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Title: Effects of linagliptin on endothelial function and global arginine bioavailability ratio in coronary artery disease patients with early diabetes

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Confidentiality Statement
This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigator team, regulatory authorities and members of the Research Ethics Committee.

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2. LIST OF ABBREVIATIONS

AUC	Area Under the Curve
sVCAM-1	Soluble Vascular Cell Adhesion Molecule-1
vWF	von Willebrand Factor
sICAM-1	Soluble Intercellular Adhesion Molecule-1
FMD	Flow Mediated Dilation
GABR	Global Arginine Bioavailability Ratio
AOR	Arginine to Ornithine Ratio
T2DM	Diabetes Mellitus Type 2
DPP4	Dipeptidylpeptidase IV
OD	Once daily
MTT	Meal Tolerance Test
CAD	Coronary Artery Disease
UKPDS	United Kingdom Prospective Diabetes Study
GLP-1	Glucagon like-peptide-1
HbA1c	Glycated haemoglobin
AST	Aspartate-Aminotransferase
ALT	Alanine-Aminotransferase
oGTT	Oral glucose tolerance test
GTN	Glyceroltrinitrate

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3. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.1	05.Aug.2013	Sourij, Tripolt	1)MTT (Fortimel compact instead of Fortisip liquid) 2)Combination of Screening and Baseline visits 3) Blood storage
2	2.2	22.Oct.2013	Sourij, Tripolt	1)Blood sampling 2)Inclusion criteria: (Age 40 to 80 years)
3	2.3	30.April 2014	Sourij, Tripolt	1)Exclusion criteria: HbA1c <6.0% (42mmol/mol) instead of HbA1c <6.5 (48mmol/mol)
4	2.4	24.October 2014	Sourij, Tripolt	1)Storage of blood samples in the Biobank

4. SYNOPSIS

Study Title	**Effects of linagliptin on endothelial function and global arginine bioavailability ratio in coronary artery disease patients with early diabetes**
Study Design	Randomised, double-blind, placebo-controlled, parallel group trial
Study Participants	Subjects at early stages of type 2 diabetes
Number of Participants	50
Follow-up duration	3 months
Planned Duration	16 months

Primary Objective	*The primary objective is to investigate the impact of a 12 week linagliptin treatment on endothelial function in patients with early T2DM.*
Secondary Objectives	The secondary objective is to investigate the effect of a 12 week linagliptin treatment on - arginine bioavailability ratios (global arginine bioavailability ratio and arginine to ornithine ratio) - biochemical markers of endothelial function (sVCAM-1, sICAM-1, vWF) - the AUC of glucose, insulin and free fatty acids during the meal tolerance test

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5. BACKGROUND AND RATIONALE

Patients with type 2 diabetes (T2DM) are at increased risk of macrovascular events as well as microvascular complications (1). It is well known, that the pathophysiologic process of type 2 diabetes starts many years before the diagnosis can be made on the basis of elevated fasting blood glucose.(2) In particular the data of the UKPDS study and the UKPDS post trial monitoring highlighted the importance of an early glucose lowering intervention in patients with T2DM with respect to micro- and macrovascular complications. (3, 4)

We (5,6) and in particular the Euro Heart survey on Diabetes and the Heart (7) demonstrated, that in a cardiovascular high risk population, namely patients with coronary artery disease (CAD), about 35% suffer from manifest type 2 diabetes. In addition, another 9 to 15% of CAD patients have postchallenge diabetes, diagnosed on the basis of an oral glucose tolerance test, which means that approximately a half of all patients with CAD have diabetes.

Recently we could demonstrate that not only established type 2 diabetes diagnosed on the basis of fasting hyperglycaemia is associated with an increased cardiovascular risk, but also postchallenge hyperglycemia (i.e. impaired glucose tolerance or postchallenge diabetes).

