Clinical Trial Protocol

	Document Number: c22769951-02
EudraCT No.:	2018-001266-42
BI Trial No.:	1361-0011
BI Investigational Product:	Empagliflozin/linagliptin/metformin extended release fixed dose combination
Title:	Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)
Lay Title:	This study in healthy people tests whether taking a low strength of empagliflozin, linagliptin, and metformin together in 1 pill is the same as taking them in separate pills
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 1))
Version and Date:	Version: 2.0 Date: 24 July 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: Empagliflozin, linagliptin, metformin HCl			
Protocol date: 15 June 2018	**Trial number:** 1361-0011		**Revision date:** 24 July 2018

Title of trial:	Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objective:	To establish the bioequivalence of two fixed dose combination (FDC) tablets of 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin extended release (XR) versus the free combination of one 10 mg empagliflozin tablet, one 5 mg linagliptin tablet, and four 500 mg metformin XR tablets administered as a single dose under fed conditions.
Methodology:	Randomised, open-label, two-way crossover design with 2 treatments (T and R) and 2 treatment sequences (TR or RT)
No. of subjects:	
total entered:	30
each treatment:	30
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male/female subjects, age of 18 to 55 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR FDC coated tablet
Dose:	10 mg empagliflozin + 5 mg linagliptin + 2000 mg metformin XR (2 FDC tablets) in treatment period T
Mode of admin.:	Oral with 240 mL of water after a high-fat, high-calorie breakfast

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Comparator products:	The comparator products consist of an empagliflozin immediate release tablet, a linagliptin immediate release tablet, and multiples of a metformin extended release tablet.
Comparator product 1:	Empagliflozin 10 mg film-coated tablet (Jardiance®)
Comparator product 2:	Linagliptin 5 mg film-coated tablet (Tradjenta®)
Comparator product 3:	Metformin XR 500 mg film-coated tablet (Glumetza®)
Dose:	10 mg empagliflozin (1 tablet) + 5 mg linagliptin (1 tablet) + 2000 mg metformin XR (4 tablets) administered together in treatment period R
Mode of admin.:	Oral with 240 mL of water after a high-fat, high-calorie breakfast
Duration of treatment:	Single dose for each treatment separated by a washout phase of at least 35 days
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-tz} and C_{max} for empagliflozin and metformin, AUC_{0-72} and C_{max} for linagliptin Secondary endpoints: $AUC_{0-\infty}$ for empagliflozin, linagliptin, and metformin
Criteria for safety:	Secondary endpoint to assess safety and tolerability of the investigational drugs is the number [N (%)] of subjects with drug-related adverse events (AEs). Further criteria of interest: AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])
Statistical methods:	The assessment of bioequivalence will be based upon two-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the primary endpoints using an acceptance range of 80.00-125.00%. This method is equivalent to the two one-sided t-tests procedure, each at the 5% significance level. The statistical model will be an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} (empagliflozin, linagliptin, and metformin)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	x		x	x	
1/2 (two identical periods with a washout of at least 35 days	2/3	-7 to -1			Ambulatory visit (in Visit 3 only)	x				x
		-1	-12:00	20:00	Admission to trial site[7]	x[5,7]				x[7]
		1	-1:30	06:30	Allocation to treatment[2] (Visit 2 only)		x[2]			x[2]
			-0:30	07:30	High-fat, high-calorie breakfast					
			0:00	08:00	Drug administration					
			0:30	08:30			x			
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00	240 mL fluid intake		x			
			2:30	10:30			x			
			3:00	11:00			x			
			4:00	12:00	240 mL fluid intake		x			
			5:00	13:00	Lunch[3]		x			x
			6:00	14:00			x			
			7:00	15:00			x			
			8:00	16:00			x			
			10:00	18:00	Dinner[3]		x			x
			12:00	20:00			x			
		2	24:00	08:00	Discharge from trial site, breakfast (voluntary)[3]		x			x
			34:00	18:00	Ambulatory visit		x			x
		3	48:00	08:00	Ambulatory visit		x			x
		4	72:00	08:00	Ambulatory visit		x			x
EOT	4	8 to 14			End-of-trial (EOT) examination[4]	x		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening and pregnancy test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.

2. The time is approximate; the procedure is to be performed and completed within 3 h prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End-of-trial examination includes physical examination, vital signs, ECG, safety laboratory, pregnancy test, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test, and pregnancy test in women.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in this Flow Chart.
7. The time is approximate; admission is to be performed no later than 10 h prior to scheduled drug administration.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve of the analyte in plasma
AUC_{0-72}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Clinical monitor local
CRA	Clinical research associate
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical trial supply unit
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
DKA	Diabetic ketoacidosis
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl-peptidase 4
δ	Bioequivalence margin
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
FDC	Fixed dose combination
GCP	Good clinical practice

gCV	Geometric coefficient of variation
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
gMean	Geometric mean
H_0	Null hypothesis
H_a	Alternative hypothesis
HPC	Human Pharmacology Centre
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
R	Reference treatment
REP	Residual effect period
RS	Randomised set
SAE	Serious adverse event
SCR	Screening
SGLT-2	Sodium-dependent glucose co-transporter 2
SOP	Standard operating procedure
T	Test product or treatment
T2DM	Type 2 diabetes mellitus
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial master file
TS	Treated set

TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
XR	Extended release

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Diabetes mellitus is characterised by either the pancreas not producing enough insulin (type 1 diabetes) or increased peripheral insulin resistance and an insulin-secretory defect that varies in severity leading to raised blood glucose levels (type 2 diabetes). Type 2 diabetes mellitus (T2DM) accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with over 300 million people estimated to be affected worldwide. Complications associated with T2DM, e.g. cardiovascular (CV) disease, lead to a significant reduction of life expectancy and are a major cause of morbidity. The risk of CV death and death from any cause is increased approximately 2-fold in patients with diabetes [R11-5199]. Diabetes-related vascular complications are currently the most common cause of adult blindness, renal failure, and amputation and lead to a 2- to 4-fold increase in CV disease risk [R06-0179]. T2DM is now a common and serious global health problem, which for most countries has evolved in association with rapid cultural and social changes, ageing populations, increasing urbanisation, dietary changes, reduced physical activity, and other unhealthy lifestyle and behavioural patterns.

Currently available oral antidiabetic drugs are efficacious, but still fail to achieve optimal blood glucose control in many patients. Modern T2DM therapy includes the combination of multiple drugs with complementary modes of action to achieve improved glycaemic control. Besides, most of the currently available antidiabetic agents have significant side effects such as hypoglycaemia, weight gain, oedema and gastrointestinal discomfort.

Empagliflozin, linagliptin, and metformin are orally available antidiabetic drugs with different modes of action approved for the treatment of T2DM. When used in combination they are expected to show improved efficacy as compared to single treatment in terms of glucose control. Boehringer Ingelheim has now developed a triple fixed dose combination (FDC) tablet for once daily dosing containing empagliflozin, linagliptin, and metformin extended release [c01678844-10, c18916941-01].

1.2 DRUG PROFILE

1.2.1 Empagliflozin

Empagliflozin is an orally administered, potent, and selective inhibitor of the renal sodium-dependent glucose co-transporter 2 (SGLT-2). Empagliflozin lowers both the saturation threshold and the transport maximum of SGLT-2 for glucose, resulting in increased glucosuria, insulin-independent reduction of plasma glucose levels with a low risk of hypoglycaemia, and a negative energy balance with weight reduction. Empagliflozin was developed by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany, and has been approved as an adjunct to diet and exercise to improve glycaemic control in adult patients with T2DM in more than 70 countries including Europe, US, and Japan. The preferred brand name is Jardiance®. In the EMPA-REG OUTCOME® trial, empagliflozin significantly reduced the risk for CV death, not-fatal myocardial infarction, or non-fatal stroke by 14% compared with placebo in patients with T2DM and established CV disease on top of standard-of-care treatment [P15-09840]. In consequence, the indication for

empagliflozin was extended to the reduction of the risk of CV death in patients with T2DM with established CV disease in more than 10 countries including the US, Canada and Australia. The standard therapeutic dose is 10 or 25 mg once daily [c01678844-10].

For a more detailed description of the drug profile of empagliflozin refer to the current Investigator's Brochure for empagliflozin [c01678844-10].

1.2.2 Linagliptin

For a more detailed description of the drug profile of linagliptin refer to the current Investigator's Brochure for linagliptin [c18916941-01].

1.2.3 Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. Unlike sulfonylureas (such as glyburide), metformin alone does not increase insulin secretion and is not associated with hypoglycaemia in either patients with T2DM or healthy volunteers. The most common adverse reactions of metformin are gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite [R17-0574].

The absolute bioavailability of metformin is 50 to 60% under fasting conditions. The intake of food decreases the extent of absorption. A 40% lower peak plasma concentration, a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (t_{max}) were reported following a single-dose administration of 850 mg metformin with food. Studies using single oral doses of 500 to 1500 mg, and 850 to 2550 mg metformin indicated that there is a lack of dose proportionality with increasing doses due to decreased absorption rather than an alteration in elimination. Metformin is negligibly bound to plasma proteins. The drug partitions into erythrocytes, most likely as a function of time. Intravenous single-dose studies in healthy subjects demonstrated that metformin is excreted unchanged in the urine and undergoes neither hepatic metabolism nor biliary excretion. Following oral administration approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 h, with a plasma elimination half-life of approximately 6.2 h [R18-1228].

Metformin is available as immediate release and extended release (XR) tablets. The maximum recommended daily dose is 3000 mg for the immediate release tablet [R17-0574] or 2000 mg for the XR tablet [R17-1647]. The standard therapeutic dose is 500 to 2000 mg once daily for metformin XR.

