Clinical Trial Protocol

	Document Number: <c12345678-01> [redacted] Number: PBDS004/21
BI Trial No.	1276-0041
[redacted] **Number**	PBDS004/21
BI Investigational Medicinal Product	JardianceDuo®, empagliflozin/metformin Fixed Dose Combination (FDC)
Title	Relative bioavailability of empagliflozin/metformin fixed-dose combination - Empaglifozin 12.5 mg + Metformin 850mg (Boehringer Ingelheim) coated tablet versus Jardiance® 10mg (Reference 1: Boehringer Ingelheim) coated tablet and Glifage® 850mg (Reference 2: [redacted]) coated tablet, administered together in healthy male and female subjects under fed conditions: an open-label, randomised, single-dose, two-way crossover study.
Clinical Phase	I
Trial Clinical Monitor	[redacted] Phone: Fax: [redacted]
Principal Investigator	[redacted] Address: [redacted] Phone: Fax: [redacted]
Status	Official Final Protocol
Version and Date	Version: 2.0 / Date: 08 Jun 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

BI trial number	1276-0041
[redacted] **number**	PBDS004/21
Title of trial	Relative bioavailability of empagliflozin/metformin fixed-dose combination - Empaglifozin 12.5 mg + Metformin 850mg (Boehringer Ingelheim) coated tablet versus Jardiance® 10mg (Reference 1: Boehringer Ingelheim) coated tablet and Glifage® 850mg (Reference 2: [redacted]) coated tablet, administered together in healthy male and female subjects under fed conditions: an open-label, randomised, single-dose, two-way crossover study.
Principal Investigator:	[redacted]
Clinical Investigator	
Trial sites	Clinical phase: [redacted] [redacted]
Clinical phase	I
Trial rationale	According to ANVISA, Brazilian Health Authority, a BE program must be conducted as part of the Empa +Met FDC registration. The BE trial must be performed as per specific local requirements following ANVISA regulation.
Trial objective	To establish whether a fixed-dose tablet of 12.5 mg empagliflozin+850 mg metformin (T1) is bioequivalent to the free dose combination of 10 mg Jardiance (empagliflozin) and Glifage 850 mg (metformin) (R).
Trial design	Randomised, single dose, open-label, two-way crossover design
Trial endpoints:	Primary endpoints: • Dose-normalized AUC0-tz and Dose-normalized Cmax of empagliflozin • AUC0-tz and C_{max} of metformin Secondary endpoint: • Dose-normalized $AUC_{0-\infty}$ of empagliflozin • $AUC_{0-\infty}$ of metformin • Tmax AUC_%Extrap_obs, HL_Lambda_z and Lambda_z of empagliflozin and metformin
Number of subjects **total entered** **each treatment**	N = 32

Main criteria for inclusion	Healthy male/female subjects, age > 18 years (inclusive) < 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive).
Test product	Drug formulation (T)
dose	Fixed-dose tablet of 12.5 mg empagliflozin+850 mg metformin
mode of admin.	Oral fed state with 200 mL of water after an overnight fast of at least 10 h and 30 min after start of a 1000 Cal high fat/high caloric meal.
Reference products	Drug formulation (R1 and R2)
dose	Glifage (metformin) 850 mg – Reference 2 Jardiance (empagliflozin) 10 mg – Reference 1
mode of admin.	Oral fed state with 200 mL of water after an overnight fast of at least 8 h and 30 min after start of a 1000 Cal high fat/high caloric meal.
Duration of treatment	One day (single dose) for each treatment
PK Collection Time points	In each period of the study blood will be collected at the following time points: at pre dose (-00:05 minutes) and 00:15, 00:30, 00:45 minutes, and 01:00, 01:15, 01:30, 01:45, 02:00, 02:20, 02:40, 03:00, 03:30, 04:00, 04:30, 05:00, 05:30, 06:00, 07:00, 08:00, 10:00, 12:00, 24:00, 48:00, and 72:00 hours after the medication dosing on Day 1 of Periods 1 and 2.
Statistical methods	The assessment of bioequivalence will be based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the primary endpoints and for secondary endpoints for Dose-normalized AUC0-∞ (empagliflozin) and AUC0-∞ (metformin) using an acceptance range of 80.00 to 125.00%. This method corresponds to the two 1-sided t-tests procedure, each at a 5% significance level. The statistical model will be an analysis of variance (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 the ANOVA and quantiles from the t-distribution. Differences in tmax, will be analysed using a non-parametric method. Descriptive statistics will be calculated for all endpoints.

Responsible for the phases of study

Study Sponsor	Boehringer Ingelheim	
Principal Investigator		[redacted]
Clinical Investigator		

Phase - Institution	Responsible	Qualification
Clinical Phase - [redacted]	[redacted]	Pharmacist
Laboratorial Exams execution [redacted]		Pharmacist Biochemisty
Analytical Phase – [redacted]		Food Chemist
Statistical Phase - [redacted]		Statistical and Mathematics
Quality Assurance - [redacted]		Biomedical

Study researchers signature

This project will be conducted according to the norms and rules of research with human beings as in Resolution Nº 466/12 and 251/97 of the National Health Committee – Health Ministry, of ICH`s GLP – Good Laboratory Practices according ICH and the Document of the Americas and the Helsinki Declaration (1964) also the Tokyo review (1975), Venice's review (1983), Hong Kong's review (1989), Somerset West's review (1996), Edinburg's review (2000), Washington's review (2002), Tokyo's (2004) and Seoul's review (2008) and Fortaleza (2013).

Study Sponsor

Boehringer Ingelheim._____Date___/___/___.

[redacted]**'s team**

Principal Investigator

[redacted] _____Date ___/___/___.

Clinical Investigator

[redacted] _____Date___/___/___.

STUDY PHASES EXECUTION PLACES

Subjects' Clinical Assessment Place:

Clinical Research Unit: [redacted].
Address: [redacted], Zip Code: [redacted]
Phone number: [redacted]

Clinical Phase Execution Place:

Clinical Research Unit: [redacted]
Address [redacted] Zip Code: [redacted]
Phone number: [redacted]

Execution Place of the Laboratorial Clinical Exams:

[redacted]

Address: [redacted]

Phone number: [redacted]

Analytical Phase Execution Place:

[redacted]

Address: [redacted]
ZIP CODE: [redacted]
PHONE/FAX: [redacted]
E-mail: [redacted]

Statistical Phase Execution Place:

Statistical Unit: [redacted]
Address: [redacted] Zip Code: [redacted]
Phone number: [redacted]

Ethics Committee responsible for the evaluation and protocol approval:

Comitê de Ética em Pesquisa do [redacted]

[redacted]

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood	12-lead ECG	Additional examination	Vital signs (BP, HR, temp)	Questioning for AEs and concomitant therapy[6]
SCR	1	-28 to -1			Screening (SCR)[1]	x		x		x	x
		-2			SARS-COV-2 RT-PCR via nasal swab				x		
1/2 (two identical periods with separated by a wash-out of at least 7 days	2/3	-1	-17:00	17:00	Admission to trial site	x[5]					x
			-17:00	17:00	Allocation to treatment2 (visit 2 only)						
			-11:30	20:30	Dinner (voluntary)						
		1	-07:00	00:00	Water ingestion restriction						
			-01:00	06:00							x
			-0:30	06:30	High fat, high calorie breakfast						
			-0:05	06:55			x			x	
			0:00	07:00	Drug administration						
			0:15	07:15			x				
			0:30	07:30			x				
			0:45	07:45			x				
			1:00	08:00			x			x	x
			1:15	08:15			x				
			1:30	08:30			x				
			1:45	08:45			x				
			2:00	09:00	200 mL fluid intake		x			x	
			2:20	09:20			x				
			2:40	09:40			x				
			3:00	10:00			x			x	
			3:30	10:30			x				
			4:00	11:00	Lunch		x			x	
			4:30	11:30			x				
			5:00	12:00			x				
			5:30	12:30			x				
			6:00	13:00			x			x	
			7:00	14:00			x				
			8:00	15:00	Snack (voluntary)[3]		x			x	
			10:00	17:00			x				
			12:00	19:00	Dinner (voluntary)[3] Discharge from trial site[7]		x			x	
		2	24:00	08:00	Ambulatory visit	x	x				x
		3	48:00	08:00	Ambulatory visit		x				x
		4	72:00	08:00	Ambulatory visit		x				x
FU	4	4 to 14			End of trial (EoTrial) 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), 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 the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.