Dipeptidylpeptidase-4 (DPP-4) inhibitors increase endogenous glucagon like-peptide-1 (GLP-1) levels and GLP-1 in turn increases the insulin release from pancreatic beta-cells in a glucose dependent manner as well as suppresses glucagon secretion from pancreatic alpha cells. Investigations in type 2 diabetic patients showed that this drug class lowers both, fasting and postchallenge or postmeal glucose levels and hence, HbA1c and is well tolerated.

However, the lowering of the surrogate measurement HbA1c has not necessarily turned out to translate into a reduced number of cardiovascular events in patients with T2DM. In contrary in particular for the thiazolidinedione Rosiglitazone concerns about an increased risk of cardiovascular events have been raised despite a robust HbA1c lowering effect. (8) Therefore the FDA (9) and the EMA (10) issued in 2008 and 2010, respectively, guidance for new glucose lowering drugs, requiring proof of at least cardiovascular safety. Cardiovascular outcome trials with Linagliptin are currently being performed (CAROLINA, CARMELINA), however, it will take a couple of years until the results are available.

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A well known and validated cardiovascular surrogate parameter is endothelial dysfunction. We and others have shown previously, that endothelial dysfunction is present in patients with coronary artery disease and early diabetes and can be improved by pharmacological intervention. (11, 12) This surrogate measurement could be helpful in better understanding the cardiovascular effects of Linagliptin while awaiting the results of the definitive outcome trials.

The aim of our current study is to investigate the effects of Linagliptin in coronary patients with early T2DM on various cardiovascular surrogate measurements including mechanical and biochemical endothelial function assessments.

6. AIMS OF THE STUDY

The overarching aim of our study is to investigate the effects of Linagliptin on endothelial function, arginine bioavailability ratios and postchallenge glycaemic control in patients with early diabetes and coronary atherosclerosis.

7. OBJECTIVES

7.1 Primary objective

The primary objective is to determine whether a 12 week Linagliptin treatment is associated with an improvement in endothelial function in patients with early diabetes.

7.2 Secondary objective

The secondary objective is to investigate the effect of a 12 week Linagliptin treatment on

- arginine bioavailability ratios (global arginine bioavailability ratio and arginine to ornithine ratio)
- biochemical markers of endothelial function (sVCAM-1, sICAM-1, vWF)
- the AUC of glucose, insulin and free fatty acids during the meal tolerance test

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8. OUTCOMES

8.1 *Primary outcome*

Changes in endothelial function (assessed by flow mediated dilatation – FMD) by a 12 week Linagliptin treatment in patients with early T2DM.

8.2 *Secondary outcome parameters*

- Changes in arginine bioavailability ratios (global arginine bioavailability ratio and arginine to ornithine ratio)
- Changes in biochemical markers of endothelial function (sVCAM-1, sICAM-1, vWF)
- Changes in the AUC of glucose, insulin and free fatty acids during the meal tolerance test

9. STUDY DESIGN

This is a single-centre, prospective, randomized, double-blind, placebo-controlled, parallel group 12 week clinical trial evaluating the effect of Linagliptin 5mg OD orally on cardiovascular surrogate measures in patients with early diabetes. 50 subjects will be randomised to receive either Linagliptin or placebo for 12 weeks. At baseline all subjects will undergo endothelial function assessment (FMD), blood sampling as well as a meal tolerance test. At the end of the 12-week treatment period all subjects will undergo a repeat FMD, blood sampling as well as a meal tolerance test.