For a more detailed description of the drug profiles of metformin and metformin XR refer to the summary of product characteristics for Glucophage® [R17-0574] and the prescribing information for Glumetza® [R17-1647].

1.2.4 Fixed dose combinations of empagliflozin, linagliptin, and/or metformin

Dual FDC tablets
Fixed dose combinations of empagliflozin and linagliptin (Glyxambi®), empagliflozin and metformin (Synjardy®), and linagliptin and metformin (Jentadueto®) have been developed by Boehringer Ingelheim and have been approved for treatment of T2DM in many countries. Furthermore, FDCs of empagliflozin and metformin XR (Synjardy XR®) and linagliptin and metformin XR (Jentadueto XR®) have been approved in the US. For information about the drug profiles of these FDCs refer to the Investigator's Brochures for empagliflozin [c01678844-10] and linagliptin [c18916941-01].

Triple FDC tablets
The newly developed FDC tablet containing all 3 antidiabetic agents (empagliflozin, linagliptin, and metformin XR) was administered to healthy male and female subjects in two completed studies (see Table 1.2.4: 1): Study 1361.1 investigated the relative bioavailability of 2 strengths of the FDC tablet, 25/5/1000 mg empagliflozin/linagliptin/metforminXR and 10/5/1000 mg empagliflozin/linagliptin/metforminXR, compared with the respective free combination of the 3 components under fed and fasted conditions [c12820904-01]. Study 1361.3 tested whether the FDC tablet 25/5/1000 mg empagliflozin/linagliptin/ metforminXR was bioequivalent to the free combination of the 3 components when administered to healthy male and female subjects under fed conditions [c20062581-01].

Table 1.2.4: 1 Completed studies with empagliflozin/linagliptin/metforminXR FDC tablets

Study number	Study type	FDC tested versus single tablets	Fed/ fasted	Number of subjects dosed
1361.1	Relative bioavailability study with 3 study arms	25/5/1000 mg empagliflozin/linagliptin/metforminXR	Fed	15
		25/5/1000 mg empagliflozin/linagliptin/metforminXR	Fasted	20
		10/5/1000 mg empagliflozin/linagliptin/metforminXR	Fed	15
1361.3	Bioequivalence study	25/5/1000 mg empagliflozin/linagliptin/metforminXR	Fed	30

1.2.5 Residual effect period

The residual effect period (REP) for the combined treatment with empagliflozin, linagliptin, and metformin, when measurable drug levels or PD effects are still likely to be present, is defined as 7 days after the last administration of trial medication.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The aim of combination drug therapy in T2DM is to enhance compliance and provide improved glycaemic control. This can be achieved by combining drugs with different mechanisms of action which work together to have an additive or synergistic antidiabetic effect. The orally available antidiabetic drugs empagliflozin, linagliptin, and metformin XR are commonly administered together and it is expected that providing the 3 drugs in a single FDC tablet will make medication intake easier for patients and reduce the risk of medication errors.

The purpose of the present study is to establish the bioequivalence of a newly developed 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR FDC tablet compared with the free combination of empagliflozin (Jardiance®), linagliptin (Tradjenta®), and metformin XR (Glumetza®) tablets under fed conditions.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to establish the bioequivalence of two 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR FDC tablets (Test, T) compared with the same doses of the individual components given in separate tablets (Reference, R) when administered together after a high-fat, high-calorie meal.

The assessment of safety and tolerability will be the secondary objective of this trial.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of a triple antidiabetic drug FDC that is expected to facilitate medication intake for patients with T2DM, to minimise the risk of medication errors, and to improve patient compliance. The participating subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to veinipuncture for blood sampling.

The total volume of blood withdrawn during the entire study per subject will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.

Drug-related risks and safety measures

Empagliflozin

In patients who received empagliflozin in placebo-controlled clinical studies the following adverse reactions were reported [R18-1111]:

- Very common (>1/10): hypoglycaemia when empagliflozin was used in combination with sulphonylurea or insulin
- Common (≥1/100 to <1/10): vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection (including pyelonephritis and urosepsis), generalised pruritus, rash, increased urination, thirst and increased serum lipids
- Uncommon (≥1/1000 to <1/100): volume depletion, dysuria, increased blood creatinine, decreased glomerular filtration rate, increased haematocrit, and urticaria
- Rare (≥1/10 000 to <1/1000): diabetic ketoacidosis (DKA).
- Not known (that is, frequency cannot be estimated from the available data): angioedema

Linagliptin

In patients who were treated with linagliptin alone or in combination with metformin the following adverse reactions were reported [R18-1110]:

- Common (≥1/100 to <1/10): increased lipase
- Uncommon (≥1/1000 to <1/100): nasopharyngitis, cough, rash, increased amylase, hypersensitivity (e.g. bronchial hyperreactivity)
- Rare (≥1/10 000 to <1/1000): angioedema and urticaria
- Not known (that is, frequency cannot be estimated from the available data): pancreatitis and bullous pemphigoid

Only when linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycaemia was increased over that of placebo.