4. At the end of trial visit the End of Trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening as well as pregnancy test in women will be done at this time. Due to COVID-19 pandemics, alcohol breath test is temporarily suspended, and the subject is evaluated clinically by a physician for alcoholic ingestion symptoms and signs.
6. AEs and concomitant therapies will be recorded throughout the trial but will be specifically asked for at the times indicated in the Flow Chart above.
7. After the dinner the subjects will be discharge from the clinical unit.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
Ae_{t1-t2}	Amount of analyte eliminated in urine over the time interval from t_1 to t_2.
AMG	Arzneimittelgesetz (German drug law)
ANOVA	Analysis of variance
ANVISA	*Agência Nacional de Vigilância Sanitária* (in Portuguese)
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 interpolated 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
BA	Bioavailability
BI	Boehringer Ingelheim
BID	Bis in die (twice daily)
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CTMF	Clinical trial master file
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
F	Absolute bioavailability factor
FDC	Fixed dose combination
gCV	Geometric coefficient of variation
gMean	Geometric mean
[redacted]	
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
MedDRA	Medical Dictionary for Regulatory Activities

MRT_{po}	Mean residence time of the analyte in the body after oral administration
NC	Not calculated
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
R	Reference treatment
SAE	Serious adverse event
SCR	Screening
SGLT(-1/2)	Sodium-glucose-transporter (1/2)
SmPC	Summary of Product Characteristics
ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma = HL_Lambda
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
T2DM	Type 2 diabetes mellitus
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
V_z	Apparent volume of distribution during the terminal phase λ_z after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase λ_z after extravascular administration

1. INTRODUCTION

Empagliflozin (BI 10773) is an orally available inhibitor of the sodium-glucose co-transporter 2 (SGLT-2), that promotes enhanced glucose excretion in the urine, thereby lowering blood glucose concentrations in patients with type 2 diabetes mellitus (T2DM).

Metformin (Met) is an oral antihyperglycemic agent that reduces plasma glucose levels by decreasing intestinal glucose absorption and hepatic glucose production and enhancing the glucose uptake and utilization of peripheral tissue.

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 415 million affected people worldwide. Complications induced by hyperglycaemia are currently the most frequent cause of adult-onset loss of vision, renal failure, and amputation in the industrialized world. Diabetes is also associated with macrovascular complications with a 2- to 4-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of life expectancy. Currently available oral antidiabetic drugs are efficacious, but still fail to achieve an optimal blood glucose control in many patients.

SGLT-2 is a member of a larger group of sodium substrate co-transporters, the sodium-glucose co-transport 5 (SLC5) gene family [R05-0939]. Under normoglycemia, glucose is almost completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at plasma glucose concentrations higher than approximately 10-11 mmol/L, resulting in increasing glucosuria typically seen in patients with diabetes mellitus. The capacity to reabsorb glucose can be decreased by inhibition of SGLT-2. In humans, empagliflozin very selectively blocks glucose transport via SGLT-2 (IC50 1.3 nM), with a 5000-fold selectivity over SGLT-1 (IC50 6278 nM).

The efficacy of empagliflozin is similar to the current oral antidiabetic drugs and can be combined with other oral antidiabetic drugs. Clinical trials demonstrated an additive efficacy in terms of glucose control when used in combination with metformin in patients with T2DM[1,2] (see Section 1.2.1).

1. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, Woerle HJ; EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014 Jun;37(6):1650-9.

2. Hadjadj S, Rosenstock J, Meinicke T, Woerle HJ, Broedl UC. Initial Combination of Empagliflozin and Metformin in Patients With Type 2 Diabetes. Diabetes Care. 2016 Oct;39(10):1718-28.

1.2 DRUG PROFILE

1.2.1 Empagliflozin (Empa)

Non-clinical assessment of safety
A comprehensive package of safety pharmacology, genetic toxicology, reproductive toxicology and general toxicology studies were conducted in mice, rats, rabbits and dogs to support the chronic administration of the two empagliflozin doses (10 mg/day and 25 mg/day) used in phase III clinical trials to humans. The compound was generally well tolerated in animals at clinically relevant plasma exposures, while adverse effects were only observed at higher doses. Noteworthy adverse findings at effect levels above the NOAEL (no observed adverse effect level) in general toxicology studies were body weight loss, lower weight gain, dehydration, nephritis and nephropathy. Human clinical exposure at 25 mg/day is well below the exposure at the NOAEL of 100 mg/kg/day in male rats after 26 weeks of and the NOAEL of 10 mg/kg/day in the dog after 52 weeks of dosing and indicates a 9 to 10 fold therapeutic window to these NOAEL's.

In the mouse 2-year carcinogenicity study with empagliflozin a drug-related renal adenoma/carcinoma response has been identified in male, but not female mice at supratherapeutic doses (highest dose group of 1000 mg/kg/day). In comparison to the exposure associated with the 25 mg daily dose in humans, the drug related renal tumours occurred in male mice at exposures of approximately 30-fold and were absent at exposures of 11-fold. No such tumour findings were observed in females at any dose level. Empagliflozin is nongenotoxic and the renal tumours in mice appear to result from chronic tubule cytotoxicity and cell regeneration. Such epigenetic mechanisms have exposure thresholds, below which they are not relevant.

In a 13-week toxicity study in rats where empagliflozin and metformin were co-administered, the NOAEL was considered to be 50 mg/kg/day for empagliflozin and 100 mg/kg/day for metformin. There were no new target organs identified when empagliflozin and metformin were combined at doses that were tolerable when each compound was dosed alone. These data support the safe administration of the combination of empagliflozin (up to 12.5 mg, BID) and the marketed compound metformin (up to 1000 mg, BID) to humans.

Clinical pharmacokinetics
In humans, empagliflozin predominantly shows linear pharmacokinetics following single oral doses and at steady state after multiple oral doses. Empagliflozin was rapidly absorbed reaching peak levels at approximately 1.5 h and showed a biphasic decline with the terminal elimination half-life ranging from 10 to 19 h. Following oral administration of [14C]-empagliflozin, approximately 41.2% and 54.4% of drug-related radioactivity was excreted in feces and urine, respectively. The majority of drug related radioactivity in plasma was parent and the most abundant metabolites were glucuronide conjugates. None of the detected metabolites were major as their systemic exposure was less than 10% compared to parent. Administration of empagliflozin tablets with a high fat and high calorie meal had no

clinically relevant effect on the overall absorption of empagliflozin. Therefore, empagliflozin tablets can be administered with or without food.
Empagliflozin exposure increased moderately with the extent of renal and hepatic impairment suggesting that no dose adjustment is needed. The observations from the phase I study in patients with renal impairment indicate a rather low efficacy of empagliflozin in patients with severe renal impairment and end-stage renal disease (ESRD), while efficacy is assumed to be unchanged with hepatic impairment.

No clinically relevant pharmacokinetic interactions were observed with metformin, glimepiride, sitagliptin, warfarin, linagliptin, verapamil, ramipril, simvastatin, digoxin, gemfibrozil and oral contraceptives (Microgynon®). There was a moderate increase in pioglitazone exposure in one of two different pioglitazone interaction studies, so that monitoring of pioglitazone side effects in patients receiving empagliflozin on top of pioglitazone in clinical studies is recommended.

Clinical efficacy and safety
Approximately 550 healthy subjects were exposed to empagliflozin (dose range: 0.5 mg to 800 mg per single dose and up to 50 mg in multiple dosing) in Phase I clinical trials. Of these, approximately 240 subjects received multiple doses with empagliflozin 25 mg or 50 mg once daily. In addition, approximately 240 Caucasian and Japanese patients with T2DM were exposed to empagliflozin (10 mg, 25 mg, 50 mg or 100 mg once daily) in phase I studies with a duration of 2-4 weeks. In the two completed Phase II studies approximately 600 patients with T2DM completed up to 12 weeks of treatment with different doses of empagliflozin up to 50 mg once daily. Of these 600 patients, approximately 550 patients continued treatment up to an additional 72 weeks.

Empagliflozin demonstrated good efficacy with approximately 70-90 g/day of urinary glucose excretion (UGE), without inducing any significant hypoglycaemia. The twelve week Phase II studies demonstrated an HbA1c reduction of up to 0.72 % (placebo subtracted), a fasting plasma glucose reduction of up to 32 mg/dL and a weight loss of approximately 1.5 kg, in both the monotherapy setting and as an add-on to metformin (≥ 1500 mg/day).

In clinical studies, empagliflozin was well tolerated in both healthy subjects and patients with T2DM up to maximal treatment duration of up to 90 weeks in completed studies. Treatment with empagliflozin resulted in similar percentage of overall adverse events (AEs) compared to placebo and active comparators. Regarding combination therapy of empagliflozin + metformin a similar percentage of overall AEs and serious AEs was found in the Phase II metformin background therapy trial 1245.10 with 38.5% overall and 2.5 % serious AEs on empagliflozin+metformin compared to 36.6% and 2.8% on placebo+metformin. Treatment with empagliflozin showed a higher frequency of genital infections and symptoms of increased micturition frequency and/or volume, yet was not associated with a higher incidence of urinary tract infections or hypoglycaemia.

A phase III study was designed to evaluate empagliflozin as an add-on therapy to metformin. In the with patients with HbA1c levels of ≥7% to ≤ 10% while receiving metformin (≥1,500 mg/day) were randomized and treated with once-daily treatment with empagliflozin 10 mg (n = 217), empagliflozin 25 mg (n = 213), or placebo (n = 207) for 24 weeks. Adverse events

(AEs) were similar across groups (placebo 58.7%; empagliflozin 49.5–57.1%). Confirmed hypoglycemic AEs were reported in 0.5%, 1.8%, and 1.4% of patients receiving placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Events consistent with urinary tract infections were reported in 4.9%, 5.1%, and 5.6% of patients, and events consistent with genital infections were reported in 0%, 3.7%, and 4.7% of patients, respectively. Both empagliflozin 10 and 25 mg significantly improved glycaemic control, weight, and BP, and were well-tolerated in the 24 weeks period as add-on to metformin therapy[1].