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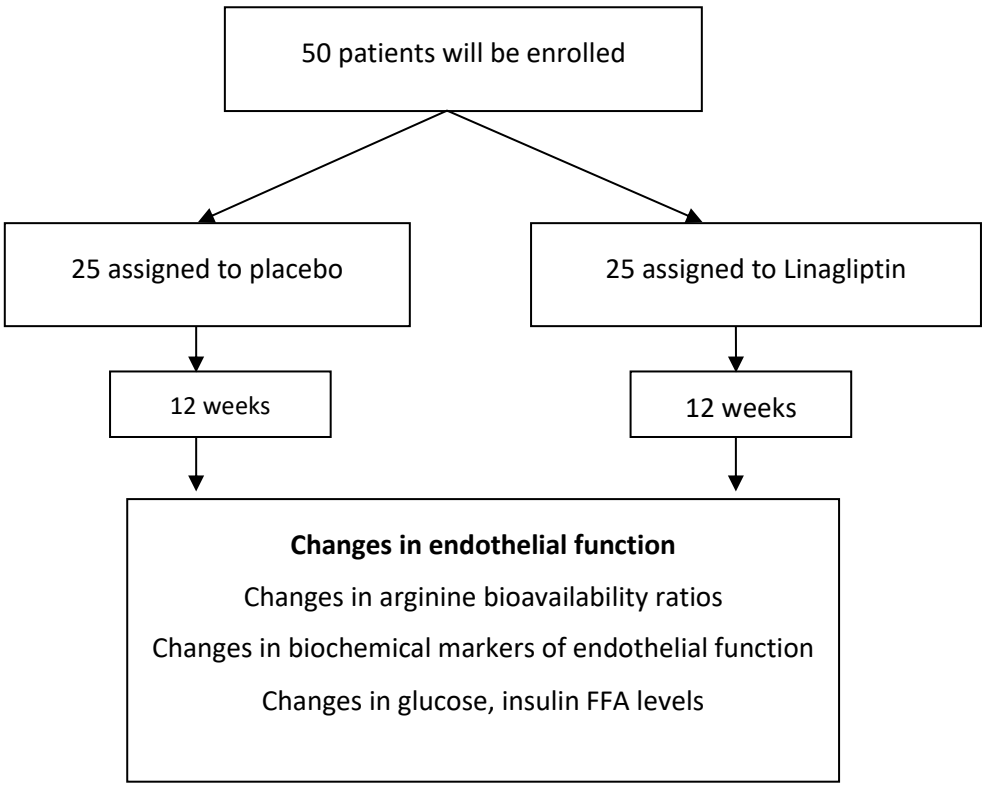
9.1 Schematic overview on study design



9.2 Duration of Study

It is anticipated that the study will run for 16 months (from first patient first visit until last patient last visit).

9.3 Source Data

Source documents comprise the CRF and hospital records, laboratory records and correspondence.

All documents will be stored safely in a confidential manner. The subject will be referred to by a unique study subject number/code, their initials and date of birth on all study-specific documentations. The only exceptions will be the signed Consent Forms, Subject Identification log and subject clinical file, all of which will be stored securely by the clinical site.

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Source data will be made available for internal and external audits or inspections by regulatory authorities to authorised personnel only.

9.4 Randomisation and Blinding

The randomisation plan will be designed by the Institute of Medical Informatics, Statistics and Documentation, Medical University Graz, Austria, which will pass the randomisation list to the Pharmacy of the University Hospital Graz for adequate labelling and blinding of the medication The labels of the study medication will display the name of the trial, the name of the investigational medicinal product and contact details of the principal investigator.

Subject numbers will be assigned sequentially as each subject enters the study.

9.5 Unblinding

In the rare case of a requirement to unblind study medication, the Prinicipal investigator will need give permission for unblinding. The unblinding list will be held by the Institute of Medical Informatics, Statistics and Documentation, Medical University of Graz, who is not involved in study investigations.

10. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

10.1 Subject Selection

The study population will consist of

- 50 subjects with early diabetes (i.e. postchallenge diabetes (2h glucose >200 mg/dl or type 2 diabetes treated with diet only or on a stable dose of metformin monotherapy)

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10.2 Subject Recruitment

Patients will be identified from the outpatient clinic at the Department of Endocrinology and Metabolism, the Division of Cardiology, via Primary Care and adverts.