In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Pancreatitis was reported more often in patients randomised to linagliptin (7 events in 6580 patients receiving linagliptin versus 2 events in 4383 patients receiving placebo) [R18-1110]. This safety finding was not reported in any of the 3 large controlled randomised CV outcome trials SAVOR (saxagliptin), EXAMINE (alogliptin), and TECOS (sitagliptin) [R13-3903, R13-3902, R15-3017] and is thus still under debate. However, a meta-analysis of these CV outcome studies of DPP-4 inhibitors found a significantly increased risk of acute pancreatitis, though still a rare event, which was suggested to be a class effect [R17-1673, P18-01841]. In Boehringer Ingelheim's premarketing studies involving healthy subjects there was no event of acute pancreatitis. Hence, the risk of pancreatitis is considered minimal after single-dose administration of linagliptin in this study. Nevertheless, subjects will be closely monitored for clinical symptoms and laboratory signs of acute pancreatitis.

Metformin

Adverse reactions which may occur under treatment with metformin are [R17-0574]:

- Very common (≥1/10): gastrointestinal disorders (nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite)
- Common (≥1/100 to <1/10): taste disturbance
- Very rare (<1/10 000): skin reactions (erythema, pruritus, urticaria), abnormalities in liver function tests, hepatitis (resolving after discontinuation of metformin), decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin, and lactic acidosis

Gastrointestinal disorders occur most frequently during initiation of metformin therapy and could therefore also occur after single-dose administration in the current trial. Usually, gastrointestinal disorders disappear within a short period of time and do not represent any safety risk for healthy subjects. Lactic acidosis is a metabolic complication with high mortality rate if not treated promptly. Risk factors for developing a lactic acidosis are renal insufficiency, impaired hepatic function, excessive alcohol intake, vigorous physical activity, and heavy fasting. Until now, a lactic acidosis in healthy volunteers has not been reported in the literature. In the current trial, renal and liver functions will be checked thoroughly as part of the screening examination; alcoholic beverages and unusual physical activities are restricted during the study.

Combination of linagliptin and metformin

Combinations of empagliflozin, linagliptin and metformin

In the present study, subjects are exposed to 2 single doses of 10 mg empagliflozin, 5 mg linagliptin, and 2000 mg metformin XR separated by a washout phase of at least 35 days. Based on previous experience with empagliflozin and linagliptin and their combination with metformin in healthy subjects and in patients, the risk for subjects participating in this trial is considered minimal and acceptable. The risk of hypoglycaemia is considered low since neither empagliflozin, nor linagliptin or metformin act primarily insulinotropic. In clinical settings hypoglycaemia was more common with these drugs when they were co-administered with insulin secretagogues such as sulfonylurea or insulin itself.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also Section 5.2.2.1, adverse events of special interest.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, two-way crossover trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R). The subjects will be randomly allocated to the 2 treatment sequences TR or RT. The treatments will be:

Test treatment (T): 2 FDC tablets 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR in the fed state

Reference treatment (R): free combination of 1 tablet 10 mg empagliflozin, 1 tablet 5 mg linagliptin, and 4 tablets 500 mg metformin XR in the fed state

There will be a washout period of at least 35 days between the 2 treatments.

For details on the treatments refer to Section 4.1. An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

The trial will be conducted at the , under the supervision of the Principal Investigator.

Safety laboratory tests will be performed by the local laboratory of the trial site

The analyses of empagliflozin concentrations in plasma will be performed at . The analyses of linagliptin concentrations in plasma will be performed at The analyses of metformin concentrations in plasma will be performed at

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Data management will be done by BI according to BI SOPs. Statistical tasks and programming will be performed by
according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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

For bioequivalence trials, the crossover design is preferred due to its efficiency: since each subject serves as his or her own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes intersubject variability from the comparison between treatments [R94-1529].

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analytes provided by a bioanalytical laboratory which is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 30 healthy male and female subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

A log of all subjects enrolled into the trial (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.

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

Subjects will only be included into the trial, if they meet the following criteria:

1. Healthy male or female subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

5. Male subjects, or female subjects who meet any of the following criteria starting from at least 30 days before the first administration of trial medication and until 30 days after trial completion:
   - Use of adequate contraception, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device
   - Sexually abstinent
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

Subjects will not be allowed to participate if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males)

16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
21. For female subjects, positive pregnancy test, pregnancy or plans to become pregnant within 30 days after study completion
22. For female subjects, lactation period

In addition, the following trial-specific exclusion criteria apply:

23. Men and women with serum creatinine levels of 1.3 mg/dL and 1.1 mg/dL, respectively, or higher values

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as pregnancy, surgery, adverse events, or diseases)
4. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end-of-trial examination will be performed if possible and the

information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 1.2.5), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication has to be stopped immediately, and the subject has to be removed from the trial. The subject is to be followed until she has given birth or until the end of pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the clinical trial report. For reporting of pregnancy and events refer to Section 5.2.2.2.