The initial combination of Empa and Met in patients with DM2 was evaluated in a phase III clinical trial This study compared the efficacy and safety of initial combinations of empagliflozin + metformin with empagliflozin and metformin monotherapy in patients with type 2 diabetes. The study randomized 1,364 drug-naïve patients (HbA1c >7.5 to ≤12% [>58 to ≤108 mmol/mol]) for 24 weeks to empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d., empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 5 mg b.i.d + metformin 1,000 mg b.i.d., empagliflozin 5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 25 mg q.d., empagliflozin 10 mg q.d., metformin 1,000 mg b.i.d., or metformin 500 mg b.i.d. The primary end point was change from baseline in HbA1c at week 24.At week 24, reductions in HbA1c (mean baseline 8.6-8.9% [70-73 mmol/mol]) were -1.9 to -2.1% with empagliflozin + metformin twice-daily regimens, -1.4% with both empagliflozin once-daily regimens, and -1.2 to -1.8% with metformin twice-daily regimens. Adverse event (AE) rates were similar across groups (56.7-66.3%). No hypoglycemic AEs required assistance. The initial combinations of empagliflozin + metformin for 24 weeks significantly reduced HbA1c versus empagliflozin once daily and metformin twice daily, without increased hypoglycemia, reduced weight versus metformin twice daily, and were well tolerated[2].

1. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, Woerle HJ; EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014 Jun;37(6):1650-9.

2. Hadjadj S, Rosenstock J, Meinicke T, Woerle HJ, Broedl UC. Initial Combination of Empagliflozin and Metformin in Patients With Type 2 Diabetes. Diabetes Care. 2016 Oct;39(10):1718-28.

In summary, empagliflozin was well tolerated in Phase I and Phase II studies in healthy male volunteers and patients with T2DM. The vast majority of AEs considered related to empagliflozin have been of mild to moderate nature and no deaths have been related to empagliflozin. Clinical and non-clinical data support the further development of empagliflozin in larger studies with treatment duration of 52 weeks and above.

Since approval (Fev2015 to Dec2020), approximately 612 726 patient-years with type 2 diabetes in Brazil have been exposed to Jardiance (and approximately 10 056 876 patient-years worldwide (April 2014 to April 2020), according to PBRER s00085859-01.

Worldwide exposure to FDC (Jardiance Duo) has been so far approximately 1 442 835 patient-years (July 2015 to April 2020) - ref. PBRER s00085859-01.

The benefit-risk balance of empagliflozin and empagliflozin/metformin remains favourable in its authorized indications – ref. PBRER s00085859-01.

For further details see empagliflozin Investigator's Brochure [c01678844-16].

1.2.2 Metformin (Met)

Metformin is an oral antihyperglycemic agent that reduces plasma glucose levels by decreasing intestinal glucose absorption and hepatic glucose production and enhancing the glucose uptake and utilization of peripheral tissue. Thus, metformin renders a reduction of basal and postprandial plasma glucose in patients with T2DM. Unlike sulfonylureas (e.g. glyburide) metformin does not increase insulin secretion and is not associated with hypoglycaemia in either patients with T2DM or healthy volunteers [R11-4761].

The absolute bioavailability of metformin is 50-60 % under fasting conditions. The intake of food decreases the extent of absorption. A 40% lower C_{max} and a 25% lower AUC (area under the curve) were reported following a single dose administration of 850 mg metformin with food. Studies using single oral doses of 500 – 1500 mg metformin indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination [R10-5341].

Metformin is negligibly bound to plasma proteins. The drug partitions into erythrocytes, which might represent a deep compartment of distribution. Intravenous studies in healthy volunteers demonstrate that metformin is excreted unchanged in the urine and neither undergoes hepatic metabolism nor biliary excretion. Following oral administration approximately 90% of the absorbed drug is eliminated via the renal route with a plasma-elimination half-life of about 6.2 hours [R10-5341].

Metformin is available as tablets for oral administration in the strengths 500, 850 and 1000 mg [R10-5341]. The maximum recommended daily dose is 3000 mg in adults [R11-4761].

In a double-blind, placebo-controlled US clinical trial involving obese patients with type 2 diabetes whose hyperglycaemia was not adequately controlled with diet alone, treatment with metformin (up to 2550 mg/day) for 29 weeks resulted in significant mean net reductions in FPG, PPG and HbA1c of 59 mg/dl, 83 mg/dl, and 1.8 %, respectively, compared to the placebo group [R10-5341].

Metformin was well tolerated by healthy male volunteers given alone (1000 mg twice daily) and in combination with empagliflozin (50 mg once daily) for 5 days [U09-1852-01]. The most frequently reported adverse events were headache, diarrhoea and nausea which were considered drug related adverse events. The incidence of these events on empagliflozin + metformin did not exceed the incidence observed under metformin monotherapy. Gastrointestinal side effects such as abdominal pain, diarrhoea and nausea represent well-known side-effects of metformin [R11-4761]. Hypoglycaemic events did not occur in any

treatment period. The pharmacokinetics of empagliflozin and metformin were similar following co-administration compared to both monotherapies alone [U06-1897-08].

1.2.1 Residual Effect Period

The Residual Effect Period (REP) of Empa is 4 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.

The Residual Effect Period (REP) of Met is 3 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Combination drug therapy should improve compliance and provide additive 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. Providing both ingredients in a single tablet will help facilitate drug dosing and compliance for patients. The actual BE study is performed as per local regulatory requirement of ANVISA in Brazil as a pre-requisite for local regulatory approval of the empagliflozin/metformin JardianceDuo fixed dose combinations.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this bioequivalence study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance for the technical validation of the oral fixed dose combination of two antidiabetic principles, empagliflozin and metformin. Subjects are exposed to risks of study procedures and 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, in rare cases, by transient inflammation of the wall of the vein. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venepuncture for blood sampling.

The total volume of blood withdrawn per patient during the entire study will not exceed 500 mL.

Drug-related risks and safety measures

Empagliflozin: The overall safety profile of empagliflozin is favourable for human studies at chronic doses up to 100 mg/day. The maximum dose administered in the single rising dose study was 800 mg and was well tolerated.

In studies with healthy subjects, the overall adverse event rate with empagliflozin was 32.4%, 20.3 % with placebo and 24.0% with the comparator groups. One volunteer had a serious adverse event (migraine with aura) that required hospitalization, this event was not assessed to be drug related. The most frequent adverse events (>2%) comprise headache (12.1 %), nasopharyngitis (4.4 %), diarrhea (3.8 %) and nausea (3.1 %). Except for headache (5.1 % in placebo) none of these AEs occurred with placebo while various comparators (e.g. metformin) had equivalent or greater incidences of these AEs [U06-1897-08].

In the present study subjects are exposed to 1 single dose of 10 mg of empagliflozin plus 850 mg of metformin and 1 single dose of 12,5mg empagliflozin plus 850 mg metformin fixed dose combination, which are separated by a wash-out phase of 1 week. Based on the previous experience with empagliflozin the safety risk to healthy subjects related to the intake of empagliflozin in this trial is expected to be low.

Metformin: Most frequent adverse events of metformin are [R11-4761]:

>10 %:	gastrointestinal disorders (nausea, vomiting, diarrhoea, stomach ache)
1-10 %:	changes in taste
< 0.01 %:	skin reactions (erythema, itching, urticaria), abnormal liver function test

In diabetic patients, the intake of metformin can cause lactic acidosis in very rare cases (< 0.01%). 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 has not occurred in healthy volunteers. Renal and liver function will be checked thoroughly as part of the screening. Alcoholic beverages and unusual physical activities are restricted during the study (see Section 4.2.2).

Gastrointestinal disorders usually occur at the beginning of a metformin therapy. Therefore, they are likely to be expected also after single dose administration of metformin in this trial, which is in line with the observations in other metformin trials. These adverse events are well characterized, disappear within a short period of time and do not represent any safety risk.

Empagliflozin+Metformin: In a pilot trial the relative bioavailability of a 12.5 mg empagliflozin/1000 mg metformin fixed dose combination tablet was compared to the respective single tablets in 16 healthy volunteers. The most frequent adverse event was diarrhea, which occurred in 6 subjects (mild intensity, drug related in each case). The second most frequent reported adverse event was headache (reported by 2 subjects), which was assessed to be drug related in one case. No further drug related AEs occurred [U11-1763-01].

To compare the pharmacokinetics of FDC tablets of empagliflozin/metformin with individual tablets taken together, three randomized, open-label studies were performed with healthy subjects received a single FDC tablet of empagliflozin/metformin in one of six dose combinations: empagliflozin 5 mg or 12.5 mg and metformin 500 mg, 850 mg or 1,000 mg in one period and the individual tablets are taken together under fed conditions in another

period. Bioequivalence was also established under fasted conditions for empagliflozin 12.5 mg/metformin 1,000 mg FDC versus individual tablets taken together. Empagliflozin/metformin FDC tablets were found to be bioequivalent to individual tablets taken together at all tested dose strengths and in both fed and fasted conditions[1].

