarify requirement of reporting of protocol violations
Section to be changed		**9.1 (published references)**
Description of change		Deletion of reference R11-2713
Rationale for change		Reference R11-2713 is not needed anymore.
Section to be changed		**10.2 (definitions of endpoint events)**
Description of change		Definitions of the adjudicated endpoints events and the principles of standardised data collection in the centralised CEC adjudication process are outlined in the current CEC Charter and process guideline. The endpoint definitions are deleted from the protocol.
Rationale for change		To reflect that the CEC charter will be maintained throughout the course of current definitions for cardiovascular endpoints.
Section to be changed		**10.3 (blood pressure measurement procedure and treatment recommendations)**
Description of change		Addition of further guidance of blood pressure measurements
Rationale for change		To clarify blood pressure measurements
Section to be changed		**Section 10.6 (clinical evaluation of liver injury)**
Description of change		Updated paragraphs of clinical evaluation of liver injury
Rationale for change		To incorporate clinical evaluation of liver injury according to BI standards

Number of CTP modification		3
Date of CTP modification		1 August 2012
EudraCT number		2009-013157-15
BI Trial number		1218.74
BI Investigational Product(s)		Linagliptin
Title of protocol		A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2

		diabetes mellitus at high cardiovascular risk. The CAROLINA Trial.
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		☐
Section to be changed		**Title page**
Description of change		Trial Clinical Monitor name and address details updated.
Rationale for change		New TCM assigned and address change.
Section to be changed		**Protocol synopsis (Objectives)**
Description of change		Inclusion of the fifth test within hierarchical testing procedure.
Rationale for change		As the classical MACE endpoint will be introduced as first key secondary endpoint, the testing hierarchy will include 5 hypothesis tests.
Section to be changed		**Protocol synopsis (Methodology)**
Description of change		Safety was crossed out as the study's focus lies on efficacy and safety.
Rationale for change		For clarification.
Section to be changed		**Protocol synopsis (No. of patients)**
Description of change		"At least" was changed into "An estimated number of".
Rationale for change		To clarify that the study is event driven and that the required number of patients is an estimation.
Section to be changed		**Protocol synopsis (inclusion criteria)**
Description of change		<u>Change 1:</u> - Myocardial infarction (≥ 6 weeks prior to informed consent) - Percutaneous Coronary Intervention (PCI) ≥ 6 weeks prior informed consent - Coronary Artery By-pass Grafting (CABG) ≥ 4 years prior to informed

		consent or with recurrent angina pectoris following surgery - Ischemic or hemorrhagic stroke (≥ 3 months prior to informed consent) *Was changed to:* - Myocardial infarction (> 6 weeks prior to informed consent) - Percutaneous Coronary Intervention (PCI) > 6 weeks prior informed consent - Coronary Artery By-pass Grafting (CABG) > 4 years prior to informed consent or with recurrent angina pectoris following surgery - Ischemic or hemorrhagic stroke (> 3 months prior to informed consent). <u>Change 2:</u> Treatment compliance requirement in the placebo-run was added.
Rationale for change		To be consistent with section 3.3.2 inclusion criteria.
Section to be changed		**Protocol synopsis (criteria for exclusion)**
Description of change		<u>Change 1:</u> Duration of short term insulin (up to two weeks) is allowed, if taken at least 8 weeks prior informed consent *was changed into:* Duration of short term insulin (up to two consecutive weeks) is allowed, if taken at least 8 weeks prior informed consent. <u>Change 2:</u> All exclusion criteria have been added.
Rationale for change		<u>Change 1:</u> For clarification and <u>Change 2:</u> to be consistent with section 3.3.3 exclusion criteria.
Section to be changed		**Protocol synopsis (duration of treatment)**
Description of change		2 to 4 weeks placebo run-in phase followed by up to 400 weeks treatment + 1 week follow-up after study drug termination.

		Observational study duration is up to 30 days after date of patients Final Visit. *Was changed into:* 2 up to 4 weeks placebo run-in phase followed by up to an estimated 400 weeks treatment period and 1 week follow-up after study drug termination. Observational study duration is up to 30 days after date of patients Final Visit.
Rationale for change		To clarify duration of treatment.
Section to be changed		**Protocol synopsis (Criteria for efficacy)**
Description of change		Inclusion of classical MACE endpoint as first key secondary endpoint and shift of previous first and second key secondary endpoints to second and third position.
Rationale for change		This endpoint was defined as first key secondary endpoint.
Section to be changed		**Protocol synopsis (Criteria for safety)**
Description of change		Change 1: non- fatal MI, non- fatal stroke, *Was changed into:* **(**non**)**- fatal MI, **(**non**)**- fatal stroke, Change 2: Silent myocardial infarction added as criteria for safety; Change 3: Reference to section 5.2 added.
Rationale for change		To be consistent with section 5.2.1 endpoints and tertiary cardiovascular endpoints as described in section 7.1
Section to be changed		**Protocol synopsis (Statistical methods)**
Description of change		Inclusion of analysis methods for key secondary endpoints.
Rationale for change		According to Annotated clinical trial protocol instructions the model used for the analysis of key secondary endpoints should be mentioned.
Section to be changed		**Flow chart**
Description of change		

		Change 1: Maximum number of days from screening (V1a) to randomisation changed from -42 into -35; Change 2: demographics obtained at Visits 1a and 1b, footnote added that the race of the patient will be collected; Change 3: additional footnotes added, re-ordered or revised; Change 4: added that placebo run-in medication will be dispensed by the IXR system; Change 5: Change 6: Change 7: additional laboratory parameters added to footnote h; Change 8: added that the MDRD considers race as an adjustment factor; Change 9: Change 10:

		Change 11: clarification of end of trial activities and guidance on re-institution of glimepiride/glimepiride placebo added.
Rationale for change		Change 1: To clarify maximum number of days between screening and randomisation; Change 2: to clarify that demographic data is obtained at Visit 1a and Visit 1b and that race will be captured in the eCRF, because T2DM treatment results maybe race sensitive. Furthermore, the renal function will be assessed using the MDRD formula. This formula considers the race as an adjustment factor, therefore, the race must be known for accurate estimation; Change 3: to adapt the footnotes to the changes in the flowchart; Change 4: to clarify that placebo run-in medication is dispensed by IXRS; Change 5: Change 6: Change 7: to clarify obtained laboratory parameters at Visit 1a; Change 8:

		to state that MDRD formula considers race as an adjustment factor; Change 9: to clarify that the number of to be obtained questionnaires is an approximation; Change 10: Change 11: to clarify end of trial activities and to add guidance on re-institution of trial medication.
Section to be changed		**Abbreviations**
Description of change		Several abbreviations added.
Rationale for change		To list all abbreviations used in the protocol.
Section to be changed		**2.2 Trial Objectives**
Description of change		Inclusion of classical MACE endpoint as first key secondary endpoint.Inclusion of the fifth test within hierarchical testing procedure.
Rationale for change		As the classical MACE endpoint will be introduced as first key secondary endpoint, the testing hierarchy will include 5 hypothesis tests.
Section to be changed		**3.1 Overall trial design and trial population**
Description of change		Change 1: The first paragraph was aligned with the methodology section in the protocol synopsis; Change 2: the minimum number of patients of 6000 was changed into an estimated number of 6000 patients, in addition it was added that the 400 weeks treatment duration is an estimated treatment duration; Change 3:

		treatment compliance criterion was added to the definition of successfully completed at least two weeks of the placebo run-in; Change 4: added that SU/glinide should not be taken in the morning of Visit 2. Change 5: the end of trial activities and requirements were clarified and Change 6: trial stop procedures, including timeframe to stop the trial and to perform last patient visits clarified.
Rationale for change		Change 1: To be consistent with the methodology section in the synopsis; Change 2: to clarify that the study is event driven and that the required number of patients and the treatment duration is an estimation; Change 3: to clarify that the treatment compliance criterion is a placebo-run requirement; Change 4: to clarify that no double doses should be taken at Visit 2; Change 5: to clarify end of trial activities and Change 6: to clarify trial stop procedures.
Section to be changed		**3.1.1 Administrative structure of the trial**
Description of change		Pancreatic adjudication was added.
Rationale for change		To set-up an adjudication committee for pancreatic events.

Section to be changed		**3.2 Discussion of trial design, including the choice of control group**
Description of change		The treatment duration was clarified e.g. by adding that the 400 week treatment duration is estimation.
Rationale for change		To clarify treatment duration.
Section to be changed		**3.3 Selection of trial population**
Description of change		Change 1: The number of patients to be screened was increased from 9000 to 10.000 patients; Change 2: at least 6000 patients *Was changed to:* estimated number of 6000 patients; Change 3: clarification of expected number of patients per site and Change 4: Requirement to obtain approval from the TCM to randomise more than 30 patients was removed.
Rationale for change		Change 1: To reflect the expected number of screened patients based on actual data and current percentage of screen failures; Change 2: to clarify that the study is event driven and that the required number of patients is an estimation; Change 3: to clarify that sites could end up with less than 8 patients due to competitive recruitment and Change 4: approval to continue recruitment beyond 30 patients in a certain sites is given by the

		TCM to the CML and therefore will be transferred to the monitoring manual.
Section to be changed		**3.3.3 Exclusion criteria**
Description of change		Duration of short term insulin (up to two weeks) is allowed, if taken at least 8 weeks prior informed consent *Was changed to:* Duration of short term insulin (up to two consecutive weeks) is allowed, if taken at least 8 weeks prior informed consent.
Rationale for change		For clarification
Section to be changed		**3.3.4.1 Removal of individual patients**
Description of change		Change 1: End of study was changed into end of trial; Change 2: inappropriateness of glimepiride treatment for renal safety issues according to local prescribing information was added as a withdrawal criterion; Change 3: the end of treatment requirements and follow-up procedures have been updated and Change 4: added that SU/glinide should not be taken in the morning of Visit 2.
Rationale for change		Change 1: To use consistent terminology in line with the protocol flow chart; Change 2: for clarification; Change 3: to clarify end of treatment activities and follow-up requirements and Change 4:

		to clarify that no double doses should be taken at Visit 2.
Section to be changed		**4.1.2 Method of assigning patients to treatment groups**
Description of change		Added that sites will receive an information manual describing all steps to randomise a patients, obtain a medication kit assignment and to acknowledge study drug.
Rationale for change		For clarification.
Section to be changed		**4.1.4 Drug assignment and administration of doses for each patient**
Description of change		Change 1: The titration requirements have been re-written; Change 2: "If applicable" was added to the sentence that patients will continue their standard metformin therapy throughout the study; Change 3: investigator judgement to change study medication was changed into investigators judgement to change glimepirde/glimepiride placebo; Change 4: added that patients should be instructed to take trial medication once daily with water; Change 5: guidance on re-institution of glimepiride/ glimepiride placebo added and Change 6: Guidance on timing of in clinic visit added.
Rationale for change		Change 1: To clarify that glimepiride/glimepiride placebo is uptitrated and not study medication, which included linagliptin/linagliptin placebo (double dummy);

		Change 2: to clarify that treatment naive patients are eligible if intolerant or contra-indicated to first line anti-diabetic treatment; Change 3 and change 4: for clarification; Change 5: to add guidance on re-institution of trial medication and Change 6: To be consistent with instruction given in section 6.1.
Section to be changed		**4.1.7 Storage conditions**
Description of change		Change 1: Added that in addition to wallets, blisters are provided; Change 2: added that a temperature log must be maintained at site and Change 3: medication return requirements were moved to the correct section in the protocol, section 4.1.8.
Rationale for change		Change 1: To clarify the use of wallets and blisters; Change 2: to clarify temperature monitoring requirements for study medication and Change 3: to move the drug accountability requirements to the corresponding section in the protocol.
Section to be changed		**4.1.8 Drug accountability**
Description of change		Drug accountability requirements was shifted from Section 4.1.7 to this Section.

Rationale for change		To add drug accountability requirement to the correct clinical trial protocol section.
Section to be changed		**4.3 Treatment compliance**
Description of change		Change 1: The requirement to use a worksheet to document treatment compliance was removed and Change 2: It was clarified that severe violation of compliance is seen as important protocol violation.
Rationale for change		Change 1: Treatment compliance should be reflected in the patient source documents and Change 2: for clarification.
Section to be changed		**5.1.1 Endpoint(s) of efficacy**
Description of change		Inclusion of classical MACE endpoint as first key secondary endpoint.
Rationale for change		This endpoint was defined as first key secondary endpoint.
Section to be changed		**5.1.2 Assessment of efficacy**
Description of change		The definition of overnight fast was made consistent with the definition given in the protocol synopsis.
Rationale for change		For consistency.
Section to be changed		**5.2.1 Endpoint(s) of safety**
Description of change		Change 1: The reporting requirements for outcome events was moved from section 5.2.2.2 to this section, describing the outcome events and Change 2: added that in case of a stroke the disability or dependence in daily activities will be collected with the modified Rankin Scale (mRS).
Rationale for change		Change 1:

		To reflect the outcome reporting requirements in the correct section of the clinical trial protocol and Change 2: to clarify that the grade of mRS is collected in case of a stroke.
Section to be changed		**5.2.2.1 Definitions of adverse events**
Description of change		Change 1: Added that all symptomatic hypoglycaemic events, all asymptomatic hypoglycaemic events with glucose levels less than 3.0 mmol/L and all asymptomatic hypoglycaemic events considered an AE by the investigator should be reported as adverse event and Change 2: clarification that hepatic injury is to be reported as SAE added.
Rationale for change		Change 1: To clarify reporting procedures for hypoglycaemic events. Change 2: To be in line with Boehringer Ingelheim standard operating procedures.
Section to be changed		**5.2.2.2 Adverse event and serious adverse event reporting**
Description of change		The reporting requirements for outcome events have been moved to section 5.2.1 of the clinical trial protocol.
Rationale for change		To reflect the reporting requirements of outcome events and AESI in the correct sections of the clinical trial protocol.
Section to be changed		**5.2.3 Assessment of safety laboratory parameters**
Description of change		Change 1: Added that the lipid profile will only be obtained at Visits: 2, 6, 9, 12, 15, 18, 21, 24, 27 and 30; Change 2:

		added that bilirubin is not measured at Visit 1a; Change 3: Change 4: additional laboratory parameters added to Visit 1a and Change 5: added that the MDRD considers race as an adjustment factor.
Rationale for change		Change 1: To clarify laboratory requirements; Change 2: to clarify that bilirubin is not measured a Visit 1a; Change 3: Change 4: to clarify obtained laboratory parameters at Visit 1a and Change 5: to state that MDRD formula considers race as an adjustment factor.
Section to be changed		**5.2.4 Electrocardiogram (ECG)**
Description of change		Added that in case of unresolved discrepancies investigators will not receive evaluated ECG reports from the vendor.
Rationale for change		To clarify that in case of discrepancies the processing timelines will be > 3 days.
Section to be changed		**5.2.5 Assessment of other safety parameters**
Description of change		Change 1:

		The requirement to use the same blood pressure instrument and weight measurement scale throughout the study was changed into a similar type of blood pressure instrument and weight scale; Change 2: the procedure for HBGM devices and corresponding reporting and site contact requirements have been clarified and Change 3: a requirement to collect the HBGM diary at each visit was added.
Rationale for change		Change 1: Use of the same blood measure instrument or weight scale device is from operational perspective not feasible taking into account treatment duration. A similar type of instrument or scale is acceptable; Change 2: to clarify HBGM procedures and corresponding reporting and contact requirements and Change 3: to avoid potential loss of source data.
Rationale for change		
Section to be changed		
Description of change		The second paragraph was deleted.
Rationale for change		To remove duplicate text.
Section to be changed		**6.2.1 Screening an placebo run-in period**
Description of change		Change 1: Transaminases was defined as ALT (SGPT) and AST (SGOT) and urine albumin and urine creatinine was added; Change 2:

		the placebo run-in duration was changed from 2 to weeks into 2 up to 4 weeks and Change 3: it was clarified that patient requiring rescue therapy during the placebo run-in are not eligible.
Rationale for change		Change 1: To clarify obtained laboratory parameters at Visit 1a; Change 2: to clarify the placebo-run in duration and Change 3: to clarify that rescue medication during placebo run-in is allowed, although the patient would not be eligible.
Section to be changed		**6.2.2 Treatment phase**
Description of change		It was clarified that glimepiride/ glimepiride placebo will be uptitrated between visits 2-6 and all end of trial activities have been transferred to section 6.2.3.
Rationale for change		To clarify that glimepiride/glimepiride placebo is uptitrated during Visits 2-6 and to transfer end of trial activities to the corresponding section of the clinical trial protocol.
Section to be changed		**6.2.3 End of trial and follow-up period**
Description of change		Change 1: End of study was changed into end of trial and Change 2: the end of treatment requirements and follow-up procedures have been updated.
Rationale for change		Change 1: To use consistent terminology in line with the protocol flow chart and Change 2:

		to clarify end of treatment activities and follow-up requirements.
Section to be changed		**7.1 Design**
Description of change		The minimum number of patients of 6000 was changed into an estimated number of 6000 patients.
Rationale for change		To clarify that the study is event driven and that the required number of patients is an estimation.
Section to be changed		**7.1 Primary endpoint**
Description of change		Patients without events will be considered censored at the end of study or at lost to follow-up, whichever comes first. *Was changed to:* If patients do not experience a primary endpoint event, they will be considered censored at their last documented study visit. If a patient died and has no primary outcome event, the patient will be censored at the date of death.
Rationale for change		Correction of description
Section to be changed		**7.1 Key secondary endpoints**
Description of change		Definition of time to the first occurrence of any of the adjudicated components of the classical MACE composite endpoint as first key secondary endpoint. Definition of previous first and second key secondary endpoints as second and third key secondary endpoints.
Rationale for change		To include the testing for superiority on the time to the first occurrence of any of the adjudicated components of the classical MACE composite endpoint into the testing hierarchy as the third test.
Section to be changed		**7.1 Secondary cardiovascular endpoints**
Description of change		Delete time to first occurrence of any of the adjudicated components of the classical MACE composite endpoint from secondary endpoints.
Rationale for change		This endpoint was defined as first key secondary endpoint.

Section to be changed		**7.2 Null and alternative hypotheses**
Description of change		Change 1: Inclusion of the superiority hypothesis with respect to time to first occurrence of any of the adjudicated components of the classical MACE endpoint to be tested thirdly. The hypotheses on second and third key secondary endpoints will be tested fourthly and fifthly, respectively, if previous tests have revealed significant results. Change 2: Any confirmatory hypothesis test will be performed on the full analysis set.
Rationale for change		Change 1: Change of testing hierarchy to include also superiority testing for classical MACE endpoint. Change 2: According to Annotated clinical trial protocol instructions the patient population should be stated in this subsection.
Section to be changed		**7.3 Planned analysis**
Description of change		Change 1: A protocol violation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint and/or key secondary endpoints. Change 2: The name of the on-treatment set was changed to 30-days-treatment set.
Rationale for change		Change 1: Explaining the details on important protocol violations. Change 2: Ensuring the name of the patient analysis set reflects the definition.

Section to be changed		**7.3.1 Primary analyses**
Description of change		Change 1: It was clarified, that the Steering Committee, which is blinded, will decide on the number and time points of the interim analyses. Change 2: Change description of testing hierarchy according to Section 7.2 and Change 3: inclusion of description of sensitivity analyses of first key secondary endpoint. Clarification of sensitivity analyses for second and third key secondary endpoints. Change 4: The name of the on-treatment set was changed to 30-days-treatment set. Change 5: In the sensitivity analyses censoring will be done at time patients are on-treatment + 30 days after permanent treatment discontinuation or end of observation, whichever comes first. Change 6: The definition of the on-treatment analysis was included.
Rationale for change		Change 1: To ensure the decision on the number and time points for the formal interim analyses are made by the steering committee, which is blinded. Change 2: Inclusion of the superiority hypothesis with respect to time to first occurrence of any of the adjudicated components of the classical MACE endpoint to be tested thirdly and Change 3:

		Clarification of sensitivity analyses of key secondary endpoints. <u>Change 4:</u> Ensuring the name of the patient analysis set reflects the definition. <u>Change 5:</u> Clarification that in the sensitivity analyses the censoring will be performed at the time patients are on-treatment + 30 days after permanent treatment discontinuation or end of observation, whichever comes first. <u>Change 6:</u> The definition of the on-treatment analysis was included based on FDA request.
Section to be changed		**<u>7.3.4 Interim analyses</u>**
Description of change		It was clarified, that the Steering Committee will decide on the number and time points of the interim analyses. The DMC will perform periodic safety reviews with a frequency as detailed in the DMC charter, but additional looks may be scheduled as needed by the DMC. In addition, the Steering Committee may also request the DMC to meet for a safety review.
Rationale for change		To ensure the decision on the number and time points for the formal interim analyses are made by the steering committee, which is blinded. It was clarified that the DMC performs periodic safety reviews.
Section to be changed		**7.5 Randomisation**
Description of change		DMC will have access to randomisation code.
Rationale for change		To clarify the role of the DMC.
Section to be changed		**7.6 Determination of sample size**
Description of change		The sentence on the decision about number and time points of the interim analyses was deleted.

Rationale for change		These details are clarified in Section 7.3.1 and 7.3.4.
Section to be changed		**8 informed consent, data protection, trial records**
Description of change		The version as of October 1996 of the declaration of Helsinki was removed.
Rationale for change		To be in line with corporate standard operating procedures.
Section to be changed		**10.3 Blood pressure measurement procedure and treatment recommendations**
Description of change		The requirement to use the same blood pressure instrument measurement scale throughout the study was changed into a similar type of blood pressure instrument.
Rationale for change		Use of the same blood measure instrument is from operational perspective not feasible taking into account treatment duration. A similar type of instrument or scale is acceptable.
Section to be changed		**10.5 Silent myocardial infarction**
Description of change		Reference to section 10.2.4 deleted.
Rationale for change		No longer a valid reference.
Section to be changed		**10.6.2 procedures**
Description of change		The procedures and testing requirement in case of clinical evaluation of liver injury have been aligned with the Boehringer Ingeheim standard operating procedure.
Rationale for change		To be in line with Boehringer Ingelheim standard operating procedures.

Number of CTP modification		4
Date of CTP modification		April 2013
EudraCT number		2009-013157-15
BI Trial number		1218.74
BI Investigational Product(s)		Linagliptin
Title of protocol		A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The CAROLINA Trial.

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		☒
Section to be changed		**Title page**
Description of change		Trial Clinical Monitor name and address details updated.
Rationale for change		New TCM assigned and address change.
Section to be changed		**Protocol synopsis (Duration of treatment)**
Description of change		Introduction of the term follow-up period
Rationale for change		To be in line with current Boehringer Ingelheim standard operating procedures
Section to be changed		**Flow chart**
Description of change		
Rationale for change		
Section to be changed		**Abbreviations**
Description of change		LADA was added to the list.
Rationale for change		For clarification
Section to be changed		**3.1 Overall trial design and plan**
Description of change		medication ~~treatment~~ permanently
Rationale for change		Typo correction
Section to be changed		**3.3.4.1 Removal of individual patients**
Description of change		Change 1: The possibility of vital status and outcome events follow up after informed consent withdrawal was added. Change 2: End of Trial was changed into End of Treatment

		Change 3: (Follow up Visit) was added after V31 Change 4: Pancreatitis was added as a reason to stop the study medication. Change 5: "Permenantly" was added.
Rationale for change		Change 1: Obtain vital status and outcome events after withdrawal. Change 2: To be in line with the Flow chart Change 3: For clarification Change 4: Safety update Change 4: For clarification
Section to be changed		**4.2.1 Rescue medication, emergency procedures and additional treatment(s)**
Description of change		For other than the protocol defined rescue medication it was specified that the study treatment should be discontinued when this rescue medication is contraindicated with the study treatment.
Rationale for change		For clarification
Section to be changed		**5.2.2.1 Definitions of adverse events**
Description of change		Change 1: Reporting of non-serious AESIs according to the SAE procedure was added. Change 2: (with differentiation of bilirubin in direct and indirect if total bilirubin is elevated)

		was added to the hepatic event bilirubin testing.
Rationale for change		Change 1: Clarification of (S)AE and AESI reporting to be in line with Boehringer Ingelheim standard operating procedures. Change 2: For clarification
Section to be changed		**5.2.2.2 Adverse event and serious adverse event reporting**
Description of change		Change 1: Introduction of the term follow-up period. Change 2: The following text was added: The investigator should report SAEs which occurred in a patient after the follow-up period, if the investigator becomes aware of them. Change 3: Paragraph regarding the immediate documentation of events was updated: The investigator must document immediately (within 24 hours of awareness ~~or the next business day whichever is shorter~~) the following events on the SAE case page form in RDC: Change 4: Reporting of all AESIs according to the SAE procedure was added.
Rationale for change		Change 1: To be in line with current Boehringer Ingelheim standard operating procedures. Change 2: Clarification of (S)AE and AESI reporting to be in line with Boehringer Ingelheim standard operating procedures. Change 3:

		Clarification of (S)AE and AESI reporting to be in line with Boehringer Ingelheim standard operating procedures. Change 4: Clarification of (S)AE and AESI reporting to be in line with Boehringer Ingelheim standard operating procedures.
Rationale for change		
Section to be changed		**6.2.3 End of trial and Follow-up period**
Description of change		Change 1: End of Trial was changed into End of Treatment Change 2: The possibility of vital status and outcome events follow up after informed consent withdrawal was added. Therefore the text about study end after ICF withdrawal was also removed.
Rationale for change		Change 1: To be in line with the Flow chart Change 2: Obtain vital status and outcome events after withdrawal.
Section to be changed		**7.1 Statistical Design – Model**
Description of change		Change 1: Change 2:

Rationale for change		Change 1: Measurements are only performed at baseline. Change 2: For clarification
Section to be changed		**7.3 Planned analyses**
Description of change		Change 1: Change 2:
Rationale for change		Change 1: For clarification Change 2:

Number of CTP modification		5
Date of CTP modification		14 September 2015
EudraCT number		2009-013157-15
BI Trial number		1218.74
BI Investigational Product(s)		Linagliptin
Title of protocol		A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The CAROLINA Trial.
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		☐
Section to be changed		**Title page**
Description of change		Trial Clinical Monitor name and address details updated.
Rationale for change		New TCM assigned and address change.
Section to be changed		**Flow chart**
Description of change		Change 1: FU period changed from 7 to 30 days Change 2: Glomerular filtration rate and Fasting Plasma glucose samples to be taken at V31
Rationale for change		Change 1: To be in line with the project FU period Change 2: To reflect actual testing done at V31
Section to be changed		**3.1 Overall trial design and plan**
Description of change		Text on Follow-up period was updated to reflect the 30d FU period
Rationale for change		For clarification
Section to be changed		**3.2 Discussion on trial design, including the choice of control group**
Description of change		Text on Follow-up period was updated to reflect the 30d FU period
Rationale for change		For clarification
Section to be changed		**3.3.4.1 Removal of individual patients**
Description of change		Retention strategy language was updated + Follow-up period was updated to reflect the 30d FU period
Rationale for change		For clarification
Section to be changed		**4.2.1 Rescue medication, emergency procedures and additional treatment(s)**
Description of change		'Including during the FU period' was added

Rationale for change		Text on Follow-up period was updated to reflect the 30d FU period
Section to be changed		**5.2.2.1 Definitions of adverse events**
Description of change		Change 1: AESI : alignment of text throughout the Lina project Change 2: addition of pancreatic cancer as AESI Change 3 : throughout this section, text was updated to reflect current standard text
Rationale for change		Change 1: For clarification Change 1: Alignment within the Lina project Change 3: AE and SAE definitions were updated to reflect the latest standard text
Section to be changed		**5.2.2.2 Adverse event and serious adverse event reporting**
Description of change		throughout this section, text was updated to reflect current standard text
Rationale for change		AE and SAE definitions were updated to reflect the latest standard text
Section to be changed		**5.2.2.3 Oncological adverse events**
Description of change		Oncological assessment was added
Rationale for change		For clarification
Section to be changed		**5.2.3.4 Renal function impairment**
Description of change		Formulas taken out and reference made to the Statistical Analysis Plan
Rationale for change		For clarification
Section to be changed		**6.2.3 End of trial and Follow-up period**
Description of change		Text adapted to be in line with section 3.3.4.1
Rationale for change		For clarification
Section to be changed		**7.1 Statistical design - model**
Description of change		Change 1 : Change 2 : Secondary diabetic related endpoints

		'Urinary' added to albumin
Rationale for change		Change 1 : For clarification Change 2 : For clarification

Number of CTP modification		6
Date of CTP modification		20 April 2016
EudraCT number		2009-013157-15
BI Trial number		1218.74
BI Investigational Product(s)		Linagliptin
Title of protocol		A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The CAROLINA Trial.
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		☐
Section to be changed		**Title page**
Description of change		Change 1: Trial Clinical Monitor name and address details updated.
Rationale for change		Change 1: Change in Trial Clinical Monitor
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		**Objectives:** Change 1: Primary endpoint changed to time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) or non-fatal stroke.

		Change 2:…then thirdly the first key secondary endpoint will be tested hierarchically *Was changed into:* …then thirdly the first key secondary endpoint will be tested hierarchically with a superiority hypothesis. **Duration of treatment:** Change 3: Estimated trial duration updated to 432 weeks. **Criteria for efficacy:** Change 4: Primary endpoint changed to time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) or non-fatal stroke. Change 5: First key secondary endpoint changed to time to the first occurrence of any of the following adjudicated components of: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris. **Criteria for safety** Change 6:…silent myocardial infarction *was changed into:* … and occurrence of and time to silent myocardial infarction.
Rationale for change		Change 1, 4, 5: Testing hierarchy revised following a unanimous request from the trial Academic Steering Committee. Change 2: For clarification. Change 3: Estimated trial duration increased due to change of primary endpoint.

		Change 6: Clarification added, that silent MI is not a by adjudication confirmed endpoint.
Section to be changed		**Flowchart**
Description of change		Change 1: Two additional visits added to the trial flow chart. Change 2: footnote 'n': …at minimum a yearly telephone call and a telephone call at study end will be asked for, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit might be recorded. *Was changed into:* …at minimum a yearly telephone call and a telephone call at study end (through the patient or alternative person designated by the patient) will be asked for, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit should be recorded.
Rationale for change		Change 1: Estimated trial duration increased due to change of primary endpoint. Change 2: for clarification.
Section to be changed		**Abbreviations**
Description of change		Abbreviations section updated.
Rationale for change		For clarification
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: Primary endpoint changed to time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) or non-fatal stroke.

		Change 2: First key secondary endpoint changed to time to the first occurrence of any of the following adjudicated components of: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris.
Rationale for change		Change 1, 2**:** Testing hierarchy revised following a unanimous request from the trial Academic Steering Committee.
Section to be changed		**3.1 Overall trial design and plan**
Description of change		Change 1: Estimated treatment time updated to 432 weeks and duration of maintenance phase updated to an estimated 416 weeks. Change 2: ...at minimum a yearly telephone call and a telephone call at study end will be asked for, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit might be recorded. *Was changed into:* …at minimum a yearly telephone call and a telephone call at study end (through the patient or alternative person designated by the patient) will be asked for, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit should be recorded. Change 3: Guidance revised on the timing of the EOT visit after study stop announcement after 631 endpoint events are reached.
Rationale for change		Change 1: Estimated trial duration increased due to change of primary endpoint. Change 2: For clarification.

		Change 3: To clarify the respective actions to stop the trial when 631 endpoint events are reached.
Section to be changed		**3.2 Discussion of trial design, including the choice of control group**
Description of change		Estimated trial duration updated to 432 weeks.
Rationale for change		Estimated trial duration increased due to change of primary endpoint.
Section to be changed		**3.3.1 administrative structure of the trial**
Description of change		Clinical Event Committee was changed in Clinical Event Committees.
Rationale for change		Correction of typographical error
Section to be changed		**3.3.4.1 Removal of individual patients**
Description of change		Change 1:...at minimum a yearly telephone call and a telephone call at study end will be asked for, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit might be recorded. *Was changed into:* …at minimum a yearly telephone call and a telephone call at study end (through the patient or alternative person designated by the patient) will be asked for, to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit should be recorded. Change 2: See further details in section 4.2 was added following the last sentence of paragraph 5. Change 3**…**Visit 31 (Follow-up) *was changed into*: Visit 33 (Follow-up).
Rationale for change		Change 1+2: For clarification Change 3: Two additional Visits added as the estimated trial duration increased due to change of primary endpoint.
Section to be changed		**4.1.4 Drug assignment and administration of doses for each patient**
Description of change		..IXRS will allocate medication kit numbers at each scheduled in-clinic visit (V2 –

		V29)….At visits 6-29 patients will receive one treatment box… *Was changed into:* ..IXRS will allocate medication kit numbers at each scheduled in-clinic visit (V2 – V31)….At visits 6-31 patients will receive one treatment box…
Rationale for change		Two additional Visits added as the estimated trial duration increased due to change of primary endpoint.
Section to be changed		**5.1.1 Endpoint(s) off efficacy**
Description of change		Change 1: Primary endpoint changed to time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) or non-fatal stroke. Change 2: First key secondary endpoint changed to time to the first occurrence of any of the following adjudicated components of: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris.
Rationale for change		Change 1, 2**:** Testing hierarchy revised following a unanimous request from the trial Academic Steering Committee.
Section to be changed		**5.2.2.1 Assessment of adverse events**
Description of change		**AESI:** the following sentence was omitted Documentation should be done on the AESI and SAE form.
Rationale for change		Covered in section 5.2.2.2 adverse event and serious adverse event reporting.
Section to be changed		**5.2.2.2 Adverse event and serious adverse event reporting**
Description of change		Immediate documentations of events:…. On the SAE to the sponsor *was changed into:* …On the SAE form to the sponsor.
Rationale for change		For clarification
Section to be changed		**5.2.3.2 Clinical chemistry**
Description of change		Visit 32 added to footnote ***

Rationale for change		Additional Visits added as the estimated trial duration increased due to change of primary endpoint.
Section to be changed		**6.2.2 Treatment phase**
Description of change		Change 1:…regularly scheduled randomization as specified.. *was changed into:* regularly scheduled Visits as specified… Change 2: *The following text was omitted* either by clinic visits or by phone **(**refer to section 6.2.3**)** and *the following text was added*: 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 (through the patient or alternative person designated by the patient) will be required, to document the occurrence of outcome events and vital status. If possible, also 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. Change 3:….even if the dose must be down titrated *was changed into:* even if the dose must be titrated
Rationale for change		Change 1: Correction of error. Change 2: For clarification and consistency with section 3. Change 3: For clarification.
Section to be changed		**6.2.3 End of trial and follow-up period**
Description of change		Change 1: The following text was added: 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 must be involved in the discussions with the patient regarding a withdrawal of consent. Change 2: …for end of treatment visit and visit 31 (follow-up) *was changed into:* or end of treatment visit and visit 33(follow-up). Change 3: Paragraph starting with patient who discontinue….removed
Rationale for change		Change 1: For clarification and consistency with section 3. Change 2: Two additional Visits added as the estimated trial duration increased due to change of primary endpoint. Change 3: Covered in section 6.2.2 and section 3.
Section to be changed		**7.1 STATISTICAL DESIGN - MODEL**
Description of change		Change 1: Estimated trial duration updated to 432 weeks. Change 2: Primary endpoint changed to time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) or non-fatal stroke. Change 3: First key secondary endpoint changed to time to the first occurrence of any of the following adjudicated components of: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris. Change 4: List "time to silent MI" separately from adjudicated tertiary cardiovascular endpoints.
Rationale for change		Change 1: Estimated trial duration increased due to change of primary endpoint. Change 2,3: Testing hierarchy revised following an unanimous request from the trial Academic Steering Committee.

		Change 4: Clarification added, that silent MI is not a by adjudication confirmed endpoint.
Section to be changed		**7.2 NULL AND ALTERNATIVE HYPOTHESES**
Description of change		First key secondary endpoint details removed.
Rationale for change		First key secondary endpoint was changed to time to the first occurrence of any of the following adjudicated components of: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris.
Section to be changed		**7.3 PLANNED ANALYSES**
Description of change		Change 1: Protocol violation is considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint and/or first key secondary endpoint. The example of limited life expectancy (<5 years) due to various medical conditions) as important protocol violations was removed. Change 2:
Rationale for change		Change 1: Clarification that important protocol violations are defined in relation to adjudicated outcome events as part of primary and first key secondary endpoint. The trial Statistical Analysis Plan describes all important protocol violations in detail. Change 2:
Section to be changed		**7.3.1 Primary analyses**
Description of change		A Bonferroni adjustment will be applied after the first DMC interim analysis for 4P-MACE and the following analyses based on 3P-MACE. The O'Brien & Fleming alpha-spending function based on the new overall alpha (after Bonferroni adjustment) defines the overall significance level for the second DMC interim analysis and final analysis. Removed sentence, that the Steering

		Committee will decide on the number of interim analyses.
Rationale for change		The change of the primary endpoint from time to first adjudicated event of the composite of 4P-MACE to the time to first adjudicated event of the composite of 3P-MACE requires adjustment of the alpha level which is addressed via a Bonferroni adjustment. The number of two interim analyses and the number of events required for each of the two interim analyses were defined by the Steering Committee to be based on approximately 190 and 411 primary endpoint events. This decision was documented in the SC minutes and the DMC Charter.
Section to be changed		**7.3.2 Secondary analyses**
Description of change		Chi square test and logistic regression for CV endpoints removed.
Rationale for change		Cardiovascular events will be analysed by a Cox proportional hazards model and occurrence of events reported with frequency and incidence rates. Analyses that do not account for the time at risk are not required.
Section to be changed		**7.3.4 Interim analyses**
Description of change		A Bonferroni adjustment will be applied after the first DMC interim analysis for 4P-MACE and the following analyses based on 3P-MACE. The O'Brien & Fleming alpha-spending function based on the new overall alpha (after Bonferroni adjustment) defines the allocation of the overall significance level for the second interim analysis and final analysis. Removed sentence, that the Steering Committee will decide on the number of interim analyses.
Rationale for change		The change of the primary endpoint from time to first adjudicated event of the composite of 4P-MACE to the time to first adjudicated event of the composite of 3P-MACE requires adjustment of the alpha level which is addressed via a Bonferroni adjustment.

		The number of two interim analyses and the number of events required for each of the two interim analyses were defined by the Steering Committee to be based on approximately 190 and 411 primary endpoint events. This decision was documented in the SC minutes and the DMC Charter.
Section to be changed		**7.6 DETERMINATION OF SAMPLE SIZE**
Description of change		Change 1: A Bonferroni adjustment will be applied between the first DMC interim analysis for 4P-MACE and the following analyses regarding 3P-MACE. The O'Brien & Fleming alpha-spending function based on the new overall alpha (after Bonferroni adjustment) defines the allocation of the overall significance level for the second DMC interim analysis and final analysis. Change 2: Assumed annual event rates updated for changed primary endpoint.
Rationale for change		Change 1: The change of the primary endpoint from time to first adjudicated event of the composite of 4P-MACE to the time to first adjudicated event of the composite of 3P-MACE requires adjustment of the alpha level which is addressed via a Bonferroni adjustment. Change 2: Lower event rates assumed for updated primary endpoint.
Section to be changed		**9.1 Published References**
Description of change		Author of IB omitted and update of published references
Rationale for change		Change in authorship and reflected of published references used for the protocol revision.
Section to be changed		**10.5 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		Clarified that Silent MI is diagnosed on relevant ECG abnormalities, clinical history and investigator reporting.