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 any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

3.3.5 Replacement of subjects

In case more than 6 subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product and comparator products

The characteristics of the test product are given below:

Test product:

Substance:	Empagliflozin/linagliptin/metformin HCl
Pharmaceutical formulation:	Coated FDC tablet, extended release (metformin)
Source:	Distributed by BI Pharma GmbH & Co. KG, Germany;

Unit strength:	5 mg/2.5 mg/1000 mg
Posology:	2-0-0
Route of administration:	p.o.

The characteristics of the reference product are given below:

Reference product 1:

Name:	Jardiance®
Substance:	Empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Distributed by BI Pharma GmbH & Co. KG, Germany;

Unit strength:	10 mg
Posology:	1-0-0
Route of administration:	p.o.

Reference product 2:

Name:	Tradjenta®
Substance:	Linagliptin
Pharmaceutical formulation:	Film-coated tablet
Source:	Distributed by BI Pharma GmbH & Co. KG, Germany;
Unit strength:	5 mg
Posology:	1-0-0
Route of administration:	p.o.

Reference product 3:

Name:	Glumetza®
Substance:	Metformin HCl
Pharmaceutical formulation:	Film-coated tablet, extended release
Source:	Distributed by BI Pharma GmbH & Co. KG, Germany;
Unit strength:	500 mg
Posology:	4-0-0
Route of administration:	p.o.

4.1.2 Method of assigning subjects to treatment groups

The randomisation list of study subject numbers and assigned treatment sequences will be provided to the trial site in advance.

According to the planned sample size, 2 cohorts are planned. Prior to start of the study, subjects willing to participate will be recruited to cohorts according to their temporal availability. In the morning of Day 1 (Visit 2), subjects will be allocated to treatment sequences prior to first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by drawing lots, and then assigned to the corresponding treatment sequence by the randomisation list. Subjects will be assigned to the 2 possible treatment sequences in a 1:1 ratio. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The aim of this study is to establish bioequivalence for a FDC tablet containing 5 mg empagliflozin, 2.5 mg linagliptin and 1000 mg metformin XR compared to the mono-tablets. Since 2 of the comparators are not available as mono-tablets in the low dose strengths of the FDC (empagliflozin is not available as a 5 mg tablet, linagliptin is not available as a 2.5 mg tablet), bioequivalence testing is only possible by doubling the dose of the FDC tablet. Still, the doses selected for this trial reflect standard clinical doses (see Section 1.2).

4.1.4 Drug assignment and administration of doses for each subject

This trial is a two-way crossover study. All subjects will receive the 2 treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substances	Formulation	Unit strength	Dosage	Total dose
T (Test)	Empagliflozin/ linagliptin/ metformin HCl	FDC coated tablet, extended release	5 mg/2.5 mg/ 1000 mg	2 FDC tablets (single dose), fed	10 mg/ 5 mg/ 2000 mg
R (Reference)	Empagliflozin	Film-coated tablet	10 mg	1 tablet (single dose), fed	10 mg
	Linagliptin	Film-coated tablet	5 mg	1 tablet (single dose), fed	5 mg
	Metformin HCl	Film-coated tablet, extended release	500 mg	4 tablets (single dose), fed	2000 mg

The medication will be administered as a single oral dose together with about 240 mL of water to a subject in the standing position under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

In each treatment period, a high-fat, high-calorie meal will be served no earlier than 30 min before drug administration. The meal must be completely consumed within the 30 min prior to drug administration. The composition of the standard high-fat, high-calorie meal will be in compliance with the FDA guidance ‘Food-Effect Bioavailability and Fed Bioequivalence Studies’ [R03-2269] as detailed in Table 4.1.4: 2.

Table 4.1.4: 2 Composition of the high-fat, high-calorie meal

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[1]	984

[1] The total caloric content was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

Subjects will be kept under close medical surveillance until 24 h following drug administration. During the first 5 h after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture). For restrictions with regard to diet see Section 4.2.2.2.

The treatments will be separated by a wash-out phase of at least 35 days.

4.1.5 Blinding and procedures for unblinding

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, since all subjects receive the same dose of different formulations in an open label design.

Pharmacokinetic samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

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.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. The clinical trial supply containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use’ (domestic language)
- Sponsor name and address

- Storage conditions
- Use-by date
- Batch number

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF.

As the trial is covered by the FDA requirements 21CFR320, packaging and labeling will be performed in such a way that the required reserve samples are available for storage by the investigational site and that the trial materials can be chosen in a random way by the Investigator. The retained medication will be stored for a minimum of 5 years after trial completion.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

The investigator will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee
- 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

Only authorised personnel as documented in the form ‘Trial Staff List’ may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch/serial numbers, expiry (‘use-by’) dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from

the sponsor. At the time of disposal, the investigator must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed except for hormonal contraceptives. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for at least 5 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (*Hypericum perforatum*) are not permitted starting 7 days before the administration of trial medication until after the last pharmacokinetic sample of each study period is collected.