1. Rojas C, Link J, Meinicke T, Macha S. Pharmacokinetics of fixed-dose combinations of empagliflozin/metformin compared with individual tablets in healthy subjects. Int J Clin Pharmacol Ther. 2016 Apr;54(4):282-92.

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 5.2.6.1.4, adverse events of special interest.

Overall assessment

In this study two antidiabetic principles are combined. However, neither the use of metformin nor of empagliflozin is associated with hypoglycaemic events which can be explained by their mode of action. Also, no hypoglycaemic signs and symptoms were observed in previous studies investigating the combination of both drugs in healthy subjects. Therefore, a regular measurement of blood glucose is not considered necessary during the present study. This will be done at any time, if clinical signs or symptoms of hypoglycaemia occur.

The volunteers in this study receive no direct medical benefit from participation in this study. Safety will be ensured by the monitoring of subjects for adverse events clinically and verbally. If the investigator should have a clinical concern, the safety of the volunteers will be paramount.

Overall, the risk for subjects participating in this trial is considered to be low and acceptable. Because of the anticipated benefit that a successful clinical development of the FDC tablet could provide to patients with type 2 diabetes the sponsor feels the benefit of a successful clinical development of fixed dose combination tablet to outweigh the risk.

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

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to establish bioequivalence of the FDC tablets (containing 12.5 mg empagliflozin/850 mg metformin) (Test, T) compared with the single tablets (10 mg empagliflozin and Glifage® 850 mg tablets) (Reference, R) following oral administration.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for empagliflozin and metformin:

- Dose-normalized AUC0-tz and Dose-normalized Cmax of empagliflozin
- AUC0-tz and Cmax of metformin

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined for empagliflozin and metformin:

- Dose-normalized $AUC_{0-\infty}$ of empagliflozin
- $AUC_{0-\infty}$ of metformin
- Tmax, AUC_%Extrap_obs, HL_Lambda_z and Lambda_z of empagliflozin and metformin

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open label, 2x2 crossover trial in healthy male and female subjects in order to compare the test treatments (treatment B) to the reference treatments (treatment A). The treatments will be:

Treatment B: 1 FDC tablet 12.5 mg Empa/850 mg metformin (test)
Treatment A: 1 tablet Empa 10 mg (Reference 1) + 1 tablet Glifage® 850 mg (Reference 2)
The subjects will be randomly allocated to one of the 2 treatment sequences:

Sequence 1	B A
Sequence 2	A B

All treatments will be taken after a high fat high caloric meal. For details refer to Section 4.1.

In accordance with the resolution RE nº. 1170, the interval between the periods (washout period), should be at least seven elimination half-lives of the active ingredient in the blood. As such, for empaglifozin and metformin, the wash out period of the study should be at least 5 days to ensure complete elimination of the drugs. In this study the two periods will be separated by a washout phase of at least 7 days to facilitate operational requirements.

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.

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

For bioequivalence trials, the crossover design is preferred because of its efficiency: since each subject serves as his/her own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between formulations. This means that the inter-subject variability is removed from the comparison between formulations [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 analyte, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 32 healthy male and female subjects will enter the study. They will be recruited from the volunteers' pool of the [redacted] trial site. There are no restrictions regarding the ethnic group.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests

2. Age of at least 18 (inclusive) to 50 years (inclusive)

3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)

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 from at least 30 days before the first administration of trial medication 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)

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) deviating from normal and assessed 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 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
5. History of relevant orthostatic hypotension, fainting spells, or blackouts
6. Chronic or relevant acute infections
7. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
8. Smoker (more than 5 cigarettes or 1 cigar or 1 pipe per day)
9. Inability to refrain from smoking on specified trial days
10. Drug abuse or positive drug screening
11. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
12. Inability to comply with the dietary regimen of the trial site
13. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
14. Research participants are submitted to surgery or who are hospitalized for any reason before the beginning of the study will be carefully evaluated by the physician regarding admission to the study, observing an exclusion period that may vary from 4 to 8 weeks;
15. Positive test for hepatitis B, hepatitis C, or HIV in pre-study tests;
16. The research participant has AST and/or ALT elevation ≥ 3 times the ULN and a total bilirubin elevation ≥ 2 times the ULN (measured in the sample of the same blood) and/or needs to be followed up according to a list of DILI verification pending in Investigator's File;
17. The research participant has a known hypersensitivity to the study drug or chemically related compounds;
18. The research participant has participated in any experimental trial or ingested any experimental drug within the six months preceding the beginning of this study (ANVISA Resolution #34, dated June 3, 2008);
19. To have used regular medication within 4 weeks previous or 5 half-lives (which have longer duration) to the beginning of this study. Only the use of contraceptive pills will be allowed to women. The eventual use of medication, that at the Investigator’s or physician in charge judgment does not interfere with the study drug pharmacokinetics, will not be considered as exclusion criterion;

20. Use of any eventual medication within 07 days prior to the beginning of the study treatment, except dipyrone and paracetamol, except for exceptions upon careful and justified evaluation by the investigator;
21. The research participant has a history of alcohol abuse or has ingested alcohol 24 hours previous to the hospitalization period;
22. The research participant has a history of drug abuse [participants using marijuana and hashish less than 6 months before the visit will be excluded. For drugs such as cocaine, phenicyclidine (PCP), crack and heroin, research participant who presented their use in less than 1 year before the visit are excluded];
23. Consumption of hepatic metabolism-inducing and/or inhibiting drugs that have a long half-life (half-life> 50 hours), fibrate, niacin and cyclosporine, within 30 days before the study drug is administered. For those drugs with a half-life of less than 50 hours, the clinical investigator will assess case by case, taking into account the drug elimination half-life;
24. Use of monoamine oxidase (MAO) inhibitors (moclobemide, iproniazid, nialamide, phenelzine, tranylcypromine) two weeks before the start of treatment;
25. Use of serotonin reuptake inhibitors (duloxetine, milnacipran, nefazodone, venlafaxine, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine);
26. The research participant with any psychiatric and/or psychological illness (including depression), unless judged clinically not significant by the clinical investigator;
27. The research participant has a clinically significant history and/or presence of gastrointestinal disease (example: chronic diarrhea, intestinal inflammatory disease), present gastrointestinal symptoms (example: diarrhea, vomiting), liver or kidney disease, or other known condition that may interfere in the absorption, distribution, metabolism or excretion of the drug. Research participants with episodes of vomiting within 24 hours before the administration of the drug must be evaluated by the clinical investigator regarding the possibility of remaining in the study;
28. The research participant has a clinically significant history or presence of neurological, endocrine or pulmonary disease (inclusive a recent history of asthma), hematological, immunological, cerebral, metabolic or cardiovascular disease, has hypo or hypertension of any etiology which requires pharmacological treatment; has history or clinical case of myocardial infarct, angina and/or cardiac insufficiency;
29. The research participant has donated or lost more than 450mL or more of blood within three months previous to the study (Consolidation Ordinance # 05, dated September 28, 2017);
30. The research participant has any condition preventing her of participating in the study according to the investigator's judgment;
31. The research participant is a vegetarian or has dietary habits that preclude ingestion of diet offered in the study;
32. The research participant has the inability to remain seated (approximately 90° plan) for 1 hour after administration of the drug, or time required at the discretion of the clinical investigator;

33. The research participant presents a positive result for the drug test during pre-hospitalization (Periods 1 or 2);
34. The research participant consumes vitamins and/or dietary supplements in a period of 07 days before the beginning of the study;
35. The research participant consumes food or beverages containing grapefruit within 48 hours prior to admission to the study and throughout the study period.
36. Electrocardiographic findings not recommended for participation in the study, at the discretion of the investigator;
37. Research participant who consume more than 05 cups of coffee or tea per day;
38. Treatment within 3 months prior to the study with any drug with known toxic potential in the large organs;
39. History of serious adverse reactions to any drug;
40. Positive βHCG test for women;
41. Breastfeeding women;
42. Detection or indeterminate / inconclusive result of the SARS-CoV-2 Coronavirus RNA in the RT-qPCR exam performed on the day before the admission of each period;
43. The research participant presents symptoms of COVID-19 infection (even if the result is "undetected" in the RT-PCR exam for COVID-19);
44. Have an average alcohol intake of more than 4 or more doses of alcoholic drinks in a day or 8 or more doses of alcoholic drinks per week for women and 5 or more doses of alcoholic drinks in a day or 15 or more doses of alcoholic drinks per week for men;
45. Have donated or lost more than 1500 mL of blood in the past twelve months;
46. Have done some intense physical exercise in the 24 hours before the hospitalization period;
47. Be unavailable for registration with the CNVB – Brazilian National Register of Volunteers in Bioequivalence Studies.

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF 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 CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.3), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.4.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events [AEs], or diseases)
5. Chew the tablet while administering the medication;
6. Study suspension;
7. The research participant ingests, during the study, some medication that contains the same substance that will be used as an internal standard during the analysis of the plasma samples;
8. Ingest during the study, any drug that contains the same substance that will be used as an internal standard when analyzing plasma samples;
9. The participant does not drink 200mL of water while administering the medication;
10. All cases in which the principal investigator considers the protocol to be flawed and which may make the study result questionable (serious adverse reaction or serious adverse event, Participant's indiscipline, dietary failure);
11. Any other condition at the discretion of the responsible researcher / doctor.
12. Failure to comply with the requirements of the protocol, instructions and restrictions related to the study; for example, uncooperative attitude, inability to return to visits and improbability to complete the study;
13. The research participant presents a positive result for the drug test during pre-hospitalization (Period 1 or 2);

14. The research participant presents during the pre-hospitalization (Period 1 or 2) a positive result for the pregnancy test;
15. Detection or indeterminate / inconclusive result of the SARS-CoV-2 coronavirus RNA in the RT-qPCR exam before the admission of each period - (Periods 1 or 2);
16. The research participant presents symptoms of COVID-19 infection (even if the result "Not detected" in the RT-qPCR test) - (Periods 1 or 2);
17. The subject experienced emesis or diarrhea that occurred at or before two times median Tmax of the respective treatment. In this study subjects with an episode of emesis or diarrhea within 10 hours after administration should be excluded. .

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow up after trial treatment discontinuation, please see section 3.3.4.1 above

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported
3. Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5 Replacement of subjects

Research participants may be replaced in the event of non-compliance with the criteria and inclusion and exclusion from the study provided they have not received any of the study treatment doses. Replacement subjects should receive the same treatment sequence as those who dropped out of a given sequence. Substitutions are only allowed prior to the administration of investigational product. Subjects who discontinue after drug administration are not eligible for replacement.

If the number of dropouts exceeds that determined in this protocol (> 8), it may be considered a complementary group as long as authorized by ANVISA.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product is manufactured by [redacted] doses will be calculated as a free base of the empagliflozin and as metformin hydrochloride salt.

The molecular weight of Empa is molecular weight is 450.91 g/mol. Empagliflozin is administered as free base. The molecular weight of metformin hydrochloride is 165.62 g/mol. Metformin is administered as HCl salt and the metformin dose (850 mg) is related to the hydrochloride salt. .

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of test product are below:

Substance:	empagliflozin/metformin
Pharmaceutical formulation:	FDC tablet
Source:	[redacted]
Unit strength:	12.5 mg empagliflozin, 850 mg metformin HCl
Posology:	1-0-0 (single dose in Treatment T only)
Route of administration:	p.o.

The characteristics of reference products are below:

Substance:	empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	[redacted]
Unit strength:	10 mg empagliflozin
Posology:	1-0-0 (single dose in Treatment R only)
Route of administration:	p.o.

Substance:	metformin (Glifage®)
Pharmaceutical form:	tablet
Source:	[redacted]
Unit Strength:	850 mg metformin HCl
Posology	1-0-0 (single dose in Treatment R)
Route of administration:	p.o.

4.1.2 Selection of doses in the trial

The dose selected for this trial is one of the standard clinical doses (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

The randomisation list will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation list.

After the randomization, substitutions are only allowed prior to the administration of investigational product (day -1). Replacement subjects should receive the same treatment sequence as those who dropped out of a given sequence.

The randomization list that should be used in the study may be found in Appendix 1.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a 2-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	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test) – treatment B	Empa/Met	Tablet	12.5 (Empa)/ 850 (Met HCl) mg	1 tablet one dose only	12.5 (Empa)/ 850 (Met HCl) mg
R (Reference) – treatment A	Empa	Tablet	10 mg Empa	1 tablet one dose only	10 mg Empa
	Met	Tablet	850 mg Met HCl	1 tablet one dose only	850 mg Met HCl

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 200 mL of water to subjects who are in a sitting position in 90 degree angle and will stand for one hour in this position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the 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 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the ANVISA guidance and drugs label orientation. For restrictions with regard to diet, see Section 4.2.2.2.

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

Ingredients	kcal
Strawberry yogurt (300 ml)	243.00
Ham and cheese Croissant (2 units)	489.60
Buttery sweet donut (1 unit)	139.00
Banana (1 unit)	70.00
Butter (half soup spoon)	58.64
Sum	1000.24

Subjects will be kept under close medical surveillance until 12 h after drug administration. During the first 1 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 90 degrees from upright posture).

The treatments will be separated by a wash-out phase of at least 5 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, because the dose of trial medication is known to investigators and subjects.

PK 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

The investigational medicinal products will be provided by [redacted]. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

For details of packing and the description of the label, refer to the ISF.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form.

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 in accordance with the recommended (labelled) storage conditions. If 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 contacted immediately.

The drug supplies will be stored under the responsibility of the [redacted] until 1 year after the most recent product expires.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- 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 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.

The investigator or designee 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 medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator’s possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the trial clinical monitor. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

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, if adverse events require 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 results of medical evaluations are acceptable.

[redacted] is equipped with an emergency room, defibrillators, mobile resuscitation apparat, a 24-hour ICU ambulance and an ICU bed in major [redacted] hospital 4 km distant.

During confinement, in each study period, the participants will be followed by the healthcare professionals during all the period viewing the detection of adverse events, including signs of toxicity.

The participants will be instructed about the potential adverse events, as well as the need to inform them immediately to the investigator or his/her team.

Each participant will be requested to report any adverse event symptoms and it has occurred. The medical team will also be requested to notify the principal investigator if the use of additional medication has been required.

The questions performed to know if the participant has had some adverse event must be limited to general questions, such as: How are you?

Any adverse events occurring after hospitalization must be immediately informed to the team by any mean (telephone, personally, e-mail, etc.).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. 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 will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the standard breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 200 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.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of each study period is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 24 h before until the last sample collecting.

Smoking is not allowed during in-house confinement while admitted to the trial site and the subject cannot smoke 24 hours before insite registration.

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of 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 of trial medication 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. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical and clinical examination

At screening, the medical examination will include demographics, 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 including determination of weight.

In the clinical evaluation, candidates for research participants should not present any obvious signs or symptoms of heart, liver, kidney, lung, neurological, gastrointestinal or haematological diseases. For such verification, the anamnesis will be carried out, as well as the evaluation of the clinical and laboratory exams listed in this protocol.

During the clinical evaluation, the research participants will be classified according to the racial group they belong. To this race classification will be used the auto declaration method, in which the participant will auto declare as part of a racial group according to the following definitions: white, black, mulatto, yellow or Indian. The physician and/or nurse have to register the declared racial group in the clinical evaluation form.

During the clinical evaluation, the physician should re-investigate any suspicious signs and/or symptoms of COVID-19. In case of any suspicions, he should be considered inapt and will be guided by the [redacted] physician to seek external medical care. The research participant will receive medical referral from the [redacted] detailing the signs and symptoms of suspected COVID-19 infection. The orientation must be delivered in writing by the responsible physician, being signed in two copies by the research participant and by the physician. One of the copies must be filed with the medical record of the research participant.

The Research Participant will only be accepted in the study if they are considered healthy as determined by the clinical evaluation and in the laboratory exams done before the beginning of the study and if the satisfy the criteria established in items 3.3 and 3.4.

After proved the state of health, they will be submitted to an interview with the doctor to evaluate their mental health, as well as the emotional state to participate in the investigation.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate will be measured by a blood pressure monitor ([redacted] at the times indicated in the Flow Chart. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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, Section 10.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	RDW, MCV	X	X
	MCH, MCHC	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes Promyelocytes, Blasts	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol. ; Promyelocytes, absol.; Blasts, absol.	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.	X	X
Hormones	Beta HCG (for women subjects)	X	
Serologies	B hepatitis (HBsAg; Anti-HBc IgM)	X	
	C hepatitis	X	
	HIV	X	
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	Albumin	X	X
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	Test name [comment/abbreviation]	A	B
Urinalysis[1] (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine ascorbid acid (qual)	X	X
	Urine density	X	X
	Urine color	X	X
	Urine aspect	X	X
	Urine pH	X	X
Urine sediment[1] (microscopic examination)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts and crystals in sediment, squamous epithelial cells, erythrocytes, leukocytes)	X	X

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 3 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that 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 tests 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.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Benzodiazepine Benzoylecgonine (cocaine) Tetrahydrocannabinol Morphine[1] Methamphetamines/MDMA/XTC Opiates[1]
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Viral analysis	RT-PCR for SARS-COV-2 at Day -1
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

1. *Due to the COVID-19 pandemic and the consequent damage to the supply of inputs in the health area,*

the drug detection test can be performed in two different ways, through the kit for detecting seven substances [Methamphetamine, Opiates, Morphine, Tetrahydrocannabinol (Marijuana/Marijuana), Amphetamine, Benzoylecgonine (Cocaine) and Benzodiazepine] or through the kit for detection of five substances [Methamphetamine, Tetrahydrocannabinol (Marijuana/Marijuana), Amphetamine, Benzoylecgonine (Cocaine) and Benzodiazepine] added to the evaluation of the use of opium derivatives and morphine via specific medical questioning, registered in RQ004 (Clinical evaluation - pre-hospitalization).