10.3 Inclusion Criteria

- Age 40-80
- Early diabetes (postchallenge diabetes (2h glucose >200 mg/dl or type 2 diabetes treated with diet only or on a stable dose of metformin monotherapy)
- Coronary atherosclerosis (diagnosed via coronary angiography or coronary computer tomography)

10.4 Exclusion Criteria

- Acute coronary syndrome or cerebrovascular event within the previous 4 weeks
- BMI > 35 kg/m^2
- HbA1c <6.0% (42 mmol/mol)
- Serum creatinine > 2.5 mg/dl
- AST/ALT > 3x upper limit of normal
- HbA1c >9.0% (>75 mmol/mol)
- Heart failure > NYHA class II
- Uncontrolled hypertension (blood pressure > 165 / 100 mmHg)
- Treatment with orally administered steroids
- New onset statin or ACE-inhibitor within the previous 6 weeks
- Known Malignancy
- Pregnancy or breast feeding women.

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10.5 Withdrawal / Drop out of subjects

Each subject has the right to withdraw from the study at any time without prejudice or compromise to future care.

The investigator may discontinue or withdraw the subjects under the following circumstances:

- Significant protocol deviation
- Significant non-compliance with treatment regime or study procedures
- An adverse event that requires discontinuation of the study medication or results in inability to continue to comply with study procedures. If a subject is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.
- Consent withdrawn
- Lost to follow up
- The study will be stopped prematurely if any information relating to the IMP or any other aspect of the study arises that may cause harm to the participant.
- Any other situation that may, in the opinion of the investigator, make it unsafe or inappropriate for the subject to continue in the trial

A drop-out rate of 10% was considered in the sample size estimate. In case of further drop-outs additional recruitment has to take place to avoid loss of statistical power.

10.6 Payment to subjects

Reimbursement of reasonable travel expenses will be considered.

10.7 End of study

The study end is defined as the last visit of the last patient. In the case of new data suggesting a significant safety concern of the study drug, the trial will be prematurely stopped.

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11 STUDY PROCEDURES

11.1 Schedule of study procedures

	Screening (V1)* (up to 1 month prior to baseline)	**Baseline (V2)** (week 0)	**Follow-up (V3)** (Week 12 ± 1)
Informed Consent	X		
Inclusion/exclusion criteria	X	X	
Randomisation		X	
Demography, medical history	X		
Concomitant medication	X	X	X
Vital signs	X	X	X
Physical examination		X	
Flow Mediated Dilatation (FMD)		X	X
GABR, biochemical markers of endothelial function (sVCAM-1, sICAM-1, vWF)		X	X
Blood sampling	X	X	X
Meal tolerance test (MTT)		X	X
Adverse Events			X
Dispense medication		X	
Drug accountability			X
Pregnancy test (females with childbearing potential)	X		X

***if blood samples to check inclusion/exclusion criteria are available within 4 weeks prior to randomisation, the screening visit and baseline visit can be performed on the same day**

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11.2 Visit Schedule

Screening contact – Visit 1 (up to 1 month prior to potential randomisation)

- Sufficient time will be provided and subjects will be encouraged to discuss all queries with the research team
- Informed consent will be obtained by an investigator
- Check inclusion and exclusion criteria
- Demographics will be obtained: date of birth, gender, race, smoking status, alcohol consumption
- Weight
- Height
- Medical history
- Concomitant medication
- Vital signs: resting pulse and blood pressure
- Blood sample for HbA1c
- Baseline safety blood tests (fasting): Full blood cell count, renal function tests, liver function tests
- Pregnancy test in female woman of childbearing age.

Baseline (week 0)

- Review inclusion and exclusion criteria
- Vital signs
- Weight
- Physical examination
- Concomitant medication review
- FMD measurement
- Blood sampling for cardiovascular surrogate measurements
- Meal tolerance test
- Randomisation: patients will be randomised to either Linagliptin 5 mg or placebo for the next 12 weeks
- Dispense study medication.

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Week 12 visit

- Weight
- Vital signs
- Concomitant medication review
- Adverse events assessment
- FMD measurement
- Blood sampling for cardiovascular surrogate measurements
- Meal tolerance test
- Drug accountability.

Phone call 28 days after week 12 visit

- Assessment of adverse events

11.3 Laboratory results

All laboratory results will be reviewed and the reports signed by the study physician who will record whether it is normal, abnormal but not clinically significant, or abnormal and clinically significant. In the latter case, the eligibility of the subject will be reviewed.

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12 METHODS

12.1 Meal Tolerance Test (MTT)

The MTT will be performed after an overnight fast (apart from water). A standard gauge cannula will be placed into a subcutaneous vein for blood sampling. In order to prevent blood clotting in the cannula and to keep the cannula working it will be occasionally flushed with sterile normal saline. Study medication will be given (time -15 mins) before the meal. A pre-meal blood sample will be taken (- 5mins) and then all subjects will be asked to drink Fortimel compact (10 kcal/kg) over a period of 2-4 mins (time 0 mins). During the meal test further blood samples will be taken at 15, 30, 60, and 120 minutes. All samples will be used for determination of glucose, insulin and free fatty acids. The blood at each time point will be placed into a fluoride oxalate tube (1ml) for plasma glucose and into a serum tube for insulin and free fatty acids.

12.2 Flow mediated dilation

Endothelial dysfunction: Endothelium-dependent FMD following reactive hyperaemia and endothelium-independent NMD following administration of GTN are examined in the brachial artery according to the guidelines described by Coretti et al (13).

Using high resolution ultrasound measurements of the right brachial artery are taken after resting, after cuff deflation (250 mmHg for 5 minutes) of the forearm and after sublingual administration of 0.4 mg glyceroltrinitrate (GTN). Scans of the brachial artery are taken proximal to the antecubital fossa with simultaneous ECG recording. Diameter measurements are taken from one media-adventitia interface to the other for three to four times at baseline (the average is taken for calculating the baseline diameter), three times after 45 to 60 seconds after cuff deflation following reactive hyperaemia and four minutes after administration of GTN. GTN is applied 15 minutes after cuff deflation to allow arterial diameter to return to baseline, which will be controlled by measuring another baseline diameter.

FMD-diameter is calculated as the average of the three diameter measurements following reactive hyperaemia. FMD and NMD are calculated as the percent change in diameter compared to baseline.

12.3 Blood sampling

Over the 3 study visits in total approximately 51 ml of blood will be taken to determine the parameters outlined below. A potential remainder of serum and plasma will be stored anonymised (patient number and visit number only) at -80°C in the Biobank of the Medical University of Graz for potential future analyses.

Twice, at baseline and after 3 months, blood (8ml LiHep) will be taken to analyse the impact of linagliptin on the number and function of endothelial progenitor cells.

Laboratory measurements

Insulin and c-peptide will be measured by chemiluminescence on an ADVIA Centaur system (Siemens Healthcare Diagnostics, Eschborn, Germany). FFA will be measured enzymatically (Wako Chemical, Neuss, Germany) on an Olympus AU640 (Olympus Diagnostica, Hamburg, Germany). Routine parameters will be determined using a cobas® analyzer (Roche Diagnostics, Mannheim, Germany).

GABR

Arginine, ornithine and citrulline will be measured in serum samples with a conventional usual amino acid analysis technique, involving separation of amino acids by ion exchange chromatography followed by postcolumn continuous reaction with ninhydrin. Global arginine bioavailability ratio will be calculated by L-arginine divided by the sum of (L-ornithine plus L-citrulline). The arginine to ornithine ratio will be calculated by dividing L-arginine by L-ornithine levels.

12.4 Data analysis and sample size estimation

Data analysis

Continuous variables will be presented as means, standard deviation, median, minimum and maximum, for categorical data frequencies and relative frequencies are used. To examine differences between groups at baseline, t-tests or Mann-Whitney U tests and chi-square tests will be used as appropriate. The primary outcome, FMD after 12 weeks, will be analysed using ANCOVA. Comparisons within groups will be performed using paired t-test or Wilcoxon rank-sum test. A p-value of <0.05 is considered to indicate

statistical significance. A statistical analysis plan will be prepared and finalized before database lock.

Sample size

Sample size was estimated using free available calculator http://www.quantitativeskills.com/sisa/calculations/samsize.htm. Assuming an improvement of endothelial dysfunction of 30% (relative) and a SD of 3% (% FMD) a total of 42 subjects will be needed to detect this difference with an alpha of 0.05 and a power of 0.90. To account for a dropout rate of about 20% each group will consist of 25 patients.

13 TREATMENT/INTERVENTION

Study Treatment/Intervention

- Placebo
- Linagliptin

13.1 Description of Treatments/Interventions

The subjects will receive either Linagliptin 5mg (licensed dose for treatment of type 2 diabetes) or matched placebo tables orally once daily for 12 weeks. The drug and placebo will be supplied by Böhringer Ingelheim as bulk ware study medication. Pharmacy at the Medical University of Graz, Austria will pack the medication as 12 weeks supplies for study participants and label study medication according to current regulatory requirements.

Patients will be asked not to adjust their antidiabetic treatment during the study period. However, if glycaemic control appears to be inappropriately high during these 12 weeks, additional glucose lowering drugs may be used at the discretion of the principal investigator. Unless contraindicated, the first choice for rescue medication should be a sulfonylurea.

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13.2 Subject Compliance

The subjects will be instructed to return all unused or part-used medication and packaging from medication at the follow-up visit. Tablets will be counted out at the end of the twelve week treatment period to verify compliance.

Significant non-compliance is defined as missing 20% or more doses of trial medication during the 12 week treatment period. In the event of study medication non-compliance, participants would continue to be followed to their last visit. These data would not be part of the per protocol analysis but would form part of an intention to treat analyses.

14 INVESTIGATIONAL MEDICINAL PRODUCT (TAKEN FROM THE SMPC)

14.1 Mechanism of action

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4, EC 3.4.14.5) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homoeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000 fold selectivity versus DPP-8 or DPP-9 activity in vitro.

14.2 Therapeutical indications

Linagliptin is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults:

as monotherapy

-in patients inadequately controlled by diet and exercise alone and for whom metformin is

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inappropriate due to intolerance, or contraindicated due to renal impairment.

as combination therapy
-in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
-in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

14.3 Undesireable effects

In the pooled analysis of the placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo was similar to linagliptin 5 mg (53.8% versus 55.0%). Discontinuation of therapy due to adverse events was higher in patients who received placebo as compared to linagliptin 5 mg (3.6% versus 2.3%). The most frequently reported adverse reaction was hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea 14.7% versus 7.6% in placebo.
In the placebo controlled studies 5.0% of patients experienced “hypoglycaemia” as an adverse reaction under linagliptin. 86.8% of these were mild and 13.2% were moderate.

14.4 Absorption

The absolute bioavailability of linagliptin is approximately 30%. Co-administration of a high-fat meal with linagliptin prolonged the time to reach Cmax by 2 hours and lowered Cmax by 15% but no influence on AUC 0-72h was observed. No clinically relevant effect of Cmax and Tmax changes is expected; therefore linagliptin may be administered with or without food.

14.5 Distribution

As a result of tissue binding, the mean apparent volume of distribution at steady state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/l to 75-89% at ≥30 nmol/l, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 30-20% were unbound in plasma.

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14.6 Excretion

Following administration of an oral [14C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 ml/min.

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15 PHARMACOVIGILANCE

Safety endpoints: All adverse events reported by the patients will be assessed and reported as outlaid below.

15.1 Definitions

Adverse Events (AE)

An adverse event is defined as

any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or clinical investigation subject administered a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment (Linagliptin).

Adverse Drug Reaction (ADR)

An Adverse Drug Reaction (ADR) is any response to a drug which is noxious and unintended.

This means that a causal relationship between study medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out.

Serious Adverse Event

A serious adverse event (SAE) is defined as any AE which:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered as serious, when base upon appropriate medical judgement that may jeopardise the patient/supject, and may require medical or surgical intervention to prevent one of the other seriousness criteria from occuring.

Patients may be hospitalised for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site). These and other hospitalisations planned at the beginning of the study do not need to be reported as a SAE in case they have been reported at screening visit in the source data and have been performed as planned

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information as documented above.

According to ICH E2A all SUSARs should be reported in an expedited manner to Competent Authorities, Ethics Committees and investigators concerned on an individual basis within timelines.

Regulatory timelines which have to be met are as follows:

- Fatal and life-threatening AEs: 7 calendar days after receipt
- Remaining serious AEs: 15 calendar days after receipt

Intensity/Severity of adverse Event

The Intensity/Severity 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 judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, dechallenge or rechallenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in case report forms.

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15.2 Reporting Procedure for all Adverse Events

All Adverse events, serious and non-serious, will be collected, documented and reported on the appropriate CRFs/SAE reporting forms once informed consent has been signed and will end 28 days after completing the trial.

The following information will be recorded:

- participant details
- adverse event description
- start date of event
- end date of event
- outcome of event
- severity of event
- treatment required
- relationship to study drug (i.e. causality/relatedness)
- assessment of relatedness to other suspect drug or device
- action taken with study drug
- whether subject withdrawn due to adverse event
- whether the event is serious
- Follow up information will be recorded as necessary

AEs considered to be related to study medication as judged by a medically qualified investigator will be followed until resolution or the event is considered stable. All related AEs that result in a subject's withdrawal from the study or are present at the end of the study will be followed up until a satisfactory resolution occurs.

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 any drug exposure during pregnancy.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up.

15.3 Reporting Procedure for Serious Adverse Events

The investigator shall report any Serious Adverse Events and non-serious Adverse Events which are relevant for a reported SAE and Adverse Events of Special Interest to Boehringer Ingelheim Pharmacovigilance Unique Entry Point, who will subsequently report the SAE to the ethics committee and local authorities.

16 STUDY MONITORING

A risk-based approach will be taken to determine the frequency of study monitoring for the study which will be agreed with the Principal Investigator. Monitoring will be undertaken according to ICH GCP and the study monitoring plan. The study monitor will be suitably trained, qualified and experienced to perform this task. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

17 ETHICS

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, GCP-ICH and according to the protocol and the requirements of the concerned regulatory authorities.

The IMP is a licensed, well tolerated drug used within the indication and the measurements taken are either non-invasive are minimally invasive (blood sampling). Therefore we consider this trial as low risk for participants.

17.1 Informed Consent

1. Informed consent will be obtained for all participants in the study by the study physician.
2. Written versions of the subject information and Informed consent will be presented to the subjects detailing:
    - The exact nature of the study
    - The implications and constraints of the protocol
    - The known side effects and any risks involved in taking part.
3. It will be clearly stated that the subject is free to discontinue their participation in the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

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4. The subject will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their usual care provider or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of subject dated signature and dated signature of the person who presented and obtained the informed consent.
5. A copy of the signed Informed Consent will be given to the subjects. The original signed form will be retained at the study site.

17.2 Ethical and Regulatory Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Ethics Committee of the Medical University of Graz, Austria. In addition, the study will be submitted for approval to the "Österreichische Agentur für Gesundheit und Ernährungssicherheit" (AGES).

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

18. FINANCE

This study will be funded by Böhringer Ingelheim Pharma GmbH und KoKG, Biberach, Germany.

19. INSURANCE

Participant insurance according to legal requirements will be contracted.

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