Alcoholic beverages are not permitted from 72 h before the administration of trial medication until after the last pharmacokinetic sample of each study period is collected.

Smoking is not allowed during in-house confinement at the trial site.

Also, methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during in-house confinement at the trial site.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the first administration of trial medication until the end-of-trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

If female subjects of child bearing potential are included, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for adequate measures).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Secondary endpoint to assess safety and tolerability of the investigational drugs is the number [N (%)] of subjects with drug-related adverse events.

Further criteria of interest:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

These parameters will be evaluated in a descriptive way only, and are therefore considered to be ‘further parameters of interest’. A confirmatory analysis is not planned (see Section 7.3).

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 in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death
- is life-threatening, which 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
- requires inpatient hospitalisation
- requires prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.2, subsections 'AE Collection' and 'AE reporting to sponsor and timelines'.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which, by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

Adverse events of special interest

The term adverse events of special interest (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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.2.2.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o an elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - o aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.
- Pancreatitis
- Hypersensitivity defined as angioedema, severe cutaneous adverse reactions, or anaphylactic responses
- Ketoacidosis
- Lactic acidosis

Intensity (severity) of AEs

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

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

Causal relationship of AEs

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.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.2.2 Adverse event collection and reporting

AE collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs

      The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). 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.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for the initial information.

Information required

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

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy, an SAE form must be completed in addition.

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designee for retests.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
Substrates	Glucose (Plasma)	X	--	X
	Creatinine	X	X	X
	eGFR (using CKD-EPI formula)	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	--	X
	C-Reactive Protein (Quant)	X	X	X
Electrolytes	Sodium	X	--	X
	Potassium	X	--	X

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Urinalysis (Stix)	Urine Nitrite (qual) Urine Protein (qual) Urine Glucose (qual) Urine Ketone (qual) Urobilinogen (qual) Urine Bilirubin (qual) Urine RBC/Erythrocytes (qual) Urine WBC/Leucocytes (qual) Urine pH	X X X X X X X X X	-- -- -- -- -- -- -- -- --	X X X X X X X X X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: Parameters to be determined at Visit 1 (screening examination)
B: Parameters to be determined at Visit 3 on Day -7 to -1
C: Parameters to be determined at Visit 4 (end-of-trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy test and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end-of-trial examination. Drug screening will be performed at screening and prior to each treatment period.

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed prior to each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qual) Hepatitis B core antibody (qual) Hepatitis C antibodies (qual) HIV-1 and HIV-2 antibody (qual)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed with the exception of the drug screening and pregnancy tests. These tests will be performed at the trial site using M-10/14-PDT test and HCG-K20 test, respectively.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart.

All ECGs will be recorded for a 10 sec duration after the subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures of the same time point to avoid impact of sampling on the ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System . Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end-of-trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded. Exact time points of plasma sampling will be derived from the study management system ClinBase™ and documented in the CRFs by the medical personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined:

- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point) for empagliflozin and metformin
- AUC_{0-72} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h) for linagliptin
- C_{max} (maximum measured concentration of the analyte in plasma) for empagliflozin, linagliptin, and metformin

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for empagliflozin, linagliptin, and metformin:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of empagliflozin, linagliptin, and metformin plasma concentrations, 7.5 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 x g to 4000 x g and at 4 to 8 °C. Six plasma aliquots (2 aliquots each for empagliflozin, linagliptin, and metformin) will be obtained and stored in polypropylene tubes. The first aliquots should contain at least 0.5 mL plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 90 min, with interim storage of blood samples in ice water or on ice. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, and planned sampling time, name of analyte, and ‘Ali-1’ or ‘Ali-2’, for first and second aliquots, respectively. Further information such as matrix and analyte may also be provided.

Plasma samples for empagliflozin analyses will be shipped to:

Plasma samples for linagliptin analyses will be shipped to:

Plasma samples for metformin analyses will be shipped to:

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of empagliflozin plasma concentration

Empagliflozin concentrations in plasma will be determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay at . All details of the analytical method will be available prior to the start of sample analysis. During sample analysis, the bioanalyst will be blinded to subject allocation and will have no access to the random code.

5.5.3.2 Analytical determination of linagliptin plasma concentration

Linagliptin concentrations in plasma will be determined by a validated LC-MS/MS assay at All details of the analytical method will be available prior to the start of sample analysis. During sample analysis, the bioanalyst will be blinded to subject allocation and will have no access to the random code.

5.5.3.3 Analytical determination of metformin plasma concentration

Metformin concentrations in plasma will be determined by a validated LC-MS/MS assay at . All details of the analytical method will be available prior to the start of sample analysis. During sample analysis, the bioanalyst will be blinded to subject allocation and will have no access to the random code.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end-of-trial examination are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days -1, 1, 2, 3 and 4 in each period). The 2 treatment periods will be separated by at least 35 days between drug administrations. Within 7 days prior to the drug administration in the second treatment period (Visit 3), the subjects will have an ambulatory appointment for safety laboratory blood sampling.

On Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration on Day 1. The subjects will then be allowed to leave the trial site after formal assessment and

confirmation of their fitness. On all other study days, the study will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for pharmacokinetic analysis, refer to Flow Chart and Section 5.5.2.

The safety measurements performed during the treatment periods are specified in Section 5.2 of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end-of-trial examination.

6.2.3 End-of-trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end-of-trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end-of-trial visit.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The objectives of the trial are stated in Section 2.2.

7.1.2 Endpoints

Bioequivalence is to be determined on the basis of the primary pharmacokinetic endpoints (see Section 5.5.1.1). The secondary pharmacokinetic parameter (see Section 5.5.1.2) will be analysed analogously but will not be interpreted in a confirmatory sense. All pharmacokinetic endpoints (see Section 5.5.1) will be calculated and analysed descriptively.

Safety and tolerability will be determined on the basis of the secondary endpoint

7.1.3 Model

For the bioequivalence analyses, pharmacokinetic endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA (analysis of variance) model. The statistical model used for the analysis of primary and secondary endpoints will be an ANOVA model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘sequence’, ‘subjects within sequences’, ‘period’ and ‘treatment’. The effect ‘subjects within sequences’ will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, where

y_{ijkm} = logarithm of response (endpoint) measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2,

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., n_i

π_j = the j^{th} period effect, j = 1, 2,

τ_k = the k^{th} treatment effect, k = 1, 2,

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

For each endpoint, the difference between the expected means for log(T)-log(R), will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval (CI) based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Although there are multiple primary endpoints an alpha adjustment is not needed because it is required that all primary endpoints meet the equivalence criterion as described below simultaneously. Therefore, a one-sided alpha of 5% will be used for testing.

The assessment of bioequivalence will be based upon two-sided 90% CIs for the ratio of the geometric means (test/reference) for the primary endpoints using an acceptance range of 80.00-125.00%. This method is equivalent to the two one-sided t-tests procedure, each at the 5% significance level (on the log scale).

In general, the hypothesis of inequivalence is tested:

Null hypothesis H_0 (Inequivalence): $\mu_T - \mu_R \leq -\delta \quad or \quad \mu_T - \mu_R \geq \delta$

where μ_T and μ_R are the means of the log-transformed endpoint for the test and reference treatments, respectively, and δ is the bioequivalence limit that defines the acceptance range on the logarithmic scale.

Thus, the null hypothesis is that the difference of the population average responses is either less than or equal to the lower bound or greater than or equal to the upper bound of the acceptance range.

Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$

that is, the difference of the population average responses is both greater than the lower bound and less than the upper bound of the acceptance range.

In this trial, the bioequivalence limit δ is ln(1.25). By back-transforming (exponentiating), this translates to an acceptance range of 80.00 to 125.00% for the ratio of the geometric means (test/reference) for endpoints on the original (linear) scale.

The above null hypothesis H_0 of inequivalence and its alternative H_a can be decomposed into two one-sided null hypotheses, H_{01} and H_{02}, with their accompanying alternatives:

H_{01}: $\mu_T - \mu_R \leq -\delta$ vs. H_{a1}: $\mu_T - \mu_R > -\delta$

H_{02}: $\mu_T - \mu_R \geq \delta$ vs. H_{a2}: $\mu_T - \mu_R < \delta$

Due to the nature of normal-theory CIs, the test of the null hypothesis H_0 at the level of significance of $\alpha = 0.05$ is equivalent to carrying out two one-sided tests of the above null

hypotheses H_{01} and H_{02} each at the level of significance of $\alpha = 0.05$. The rejection of both null hypotheses at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% CI for $\mu_T - \mu_R$ in the acceptance range $(-\delta, \delta)$.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The pharmacokinetic endpoints listed in Section 5.5.1 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472].

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the clinical trial report.

Relevant protocol violations may be:

- Incorrect trial medication taken, that is, the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example:

- The subject experiences emesis that occurred at any time during 24 hours after drug administration
- A pre-dose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

The following analysis sets will be defined for this trial:

- Randomised set (RS):
  This subject set includes all randomised subjects, whether treated or not
- Treated set (TS):
  This subject set includes all subjects from the RS who were documented to have received one dose of study drug. This is the full analysis set population in the sense of ICH-E9
- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects in the TS who provide at least one primary or secondary PK parameter that was not excluded according to the description above.

Thus, a subject will be included in the PKS even if he/she contributes only one PK parameter value for one period to the statistical assessment.

Point estimates of the ratios of the geometric means (test/reference) for the primary and secondary endpoints (see Sections 5.5.1.1 and 5.5.1.2), and their two-sided 90% CIs will be provided.

Bioequivalence is considered established if the 90% CIs of the ratios of the geometric means for the primary endpoints (see Section 5.5.1.1) are contained in the pre-defined acceptance range (see Section 7.2).