To encourage compliance with alcoholic restrictions, a clinical evaluation of alcohol ingestion 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; as per COVID-19 pandemics, alcohol breath test is temporarily suspended. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] partner analytic laboratory, with the exception of drug screening and pregnancy tests. These tests will be performed at the trial site using using Inlab® test (or according availability), respectively, or comparable test systems.

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 ([redacted] at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

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

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

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Assessment of adverse events

5.2.5.1 Definitions of adverse events

5.2.5.1.1 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.

5.2.5.1.2 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 jeopardize 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 hospitalization or development of dependency or abuse

5.2.5.1.3 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 trial medication and must be reported as described in 5.2.6.2, 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.

A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described above.

5.2.5.1.4 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 5.2.6.2.2.

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation:

- an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin > 2 fold ULN measured in the same blood draw sample, and/or
- isolated elevation of ALT and/or AST ≥ 5 fold ULN.

These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory abnormalities need to be followed up according to the "DILI checklist" provided. 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 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. [BI-KMED-PV-CLT-0015].

5.2.5.1.5 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

5.2.5.1.6 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, considering 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

5.2.5.2 Adverse event collection and reporting

5.2.5.2.1 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 time, 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 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.

5.2.5.2.2 AE reporting to the 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. 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.

The contact information is:

[redacted]

Pharmacovigilance and Customer Service [redacted]

[redacted]

Tel.: [redacted]

Cel: [redacted]

Fax.: [redacted]

The toll-free [redacted] and the [redacted] e-mail can also be used for communications.

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 initial information.

5.2.5.2.3 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.

5.2.5.2.4 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 well as non-trial specific information and consent for the pregnant partner.

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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of analyte concentrations in plasma, 8 mL of blood will be drawn from an antecubital or forearm vein into an 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 venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged within 45 minutes after collection while stored in an ice water bath. The samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Four plasma aliquots will be obtained and stored in polypropylene tubes. Each aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples and aliquots in ice water or on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site.

The third and fourth aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first and second aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

Empagliflozin and Metformin concentrations may be measured either by use of the same or different aliquots.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

Plasma samples will be discarded at latest 6 months after the final clinical trial report has been signed.

6. STUDY PROCEEDINGS

6.1 SITE AND FORM OF CONFINEMENT

6.1.1 Site

Clinical Site: [redacted].
Address: [redacted]
Phone: [redacted]

6.1.2 Form of confinement of the search participant

The healthy research participants will remain confined in the premises of cinical unit of [redacted], under the responsibility of the medical team and under the care of the nursing team.

Due to the COVID-19 pandemic, research participants will have to attend staggered without agglomeration. Therefore, the day before the administration of the drug, research participants must attend the [redacted] on a staggered basis from 5 pm.

On the day of drug administration, the nursing professional will start the routine procedures predicted for the participant during confinement including measurement of systolic blood pressure, diastolic blood pressure, heart rate and temperature. The pharmacist in charge will release the medication following the list of randomization contained in the Annex 2, also providing to the nursing professional and the team involved in the collection of blood samples, the instructions related to the protocol. Therefore, the phlebotomists will install the heparinized intravenous catheters to perform the collections of sample zero (pre-dose) and those predicted throughout the day. The staff in charge for the collection will remain at the confinement site throughout hospitalization. There will be frequent visits of the nursing team to the bed where each participant is kept during the entire hospitalization period.

6.2 BIOSAFETY PROCEDURES DUE TO COVID-19

The World Health Organization (WHO) declared, on January 30, 2020, that the outbreak of the disease caused by the new coronavirus (COVID-19) constitutes a Public Health Emergency of International Importance - the Organization's highest alert level, as provided for in the International Health Regulations. On March 11, 2020, COVID-19 was characterized by WHO as a pandemic. For this reason, hospitalizations of research participants must follow strict biosafety criteria. According to POP "COVID-19-001 - Measures for the prevention and

control of environments and people in the clinical unit during the COVID-19 pandemic", the admission of research participants should be carried out without agglomeration. Therefore, the entrance of the participants will be carried out in a staggered manner and will take place in a reception separate from the main building.

Also at the entrance before entering the unit (that is, at the unit door), a questionnaire on symptoms of COVID-19 infection will be carried out.

The following procedures must be followed:

1. At the entrance of the [redacted], the research participants will be asked regarding specific symptoms for COVID-19 infection (pre-screening):

a. Do you have or have you had a fever in the last 14 days?

( )YES ( ) NO

b. Do you have or have you had any signs and/or symptoms of flu in the last 14 days?

( )YES ( ) NO

c. Do you have or have you had difficulty breathing in the last 14 days?

( )YES ( ) NO

d. Do you have or have you had a cough in the last 14 days?

( )YES ( ) NO

e. Do you have or have you had a sore throat in the last 14 days?

( )YES ( ) NO

f. Did you have contact with any person suspected or confirmed of infection with

new coronavirus?

( )YES ( ) NO

g. Do you have changes in taste and/or smell?

( )YES ( ) NO

h. Have you had vomiting or diarrhoea in the last 14 days?

( )YES ( ) NO

i. Temperature: ____°C

2. The temperature of the research participants must be checked by a non-contact infrared thermometer. The temperature must be below or equal to 37 ° C;

3. If the research participant answers YES to any of the questions or has a temperature above 37ºC he/she cannot enter the [redacted] facilities and must be instructed by the [redacted] medical team to seek medical assistance outside the [redacted]. The guidance must be writing by the [redacted] responsible

physician, and must be signed in two copies by the research participant and the physician. One of the copies must be filed with the research participant's medical record.

4. All research participants must disinfect their hands with 70% alcohol before entering the [redacted] facilities. Every 2 hours the nursing team must request that the research participants wash their hands with soap and water and then disinfect with 70% alcohol. During sleep times, research participants may remain with a longer interval between sanitizations.

5. Disposable masks must be made available and they must be changed every 2 hours. Research participants must wear the masks for the entire period they are on the [redacted] premises;

6. Participants must hand over their personal belongings to the nursing staff and after disinfection with 70% alcohol or another disinfectant product, they will be placed in a sealed plastic bag and stored in a specific place and will be returned at the time of discharge from hospital.

7. Research participants must go to the nursing area and immediately take a shower (including hair) and change clothes (clothing provided by [redacted]);

8. The clothes of each participant will be placed in a sealed plastic bag and allocated with their personal objects that will be returned at the time of discharge from hospital.

9. The entire environment should be kept ventilated with the opening of the windows, if possible. In the event of natural phenomena, such as rain, the windows may be closed;

10. All meals will be carried out on the bed in previously disinfected and disposable containers (including cutlery and glasses).

6.3 UNITARIZATION

The study drugs will be unified according to POP CLIN 016 (Preparation and Administration of Medicines).
After receiving the drugs in study, the date on which the unitarization will take place will be defined, this may happen before the day of medication administration (blistered drugs) or on the day of medication administration (un-blistered drugs).

The dosage will be performed according Section 4.1.4.

6.4 FASTING AND FEEDING TIMES

The night before drug administration the research participant will go to the Clinical Unit of [redacted] and must have their last meal until 08.30 p.m., and they will remain in fast of at least 10 hours, subjects will receive a standardized high fat breakfast at approximately 06:30AM. Breakfast must be consumed within 25-30 minutes.

In order to maintain the standardization of the treatment groups, the diet (food and liquids) to be provided will follow the same standard, in all periods of confinement, for all research participants and must be free of fried and fat foods. To plan the menu, the nutrition professional

will use as caloric reference the established in Ordinance nº 193 dated 12/5/2006, article 5, paragraph 3 of the Worker Feeding Program ("PAT"). This way the meals provided will follow the following caloric quantities:

- Breakfast (before dose): must contain approximately 1000 calories;
- Main meals (lunch and dinner): must contain from 684 to 930 calories;
- Minor meals (snack): must contain from 200 to 400 calories;
- Minor meals (breakfast in extra collections): must contain from 170 to 200 calories.

The person in charge for the clinical step will provide the instructions to the Nutrition Service about the standardized diet that will be provided to the healthy research participant, also highlighting the prohibition of the intake of beverages or foods containing caffeine or xanthines (black and mate tea, coffee, cocoa milk, cola sodas, guaraná, foods containing chocolate and others). The composition of the meals is on Appendix 3.

Meal times

- Dinner – minimum of 10 hours of fasting;
- Breakfast – 30 minutes before the administration of the drug;
- Lunch – 4 hours after the administration of the drug;
- Snack - 8 hours after the administration of the drug;
- Dinner – 10 hours after the administration of the drug.

Liquids

- Allowed at ease – until 7 hours before the administration of the drug and after two hours of the administration of the drug;
- During the breakfast – 300 mL of yogurt;
- Prohibited ingestion of liquids – from 7 hours before the administration of the drug until two hours after the administration of the drug, except 300 mL of yogurt during the breakfast and 200 mL of water during the drug administration.

6.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

6.5.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

6.5.2 Methods of sample collection

6.5.2.1 Blood sampling for pharmacokinetic analysis

For quantification of analyte concentrations in plasma, 8 mL of blood will be drawn from an antecubital or forearm vein into an tube K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart.

The first 22 collections (pre-dose + 21 pharmacokinetic samples) will be performed through a heparinized intravenous catheter introduced in superficial vein of the research participant. The other collections will be carried out by means of direct venipuncture.

If there is any difficulty in intravenous collection due to catheter block, blood will be collected by means of direct puncture or a new intravenous catheter will be inserted into the research participant.

After each blood collection performed through the intravenous catheter, it will be washed with 0.5mL of sodium heparin solution to prevent catheter blockage. Therefore, before each collection performed through the intravenous catheter, 0.5mL of blood will be drawn and the same will be discarded.

The pre-dose collection (collection 1) will be carried out before the medication is administered. In total, 1 sample of 15mL of blood will be collected to perform the pre-study exams), 50 blood samples of 8 mL for PK, 44 blood samples of 0.5mL for washing the catheter and 1 blood sample of 15 mL to perform the post-study exams. The total blood volume is described in Table 6.5.2.1: 1.

Table 6.5.2.1: 1– Amount of blood to be collected.

Sample type	*Blood volume* (mL)	*Number of collections*			*Total volume* (mL)
		Pre-study exams	*During the study*	*Post-study exams*	
Laboratory tests	15 mL	1	NA	1	30 mL
Pharmacokinetic samples	8 mL	NA	50	NA	400 mL
*Discarded blood**	0,5 mL	NA	44	NA	22 mL
Total					452 mL

**Before each collection, (up to the 12-hour collection) approximately 0.5 mL of blood will be discarded in order to remove the heparin solution used for washing and maintaining the intravenous catheter.*

The blood pressure, temperature and pulse of the research participants will be measured in the pre-hospital clinical evaluation and in the clinical evaluation of hospital discharge. During the confinement period, vital signs will be measured at pre-established times according to Table 6.5.2.1:2. When the time scheduled for the measurement of vital signs coincides with the collection time, blood collection should be prioritized, with an interval of ±30 minutes for the measurement of vital signs. The measurements that happen to exceed this interval will be considered in the clinical report as a protocol deviation. The vital signs measured during the confinement period will be described in the clinical study report. Vital signs measured during hospitalization that are outside the reference values defined in standard operating procedures will be assessed by the physician as to their clinical significance. Only adverse events considered clinically significant by the physician will be considered adverse events.

It is important to note that research participants will be released from hospitalization after 12-hour collection and will return for collections between 24:00, 48:00 and 72:00 hours. For extra collections, an interval of ± 1 hour from the actual collection time, as described in the clinical protocol, will be accepted. Extra collections performed outside the ± 1 hour interval of the actual time will be considered in the clinical report as protocol deviations. For collections made during the confinement period, all delays and advances will be considered as a protocol deviation. The actual collection times will be described in the clinical report.

Table 6.5.2.1:2. – *Activities performed by the research participant during the confinement in periods 1 and 2.*

Nº of collection	*Time (h)*	*Volume collected*	*Safety evaluation*
Pre-dose C-01	*Before the administration of the drug (5 minutes before)*	8 mL	*BP, pulse, temperature*
C-02	00:15	8 mL	
C-03	00:30	8 mL	
C-04	00:45	8 mL	
C-05	01:00	8 mL	*BP, pulse, temperature*
C-06	01:15	8 mL	
C-07	01:30	8 mL	
C-08	01:45	8 mL	
C-09	02:00	8 mL	*BP, pulse, temperature*
C-10	02:20	8 mL	
C-11	02:40	8 mL	
C-12	03:00	8 mL	*BP, pulse, temperature*
C-13	03:30	8 mL	
C-14	04:00	8 mL	*BP, pulse, temperature*
C-15	04:30	8 mL	
C-16	05:00	8 mL	
C-17	05:30	8 mL	
C-18	06:00	8 mL	*BP, pulse, temperature*
C-19	07:00	8 mL	
C-20	08:00	8 mL	
C-21	10:00	8 mL	
C-22	12:00	8 mL	*BP, pulse, temperature*
C-23	24:00	8 mL	*BP, pulse, temperature**
C-24	48:00	8 mL	*BP, pulse, temperature**
C-25	72:00	8 mL	*BP, pulse, temperature**

** If necessary.*

6.5.3 Procedures for the handling and storage of biological samples

6.5.3.1 Internal transportation of biological samples

A professional from the samples processing lab will collect the tubes containing the blood sample of each one of the research participant, immediately after the collections. These samples will be placed in appropriate racks, inside a thermal box, containing solid ice and with temperature control (2 - 8°C).
The internal transportation of biological samples will be performed through ramps, whereas the search participant flow, clothes, food, and drugs distribution times must not coincide with the internal transportation of the biological samples.

6.5.3.2 Identification of the samples

All the sample storage tubes must be labeled with the following information:

- Research participant number (01);
- Collection number (C-02);
- Collection time (00:00; 00:15, etc.);
- Period of treatment (1 or 2);
- In cases of retain samples: (R);
- Actives ingredients codes (EMP/MET);
- Biological matrix (plasma)
- Number of protocol.

6.5.3.3 Handling, storage and transportation

The EDTA-anticoagulated blood samples will be centrifuged within 45 minutes after collection while stored in an ice water bath. The samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Four plasma aliquots will be obtained and stored in polypropylene tubes. Each aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples and aliquots in ice water or on ice.

After frozen, the samples will be organized by study period and stored in plastic bags labelled with the protocol number, active's principle code, number of research participants and study periods (Period 1 or 2) and in the case of samples retains the description "R".

The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site.

After the end of the clinical step and freezing, the samples for analysis (first, second and third aliquot) must be transferred from [redacted] clinical site to [redacted] in [redacted]:

Address: [redacted]
ZIP CODE: [redacted]
PHONE/FAX: [redacted]
E-mail: [redacted]

At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

The amount of dry ice to be used will be enough to keep the samples frozen for at least 72 hours. The samples will be shipped to the analytical site, according to the [redacted] SOP. The packaging of the samples will meet the Biosafety rules and International Air Transport Association (IATA) recommendations related to the documentation and package.

The samples of each subject will be packaged in a heat-sealed plastic bag. These individual sample bags will be grouped at every four and placed in a larger, duly sealed plastic bag. Then, they will be placed into a Styrofoam box, organized as follows: a first layer of dry ice followed by the packaged samples, and a second layer of dry ice covering all the samples. Above this second ice layer a layer of newsprint will be placed and the box will be closed. A cardboard box will also be used as outer package. The shipment will be followed by a letter containing the information stated to the Port Health Authorities attached to the outer wall of the cardboard package. This letter will contain a statement signed by the responsible of the clinical phase in charge explaining the purpose of the samples shipment, the list of subjects' initials, as approved by the Ethics Committee, and the study drug. A second copy will be send to the destination lab, and another copy will be kept in the [redacted] Clinical Site. The previous contact will be established with the transportation company and the recipient, in order to guarantee that the samples are immediately opened and their physical integrity and checked. The confirmation of the shipment will be made by email. The recipient will be immediately informed of all sample delivery data. The delivery will be made directly to the Analytical Laboratory, and the recipient will e-mail a receipt confirmation after confirming its integrity. A copy of the process will be maintained in the [redacted] for ANVISA consultation.

The samples will be transported followed by a data logger for temperature control, Delivery Check List and Biological Samples Checking listing the box content, the number of samples and other information related to the study.

The person in charge for the analytical step must receive and check the samples immediately after receiving them, writing down the temperature at the moment of receipt and signing the Delivery Check List and Biological Samples Checking.

The Delivery Check List and Biological Samples Checking must be completed at the Analytical site. Any complication, when applicable, must be informed by the Analytical Site technician to the [redacted] clinical site.

Empagliflozin and Metformin concentrations may be measured either by use of the same or different aliquots.

The retention biological samples (fourth aliquot) will be stored in freezer at approximately -20°C according to Resolution n° 441[8] from May 12, 2011 from Health National Council under [redacted] responsibility and management of the Principal Researcher and will be discarded after Sponsor authorization.

6.5.4 Analytical determinations

6.5.4.1 Analytical determination of analyte plasma concentration

Concentrations of empagliflozin and metformin in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay at [redacted], [redacted]. 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.

6.6 ASSESSMENT OF BIOMARKER(S)

Not applicable.

6.7 BIOBANKING

Biological samples will be stored in accordance with Resolution No. 441 of May 12, 2011 of the National Health Council, which determines guidelines and conditions to be considered for the storage of biological samples, and will be used to verify through a single-dose study, if the test treatment (in a combination of 12.5mg of empagliflozin + 850mg of metformin) is bioequivalent to Jardiance 10mg references (empagliflozin - Reference 1) and to Glifage 850mg (metformin - Reference 2) managed together. Any new research to be done with the material will be submitted to approval of the CEP/CONEP system (National Research Ethics Commission) and the research participant must give their consent to the use of these samples, signing a new Informed Consent Form.

6.8 OTHER ASSESSMENTS

Not applicable.

6.9 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.

7. INVESTIGATIONAL PLAN

7.1 VISIT SCHEDULE

Exact times of measurements will be documented. The acceptable time windows for screening and the end of trial examination are provided 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 2 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min.

If scheduled in the Flow Chart at the same time as a meal, vital signs, and 12-lead ECG recordings, blood sampling, have to be done first..

For planned blood 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 the determination of pharmacokinetic parameters. If a subject misses an appointment, it will be rescheduled if possible.

DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

7.2

Screening

After having been informed about the trial, all subjects will provide 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.

7.2.1 Treatment periods

Each subject is expected to participate in 2 treatment periods (2 Days before treatment -2,-1 and Days 1, 2, 3, and 4 in each period). At least 7 days will separate drug administrations in the first and second treatment periods.

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 12 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, subjects will be treated in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.3 of this protocol and in the Flow Chart. For details on times of 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.

7.2.2 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up 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 EoTrial Visit.

All abnormal values (including laboratory parameters) that are assessed as 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 a subject's EoTrial Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

[redacted]

8. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to establish the bioequivalence of 12,5 mg of Empa/ 850 mg of Met in a FDC tablet (Treatment B) compared with 10 mg of Empa tablet and 850 mg tablet of Met (treatment A) following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

These pharmacokinetic parameters will be assessed by descriptive statistics.

8.2 NULL AND ALTERNATIVE HYPOTHESES

Although there are multiple endpoints, an alpha adjustment is not needed because it is required that all primary endpoints and the AUC $0\text{-}\infty$ secondary 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% confidence intervals (CIs) for the ratio of the geometric means (B/A) for the primary and secondary only $AUC_{0\text{-}\infty}$ endpoint using an acceptance range of 80.00 - to 125.00% for both Empa and Met. This method is equivalent to the two-sided t-test procedure, each at the 5% significance level.

The following hypotheses are 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. Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$

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 scale.

The rejection of the null hypothesis at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range $(-\delta, \delta)$.

8.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated Set (TS): The treated set includes all participants in the research that were randomized and treated with at least one dose of study medication. The treated set will be used for analysis of security.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects who provide all PK endpoints for all treatment periods that were defined as primary (Cmax and AUC0-tz) and was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Model-based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification file, iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

Pharmacokinetics

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 deviation 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 CTR.

Relevant protocol deviations may be

- Incorrect trial medication taken, i.e. 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 experienced emesis that occurred at or before two times median t_{max} of the respective analytes (Median t_{max} is to be determined excluding the subjects experiencing emesis).
- Missing samples/concentration data at important phases of PK disposition curve

The plasma concentration data and parameters of a flagged research participant for exclusion will be reported with their individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

Only concentration values within the validated concentration range 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).

8.3.1 Primary and key secondary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints and the key secondary endpoint AUC0-inf will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. 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 measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^o sequence effect, i = 1, 2,

s_{im} = the effect associated with the m^0 subject in the i^a sequence, m = 1, 2, ..., n_i

π_j = the j^0 period effect, j = 1, 2,

τ_k = the k^0 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.

where $s_{im} \sim N(0, \sigma_B^2)$ i. i. d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

This analysis will be restricted to subjects that have PK evaluable parameter values for both treatment periods.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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). Additionally, their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Bioequivalence is considered established if the 90% confidence intervals of the geometric means for the primary (and secondary $AUC_{0-\infty}$) endpoints are contained in the pre-defined acceptance range, see Section 7.2.

[redacted]

[redacted]

[redacted]

8.4 INTERIM ANALYSES

No interim analysis is planned.

8.5 HANDLING OF MISSING DATA

8.5.1 Safety

It is not planned to impute missing values for safety parameters.

8.5.2 Pharmacokinetics

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

8.6 RANDOMISATION

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

The randomization list will be generated using a software developed by [redacted]) called vWEB BIO, that will randomize the subjects for each one of the sequences automatically, and at the same time, it will stratify the genders (if the study uses two genders) of the subjects in a balanced way (treatment A – treatment B [AB] or treatment B – treatment A [BA]). The program developed also estimates (conforming to item 1.k from Resolution RE Nº 1170, from April 19th 2006) that the genders (if the study uses two genders) are equally distributed/stratified within each sequence in a random way so that stratification bias/confounding factors do not compromise the results.

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

8.7 DETERMINATION OF SAMPLE SIZE

The sample size for this trial was determined using assumptions on the intra-individual variability of the primary endpoints based on previous studies -performed at [redacted] For both actives, empagliflozin and metformin,Cmax the geometric coefficient of variation (gCV) was estimated to be between 9% and 23%, while for AUC the gCV was between 9% and 23%.

Due to the high correlation between the primary endpoints, only C_{max} will be considered for power calculations. Using a sample size of 24 subjects (12 per sequence group), the power to reject both one-sided null hypotheses for one parameter each at the 5% level of significance in favour of bioequivalence is displayed in Table 7.7: 1, under various assumptions for the T/R ratio. To account for the uncertainty of the assumed gCV, a range of gCVs around 20% is also presented.

Table 7.7: 2 Power for concluding bioequivalence (acceptance range 80-125%) based on a geometric coefficient of variation around 20% and for different expected ratios of geometric means (test/reference) in a 2x2 crossover trial (N=24)

	Ratio [%]*				
gCV [%]	***90***	***92.5***	***95***	***97.5***	***100***
18	*71.5*	*86.1*	*94.3*	*98.0*	*98.9*
20	*63.7*	*79.2*	*89.6*	*95.1*	*96.7*
23	*53.8*	*68.9*	*80.7*	*87.8*	*90.2*

**Ratio of geometric means (test/reference) for a PK endpoint is defined by $exp(\mu_T)/exp(\mu_R)$.*

From the above table, a sample size of 24 will yield approximately 90% power to conclude bioequivalence for an assumed gCVof 20% if the ratio is not more than 5% different from the ratio of 100% which reflects no difference in exposure. In addition, this sample size still provides approximately 80% power in case the ratio is not more than 7.5% different from 100% or the gCV is 23%, and about 70% in case the ratio is 7.5% different from 100% and the gCV is 23%.

Accounting for up to 24 non PK evaluable subjects, a total of N = 24 + 08 subjects subjects are planned to be entered into the trial.

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

9. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to archiving of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

9.1 TRIAL APPROVAL, SUBJECT INFORMATION, 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 retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form.

If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

9.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

9.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section 4.1.5 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

9.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

9.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

9.3.3 Storage period of records

Trial site:
The trial site(s) must retain the source and essential documents (including ISF) according to contract and the local requirements valid at the time of the end of the trial.

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

9.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

9.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site 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.

9.5.1 Collection, storage and future use of biological samples and corresponding data

The biological samples will be stored for non-commercial use in accordance with Resolution No. 441 of May 12, 2011 of the National Health Council, which provides guidelines and conditions to be considered for storing biological samples, and will be used to To establish whether a fixed-dose tablet of 12.5 mg empagliflozin+850 mg metformin (T1) is bioequivalent to the free dose combination of 10 mg Jardiance (empagliflozin – Reference 1) and Glifage 850 mg (metformin – Reference 2) (R).
Every new research will be submitted for approval of the CEP / CONEP system (National Committee for Research Ethics) and you must consent the use of these samples, by signing a new free and informed consent form.
Biological samples are stored in storage tubes identified by its research participant number with the aim of maintaining confidentiality and secrecy.

9.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') 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.

Early termination of the trial is defined as the premature termination of the trial for any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

9.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required trial 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, and investigators of participating trial sites

The trial will be conducted at the [redacted], under the supervision of the principal investigator.

The trial medication will be provided by [redacted]

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted] to inform)

The analyses of empagliflozin and metformin concentrations in plasma will be performed at [redacted].

The trial is sponsored by [redacted].

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

Data management and statistical evaluation will be done by [redacted] and BI 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.

10. REFERENCES

10.1 PUBLISHED REFERENCES

R03-2269 Guidance for industry: food-effect bioavailability and fed bioequivalence studies. In: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2002:1-9.

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R15-1331 Elashoff JD. nQuery Advisor version 7.0 user's guide. http://www.statsols.com/wp-content/uploads/2013/10/nQ70_version2_manual.pdf (access date: 20 March 2015) ; Los Angeles: Statistical Solutions; 2007.

R94-1445 Diletti E, Hauschke D, Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. Int J Clin Pharmacol Ther Toxicol 1992; 30 (suppl 1): S51-S58.

R94-1529 Chow SC, Liu JP, editors. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker Inc., 1992.

10.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

c01678844-16 Empagliflozin Investigator’s Brochure

BI-KMED-PV-CLT-0015 POTENTIAL DRUG-INDUCED LIVER INJURY (DILI) CHECKLIST APPENDICES

Anexo1_Randomizacao.pdf

Randomization list (in Portuguese)

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		*<Give the date of the final revised CTP, i.e. the date of the global amendment, in the format dd Mmm yyyy>*
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
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		
Description of change		
Rationale for change		

11.2 GLOBAL AMENDMENT 2

Date of amendment		*<Give the date of the final revised CTP, i.e. the date of the global amendment, in the format dd Mmm yyyy>*
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		

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		
Description of change		
Rationale for change		