7.3.2 Secondary analyses

The secondary safety endpoint as specified in Section 5.2.1 will be derived according to BI standards. The analysis will be based on all treated subjects and will be descriptive in nature (see Section 7.3.3 for details).

7.3.3 Safety analyses

Safety will be assessed as defined by the secondary endpoint and further parameters listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by ‘treatment at onset’.

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see Section 1.2.5) will be assigned to the treatment period. Events after the residual effect period but prior to next intake or end-of-trial examination will be summarized as ‘follow-up’. The follow-up will be summarised according to previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. AEs occurring after the last per-protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening and post-study intervals).

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 will be calculated according to the relevant BI SOP [001-MCS-36-472].

Individual plasma concentration data and the pharmacokinetic parameters will be tabulated, graphically displayed and summarized by descriptive statistics. Descriptive and inferential statistics of PK endpoints will be based on PKS.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

If a pre-dose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a pre-dose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration-time profiles

Handling of missing PK data will be performed according to the relevant BI SOP [001-MCS-36-472].

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the pre-dose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant BI SOP [001-MCS-36-472].

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

Subjects will be randomised to 1 of the 2 treatment sequences in a 1:1 ratio. The block size will be documented in the clinical trial report.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

The randomisation list will contain additional blocks to allow for subject replacement (refer to 3.3.5).

7.6 DETERMINATION OF SAMPLE SIZE

The function CVpooled() of the R package PowerTOST was used to estimate an 80% upper confidence limit of the pooled geometric coefficient of variation (gCV).

The following table summarizes the underlying C_{max} data regarding the gCV.

For AUC the gCVs were generally lower. Therefore and because AUC and C_{max} are highly correlated, the (overall) power calculations are done for C_{max} only.

The overall power to reject the null hypothesis of bioinequivalence for all analytes in favor of equivalence at the 5% level of significance is given by the product of the individual power values for each of the analytes, assuming that all three analytes are independent of each other. Using the assumptions as stated above,

Furthermore, this sample size still provides approximately

Accounting for up to 6 non PK evaluable subjects, N = 24 + 6 = 30 subjects are planned to be randomized into the trial.

The calculations for single power values were performed as described by Diletti et al. [R94-1445] using the function power.TOST() of the package PowerTOST Version 1.4-7 in R version 3.4.2.

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 SOPs.

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

As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT 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 a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject'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 subject information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, 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.

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 the trial master file (TMF).

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

is operated for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

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

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

Data directly entered into ClinBase™ (that is, without prior written or electronic record) are considered to be source data. The place where data is entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ are available for inspection at any time.

The investigator may need to request previous medical records or transfer records, depending on the trial.

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 and all source documents, including progress notes (if applicable) 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/on site monitor and auditor may review all CRFs, 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 period of records

Trial site:
The trial site must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

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

Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject'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, that is, the CA.

8.6 COMPLETION OF TRIAL

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

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		24 July 2018
EudraCT number		2018-001266-42
BI Trial number		1361-0011
BI Investigational Product(s)		Empagliflozin/linagliptin/metformin extended release fixed dose combination
Title of protocol		Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)
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	n/a 2.2) 2.3) 4.1.3) 5.2.1) 5.2.2) 7.1.2) 7.3.2) 7.3.3)	Synopsis Trial objectives Benefit-Risk Assessment Selection of doses in the trial Endpoints of safety Assessment of adverse events Endpoints Secondary analysis Safety analysis

Number of global amendment		1
Description of change	1) 2.2) 2.3) 4.1.3) 5.2.1) 5.2.2) 7.1.2) 7.3.2) 7.3.3)	Test and comparator products described consistently; safety criteria defined as secondary endpoints. Safety and tolerability defined as secondary objectives. Moved a statement about expected AEs with dose of 2000 mg metformin; extended the summary of possible AEs with 2000 mg metformin by referral to 1288.11. Provided rationale for selection of doses in the trial. Defined safety and tolerability as secondary endpoint. Added ‘lactic acidosis’ as AESI. Adapted the basis for determination of safety and tolerability. Defined the derivation and analysis of the secondary safety endpoint; clarified endpoints mentioned are pharmacokinetic. Clarified assessment of safety.
Rationale for change	1) + 2.2) + 2.3) + 4.1.3) + 5.2.1) + 5.2.2) + 7.1.2) + 7.3.2) + 7.3.3) +	Requests by competent authority and request by ethics committee Requests by competent authority Requests by competent authority Requests by competent authority Requests by competent authority Requests by competent authority Requests by competent authority Requests by competent authority Requests by competent authority

APPROVAL / SIGNATURE PAGE

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Title: Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		27 Jul 2018 11:57 CEST
Author-Trial Clinical Pharmacokineticist		29 Jul 2018 20:07 CEST
Author-Trial Clinical Monitor		30 Jul 2018 07:18 CEST
Verification-Paper Signature Completion		30 Jul 2018 10:21 CEST
Approval-Therapeutic Area		04 Aug 2018 09:05 CEST
Author-Trial Statistician		20 Aug 2018 09:32 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed