Clinical Trial Protocol

Doc. No.: c01945509-06

BI Trial No.:	1245.29
BI Investigational Product:	Empagliflozin
Title:	A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus
Clinical Phase:	IIIb
Trial Clinical Monitor:	[redacted] Tel: [redacted] Fax: [redacted]
Co-ordinating Investigator:	[redacted] Phone [redacted] Fax: [redacted]
Status:	*Final Revised Protocol* (based on global amendment 4)
Version and Date:	**Version: 5.0** **Date: 18 July 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: NA			
Name of active ingredient: Empagliflozin			
Protocol date: 15Apr2014	**Trial number:** 1245.29		**Revision date:** **18 July 2016**
Title of trial:	A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus		
Co-ordinating Investigator:	[redacted]		
Trial sites	Multi-centre trial		
Clinical phase:	IIIb		
Objectives:	The objective of the current study is to investigate the efficacy and safety of empagliflozin (10 mg or 25 mg) compared to placebo on glucose control over 24 weeks in hypertensive black/African American patients with Type 2 Diabetes Mellitus (T2DM). A second objective of the study is to investigate the efficacy and safety of empagliflozin (10 mg or 25 mg) compared to placebo on BP over 12 weeks and on weight at 24 weeks in the same patient population. The study is designed to show superiority of empagliflozin over placebo.		
Methodology:	Randomised, double-blind, placebo-controlled, parallel group comparison		
No. of patients:			
total entered:	154 randomised hypertensive black/African American patients with type 2 diabetes mellitus (T2DM)		
each treatment:	77 patients on empagliflozin 10 mg/25 mg 77 patients on placebo		
Diagnosis :	T2DM and hypertension		

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Main criteria for inclusion:	1. Diagnosis of T2DM prior to informed consent. *Note: Documentation should be available before randomisation at latest. Confirmation can be in the form of formal documents or by verbal communication of the date of diagnosis from a patient or from their primary care physician (if records are not available). It is up to the medical judgment of the Investigator to deem if the information is accurate.* 2. Male and female black/African American patients on diet and exercise regimen who are EITHER: drug-naïve (defined as absence of any oral antidiabetic therapy , glucagon like peptide-1 (GLP-1) analog or insulin for 12 weeks, 16 weeks for pioglitazone prior to randomisation), OR pre-treated with stable dose of metformin only, or sulfonylurea (SU) only, or DPP-4 inhibitor only, or metformin plus sulfonylurea, or metformin plus DPP-4 inhibitor. Treatment has to be unchanged for a minimum of 12 weeks prior to randomisation Dose for metformin: maximum tolerated dose The maximum daily dose of SU or DPP-4 inhibitor should not exceed that stated in the local label . 3. HbA1c of ≥ 7.0% (53 mmol/mol) and ≤ 11.0% (97 mmol/mol) at Visit 1 (screening) 4. Mean seated SBP 140-180 mmHg at Visit 1 (screening) 5. Successful completion of baseline ambulatory blood pressure (ABPM) testing with a mean systolic blood pressure (SBP) 135-175 mmHg prior to randomisation 6. Treatment with stable doses of at least one but no more than 4 antihypertensive medication ≥ 4 weeks prior to randomisation. 7. Age ≥18 years at Visit 1 (screening) 8. Signed and dated written informed consent by date of Visit 1 in accordance with Good Clinical Practice (GCP) and local legislation
Test product:	Empagliflozin
dose:	10 mg / 25 mg, once daily
mode of admin.:	Tablets per os
Comparator product:	Placebo matching empagliflozin
dose:	NA, once daily
mode of admin.:	Tablets per p.o.

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Name of finished product: NA			
Name of active ingredient: Empagliflozin			
Protocol date: 15Apr2014	**Trial number:** 1245.29		**Revision date:** **18 July 2016**
Duration of treatment:	• 2 weeks placebo run-in • 24 weeks double-blind treatment with either empagliflozin 10 mg or empagliflozin 25 mg after dose escalation or placebo followed by two weeks follow up post study drug termination		

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Name of finished product: NA			
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Protocol date: 15Apr2014	**Trial number:** 1245.29		**Revision date:** **18 July 2016**
Criteria for efficacy: ***pharmacokinetics:*** ***pharmacodynamics:***	The primary endpoint in this study is change from baseline in HbA1c at 24 weeks of treatment. Key secondary endpoints are change from baseline in mean 24-hour ambulatory SBP at 12 weeks of treatment, change from baseline in mean trough ambulatory SBP at 12 weeks, change from baseline in body weight in kilograms (kg) at 24 weeks of treatment, and change from baseline in trough seated SBP at 12 weeks of treatment. Other secondary endpoints are described in Section 5.1.1.		
Criteria for safety:	All adverse events including hypoglycaemic events and adverse events of special interest (AESI) and clinical laboratory values		

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Name of finished product: NA			
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Statistical methods:	For change from baseline in HbA1c up to 24 weeks of treatment a restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis will be used to obtain adjusted means for the treatment effects on the full analysis set (FAS). This model will include treatment, visit, and the stratification factors renal function at baseline, and pretreatment with Metformin at screening as discrete fixed effects, baseline HbA1c as a continuous fixed effect, and interaction between visit and treatment, and an interaction between visit and baseline HbA1c. The primary treatment comparisons will be the contrast between treatments at the endpoint visit at 24 weeks of treatment. For the change from baseline in trough seated SBP up to 12 weeks of treatment and the change from baseline in body weight in kg at 24 weeks as well a restricted maximum likelihood estimation based on mixed-effect model**s** for repeated measures analysis will be used to obtain adjusted means for the treatment effects on the FAS. These models will include the same discrete fixed effects as the model for the primary endpoint and baseline HbA1c as continuous fixed effect, as well as interaction between visit and treatment, and interaction between visit and baseline measurement of the key secondary endpoint, as well as the corresponding baseline measurements of the key secondary endpoint as continuous effect . The primary treatment comparisons will be the contrast between treatments at the 12 week visit for seated SBP and 24 week visit for body weight. The key secondary endpoint change from baseline in 24-hour ambulatory SBP and change from mean trough ambulatory SBP at 12 weeks will be analyzed by using an analysis of covariance (ANCOVA) approach in the FAS with last observation carried forward (LOCF) for missing data. The model will include randomised treatment, renal function at baseline, pretreatment with Metformin at screening as discrete fixed effects and the baseline of the key secondary endpoint and HbA1c at baseline as continuous fixed effects. The overall type I error across the hypotheses tests in the confirmatory analysis will be maintained at a level of $\alpha \leq 0.05$ using a hierarchical testing sequence. The sample size of 154 patients per group was derived (assuming n=64 per groups plus a 20% drop-out rate) based on the requirement that the comparisons of empagliflozin versus placebo with respect to the HbA1c, BP and body weight should have a power of at least 80% at the two-sided α level of 5%. Explorative statistical models and descriptive statistics will be used for the other secondary endpoints and safety parameters.		

FLOW CHART

Trial Period	**Screening**	**Placebo run-in period**		**Randomised period**							**PTD** **Premature Treatment Discontinuation only** [S]	**Follow-up period**
Visit	**1** [A]	**2.1**	**2.2** [B]	**3**	**4**	**5.1** [B]	**5.2**	**6** [O]	**7.1** [B]	**7.2**		**8**
Study week	**-3**	**-2**	**-1**		**4**	**11**	**12**	**18**	**23**	**24**		**26**
Study day	**-21**	**-14**	**-7**	**1**	**29**	**78**	**85**	**127**	**162**	**169**		**183**
Visit window (in days)	**+/-7**	**-7**	+7	na	-7/+3	+7	-7/+7	+/-7	+14	**+7**		**+7**
Informed Consent	X											
Medical history / concomitant diagnoses	X											
Demographics	X[H]	X										
In-/Exclusion criteria	X	X		X								
Physical examination		X								X	X	
Vital signs	X	X		X	X		X			X	X	X
[redacted]				X			X			X	X	X
Height	X											
Weight	X			X	X		X			X	X	X
[redacted]				X			X			X	X	
Diet and exercise counselling [C]		X[C]		X[C]	X[C]		X[C]			X[C]	X[C]	
Food intake booklet completion		X[R]		X	X		X			X	X	
12-lead ECG[D]	X											
Pregnancy test [E]	X			X	X		X			X	X	
Safety lab tests [F] (urine and blood)	X[G]	X		X	X		X			X	X	X
FPG sample		X		X	X		X			X	X	X
HbA1c	X			X	X		X			X	X	
Lipid lab panel				X			X			X	X	X
[redacted]				X			X			X	X	
ABPM device attachment and removal [I]			X			X			X			

Trial Period	**Scree-ning**	**Placebo run-in period**		**Randomised period**							**PTD** **Premature Treatment Discontinuation only** [S]	**Follow-up period**
Visit	**1** [A]	**2.1**	**2.2** [B]	**3**	**4**	**5.1** [B]	**5.2**	**6** [O]	**7.1** [B]	**7.2**		**8**
Study week	**-3**	**-2**	**-1**		**4**	**11**	**12**	**18**	**23**	**24**		**26**
[redacted]							[redacted]			[redacted]	[redacted]	
[redacted]				X								
Home Blood Glucose Monitoring [L]		X		X	X		X			X	X	X
Adverse events		X		X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X		X	X		X	X		X	X	X
Dispense placebo run-in medication [M]		X										
Randomization (via an IRT system) [Q]				X								
Dispense study medication [M]				X	X		X					
Dose escalation [N]					X							
Medication compliance check				X	X		X			X	X	
Study medication termination										X	X	
Trial completion												X

A The screening procedures can be done on different days within the time window.

B Patients will undergo 24-hour ABPM testing. If patients fail the test, this procedure should be repeated. Each patient will be allowed a maximum of two attempts within the visit window to obtained one successful measurement starting at each of the ABPM time points (Visit 2.2, 5.1 and 7.1). If the ABPM testing is successful, procedures for the subsequent visit can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken.

Visit 2.2 ABPM and any repeat measurements if required should be performed during the run-in period within 7 days prior to Visit 3 (Day 1). Day 1 is the day of randomisation, not the day ABPM is applied.
Visit 5.1 ABPM and any repeat measurements if required should be performed within 7 days prior to Visit 5.2 (Day 85).
Visit 7.1 ABPM and any repeat measurements if required should be performed within 7 days prior to Visit 7.2 (Day 169). dx

C Diligent diet and exercise counselling by a diet specialist or trained staff member at visit 2.1. Counselling is based on local diet recommendations and should include a food log (recording of food intake for 3 consecutive days in the week before the actual visit). At all visits, patients should be reminded about the importance to follow the recommended diet and exercise plan.

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

E For female patients (local urine pregnancy test in women of child-bearing potential).

F Fasting blood and urine samples to be collected~~,~~ for central labs at each visit indicated (refer to Lab manual). A urine dipstick to be done locally~~,~~; upon positive result at site for leukocyte esterase (WBC) or nitrites a midstream urine sample should be taken and sent for urine culture analysis (central lab).

G For the screening Visit 1, laboratory tests only include liver transaminases, alkaline phosphatase, serum creatinine, TSH and urinalysis. Patients do not have to be fasting.

H Only screening relevant demographics (gender, date of birth).

I The ABPM **device** is attached on the mornings of Visit 2.2, 5.1 and 7.1 before medication intake for measuring ABPM. This also applies to visits for repeat ABPM testing if required. Patients must have a successful completion of V2.2 ABPM prior to randomisation. Do NOT contact IRT system or dispense randomised study drug until after a successful 24-hour ABPM is complete. If after two attempts a successful reading is not achieved at either Visit 5.1 or Visit 7.1, patients should continue with the next scheduled visit (Visit 5.2/Day 85 or Visit 7.2/Day 169 respectively).
In case the ABPM must be repeated, the patient should continue taking trial medication. If possible, ABPM should take place within the visit window in the Flowchart. If two doses of study medication are taken when the monitor is attached, then the ABPM should be repeated.

At the conclusion of each attempt, patient should be allowed to rest for at least 15 minutes after removal of the ABPM and a trough seated blood pressure measurement should be taken prior to intake of study medication.

[redacted]

L Instruction and handover of device at Visit 2.1. Daily measurements during Run-in and Follow-up should be performed. During the treatment period, a weekly test is recommended. During the whole trial participation, additional measurements should be done in case of hypo- or hyperglycemia related symptoms.

M At all visits the respective kit number has to be allocated to the patient via an interactive response technologies (IRT) system. All visit activities must be completed before contacting IRT.

N At Visit 4 all patients will be dose escalated through an IRT system.

O Visit 6 will be conducted as a phone visit.

[redacted]

Q All visit activities must be completed and continued eligibility for randomisation or dosing confirmed prior to using IRT.

R At Visit 2.1 the food log is dispensed only and to be completed for three consecutive days prior to Visit 3.

S A Premature Treatment Discontinuation (PTD) Visit, as well as a Follow-up Visit 8, should be performed for any patient who discontinues study medication prematurely and are willing to be followed up; the PTD Visit should be completed as soon as possible after study medication is stopped. PK sampling can be omitted if the PTD Visit is not performed within 24 hours of the last dose of study medication. Visit 8 should be performed 2 weeks after the PTD visit, and where possible, patients should then be followed up according to the visit schedule. For further details see Section 6.2.3

TABLE OF CONTENTS

[redacted]

[redacted]

ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitor
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ANCOVA	Analysis of Covariance
BI	Boehringer Ingelheim
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
CK-18	Cytokeratin-18
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cl^-	Chloride
CML	Local Clinical Monitor
CO	Competent Authority
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
dl	decilitres
DNA	Deoxyribonucleic Acid
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP-1	Glucagon Like Peptide-1
HbA1c	Glycated hemoglobin
HBGM	Home Blood Glucose Monitoring
HCO_3^-	Bicarbonate
HDL	High Density Lipoprotein

HPLC	High-performance liquid chromatography
hr	Hour
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPV	Important Protocol Violation
IRB	Institutional Review Board
IRT	Interactive Response Technologies
ISF	Investigator Site File
IUD	Intra Uterine Device
IUS	Intra Uterine System
JNC8	Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
kg	kilogram
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
m^2	Meters squared
MedDRA	Medical Dictionary for Drug Regulatory Activities
mEq/L	milliequivalents per litre
mg	milligrams
mg/dl	milligrams per decilitre
min	minutes
mL	millilitres
mmol/l	Millimoles per litre
MMRM	Mixed Model Repeated Measure
Na^+	Sodium
NAFLD	Non-alcoholic Fatty Liver Disease
nM	nanomoles
nmol/L	nanomoles per litre
NOAEL	No Observed Adverse Effect Level
OPU	Operative Unit
p.o.	per os (oral)
PG	Pharmacogenomics
PK	Pharmacokinetics
PPS	Per Protocol Set
PTD	Premature Treatment Discontinuation
RBC	Red Blood Cells
RDC	Remote Data Capture
REP	Residual Effect Period
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SGLT-2	Sodium-Glucose Co-Transporter-2
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase

SOP	Standard Operating Procedure
STEMI	ST Wave Elevated Myocardial Infarction
SU	Sulfonylurea
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TCM	Trial Clinical Monitor
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WBC	White Blood Cells

1. INTRODUCTION

Empagliflozin 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).

1.1 MEDICAL BACKGROUND

T2DM accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 285 million affected people worldwide. Its incidence is expected to increase to approximately 440 million people during the next twenty years. Complications induced by hyperglycemia 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 5-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of life expectancy.

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 normoglycaemia, 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 highly and selectively block glucose transport via SGLT-2 (IC_{50} 1.3 nmol/l), with a 5000-fold selectivity over SGLT-1 (IC_{50} 6278 nM).

The efficacy of empagliflozin is similar to the current oral antidiabetic drugs. It has the potential to be combined with other oral antidiabetic drugs and has shown additional efficacy in terms of glucose control when used in combination with insulin in diabetic patients.

Hypertension is four times more common in black/African Americans than in Caucasians. One of the risk factors for hypertension is sodium sensitivity and approximately one third of the essential hypertensive population is responsive to sodium intake. There is a higher association of hypertension with sodium sensitivity in black/African American patients with T2DM. This study will investigate the potential of empagliflozin to reduce sodium as well as glucose reabsorption by blocking the SGLT2 co-transporters and the possibility of adjustment to sodium sensing in the distal segment of the nephron that may affect renin secretion.

1.2 DRUG PROFILE

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 empagliflozin to humans. The compound is well tolerated in animals at clinically relevant plasma exposures, while adverse effects were observed at higher exposures. Noteworthy adverse findings at effect levels above the no

observed adverse effect level (NOAEL) 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 dosing 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 NOAELs. These toxicology data suggest empagliflozin can be safely administered to humans at 50 mg/day in long term-studies. Empagliflozin is not known to be carcinogenic.

Clinical pharmacokinetics

In humans, empagliflozin predominantly shows linear pharmacokinetics. Empagliflozin reaches peak levels at approximately 1.5 hr and shows a biphasic decline with the terminal elimination half-life of 12.4 h. Following oral administration of [14C]-empagliflozin, approximately 41.2% and 54.4% of drug-related radioactivity was excreted in feces and urine, respectively. None of the detected metabolites were major. Empagliflozin tablets can be administered with or without food. Empagliflozin exposure increases with hepatic and renal impairment; however, no dose adjustment is recommended for patients with renal and hepatic impairment as the observed changes in empagliflozin exposure were not clinically meaningful. No clinically relevant pharmacokinetic interactions were observed with metformin, glimepiride, pioglitazone, sitagliptin, warfarin, linagliptin, verapamil, ramipril, simvastatin, digoxin, hydrochlorothiazide, torasemide, gemfibrozil, rifampicin, probenecid and oral contraceptives (Microgynon®).

Clinical efficacy and safety

In clinical studies of over 12000 patients of which 3311 were treated with empagliflozin 10 mg and 4285 patients treated with 25 mg, empagliflozin was well tolerated in both normal healthy volunteers and patients with type 2 diabetes mellitus up to maximal treatment duration of 104 weeks in completed studies. The phase III studies have shown that treatment with empagliflozin 10 mg or 25 mg once daily for up to 24 weeks results in a reduction of glycated haemoglobin (HbA1c) up to 0.85%, body weight up to 2.2 kg and systolic blood pressure (SBP) up to 4.8 mmHg compared to placebo. This was consistently observed with empagliflozin as monotherapy, add on to metformin, to metformin + sulphonylurea, to pioglitazone with or without metformin, and to basal insulin with metformin and/or sulphonylurea. Treatment with 10 mg or 25 mg empagliflozin for 12 weeks in a study using ABPM to measure changes in blood pressure (BP) (1245.48) resulted in a reduction of HbA1c of up to 0.65%, mean 24 hr SBP up to 4.16 mmHg, diastolic blood pressure (DBP) up to 1.72 mmHg and body weight up to 1.98 kg. In this study, the proportion of patients with a positive orthostatic BP test after 12 weeks was measured to be 28% in placebo and up to 39.9% in empagliflozin treatment arms. These proportions returned to baseline levels 2 weeks after end of treatment. None of the patients in the empagliflozin treatment groups reported adverse events such as hypotension or orthostatic hypotension that were related to changes in orthostatic blood pressure or volume depletion. African American accounted for 5.0 % of the total number of patients in the 1245.48 study. Subgroup analysis by race measured a reduction of HbA1c of up to 0.95% in African Americans. While a reduction in

mean 24hr SBP up to -0.65 mmHg was observed in the African American group, there were too few patients for reliable blood pressure results.

Longer-term phase 3 data support sustained and durable effect of empagliflozin. In a double-blind, controlled independent extensions of the 4 pivotal trials (at least 76 weeks), which conducted under a single trial number (1245.31) with one trial protocol and one trial report (1245.31). In these trials, patients continued on the randomised trial treatment and the background medication they had taken in the initial trials. Sustained empagliflozin efficacy compared with placebo was demonstrated for glycaemic control (HbA1c, fasting plasma glucose **(**FPG**)**), body weight reductions, and lowering of blood pressure. In a head to head comparison with glimepride, after 104 week empagliflozin showed greater HbA1c, weight, and blood pressure reduction with fewer hypoglycaemic events compared with glimepiride in patients with type 2 diabetes mellitus and insufficient glycaemic control despite background therapy with metformin.

In addition, empagliflozin 25 mg resulted in a clinically meaningful and significant reduction in HbA1c in patients with moderate renal impairment. The frequency of overall adverse events (AE)s, AEs leading to discontinuation and serious adverse events (SAE)s were comparable to placebo. There was no significant increase in frequency of hypoglycemia with empagliflozin compared to placebo except when used in combination with a sulphonylurea or basal insulin. In general there was no increase in frequency of urinary tract infection compared with placebo, in female patients there was an increase in urinary tract infection (UTI) frequency with empagliflozin compared to placebo. No changes in electrolytes were observed with empagliflozin. There was a reduction in glomerular filtration rate (GFR) which gradually returned toward baseline values over the treatment period in the trials. Furthermore, estimated glomerular filtration rate **(**eGFR**)** returned to baseline when empagliflozin was discontinued.

For further details see the current version of the empagliflozin Investigator's Brochure [c01678844].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is designed to investigate the efficacy and safety of empagliflozin compared with placebo in hypertensive black/African Americans with T2DM. Since hyperglycemia and hypertension are key risk factors for both micro- and macrovascular complications, assessment of both glucose and blood pressure lowering effects of empagliflozin in hypertensive black/African American patients with T2DM could provide clinically relevant information for the use of empagliflozin.

The treatment duration of this trial (24 weeks) will enable assessment of the clinically relevant endpoint of a decrease in HbA1c, a well-accepted measurement of chronic glycaemic control, and change in body weight at week 24 whilst the key secondary endpoints of decreases in systolic BP (SBP) should be observable by 12 weeks.

2.2 TRIAL OBJECTIVES

The objective of the current study is to investigate the efficacy and safety of empagliflozin (10 mg or 25 mg) compared to placebo on glucose control over 24 weeks in hypertensive black/African American patients with T2DM. A second objective of the study is to investigate the efficacy and safety of empagliflozin (10 mg or 25 mg) compared to placebo on weight at 24 weeks and on BP 12 and 24 weeks in the same patient population. The study is designed to show superiority of empagliflozin over placebo.

2.3 BENEFIT - RISK ASSESSMENT

Both empagliflozin 10 mg and 25 mg consistently demonstrate sustained clinically meaningful and statistically significant efficacy in patients with T2DM and eGFR $\geq$ 45 mL/min/1.73m^2. Since empagliflozin 10 mg provides substantial efficacy with lower exposure, 10 mg is recommended as a starting dose. In patients tolerating empagliflozin 10 mg once daily, the dose can be increased to the maximum once daily dose of 25 mg. In general, both doses were well tolerated and there were no meaningful differences between the overall safety profiles of both doses.

In addition, beneficial effects on BP lowering and body weight reduction have been observed in a phase III placebo controlled study in 825 patients with T2DM and hypertension (1245.48). In this study, BP was monitored using ABPM devices and empagliflozin 10 and 25 mg was found to significantly reduce hourly mean SBP and DBP including daytime and night time SBP and DBP after 12-weeks of treatment. Of the patient on 10 mg or 25 mg empagliflozin, 4% and 12% respectively had clinically significant reductions in body weight relative >5% from baseline [c01678844].

According to the drug assignment planned in this trial, 1/2 (50.0%) of patients participating in this trial may derive a direct benefit from being treated with an additional active compound and not a placebo. The patients will receive empagliflozin at doses which have demonstrated favorable HbA1c, glucose and BP changes multiple phase II and phase III studies [c01678844]. Patients in the placebo group (50.0%) have a higher probability of not getting an additional treatment benefit, i.e. no reduction in FPG or HbA1c values or no reduction in BP due to the absence of an additional treatment. However, the placebo arm is required for this study and is acceptable up to 31 weeks given that diet and exercise instructions are provided to the patients and they are monitored and if necessary rescued properly for significant hyperglycemia or high blood pressure. The patients enter the study in a stable condition with regard to glucose control for at least 12 weeks and BP control for at least 4 weeks before randomisation and appropriate criteria for rescue therapy (Section 4.2.1) or patient discontinuation (Section 3.3.4) will ensure an adequate treatment in case of any clinical concern.

Because of the mechanism of action of empagliflozin, the risk of hypoglycemic episodes is low. The incidence of hypoglycemia was slightly higher for empagliflozin treated patients compared with placebo in patients treated on backgrounds of sulfonylurea (SU) or insulin. However, the observed difference was not due severe hypoglycemia. Symptoms attributed to hypo- or hyperglycemia, as well as hypo- or hypertension will be closely monitored in the trial.

Special attention will be paid to monitor for diabetic ketoacidosis (DKA). A potential risk for DKA has been reported by the Food and Drug Administration **(**FDA**)** in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dl).

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. In addition it needs to be taken into account that, due to the insulin independent mode of action, there is a possibility that ketoacidosis in patients treated with SGLT2 inhibitors is not accompanied by typical hyperglycemia as usually expected for DKA.

Patients who may be at higher risk of DKA while taking SGLT2 inhibitors include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), severely dehydrated patients, and patients with a history of ketoacidosis or who are known to have a low beta-cell function reserve.

As with all drugs, the potential for hypersensitivity and allergic reactions must be taken into consideration when empagliflozin is administered. Other risks to the patients are the risks inherent to any clinical trial such as unexpected adverse clinical or laboratory events.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients safety.

There are no adequate and well-controlled studies of empagliflozin in pregnant women. Empagliflozin is category C for pregnancy. Therefore, women who are of child-bearing potential will be included in this study provided that they are using adequate contraceptive methods.

All patients taking part in the trial may derive general medical benefit from careful and close monitoring by medical personnel during the study. Safety will be ensured by monitoring the patients for AEs both clinically and by laboratory testing and by the home blood glucose monitoring (HBGM). Patients who are not adequately controlled with regard to hyperglycemia and hypertension, as evidenced by a confirmed high FPG, HbA1c or BP value (refer to Section 4.2.1), will receive rescue therapy to ensure their safety or will be excluded from further study participation if no further benefit from the rescue medication can be achieved (refer to Section 3.3.4.1). Special measurements are performed like follow-up on urinary tract infections (urine culture), in order to evaluate if possible side effects observed for other SLGT-2 inhibitors are also present for empagliflozin.

The potency, selectivity, and efficacy in patients with T2DM suggest that empagliflozin would address the significant unmet medical need in hypertensive patients with T2DM. Given the good safety profile in the toxicity studies of empagliflozin and the good safety and tolerability seen in over 12000 patients with T2DM, the careful monitoring during the study visits and the blood glucose monitoring performed by the patients at home, the sponsor feels the risks to the participating patients are minimized and justified when compared with the potential benefits that a successful clinical development of empagliflozin could provide for hypertensive patients with T2DM.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, multi-national, and 2 parallel groups study compares 10 mg or 25 mg doses of empagliflozin to placebo in hypertensive black/African American patients with T2DM.

In total, approximately 154 hypertensive black/African American patients with T2DM who meet the entry criteria are planned for inclusion in this trial.

Patients are considered included in the study once they have signed the informed consent. All patients suitable after screening undergo a 2-week placebo run-in period before randomisation. Patients who successfully complete this period and who still meet the inclusion/exclusion criteria will be randomised to the 24-week randomised period of the study in which they will receive 10 mg empagliflozin or matching placebo (Figure 3.1:1).

At Week 4 /Visit 4, patients will be dose escalated to 25 mg empagliflozin or matching placebo.

Current antihypertensive and antidiabetic therapy should be administered during the entire trial duration (including placebo run-in and follow-up period) in an unchanged dosage.

The patient's participation is concluded when they have undergone the last planned visit (Visit 8).

For information regarding Adverse event and serious adverse event reporting, please refer to Section 5.2.2.2.

The end of the trial is defined as "last patient out", i.e. last visit completed by last patient.

The overall trial design is displayed in Figure 3.1:1 below.

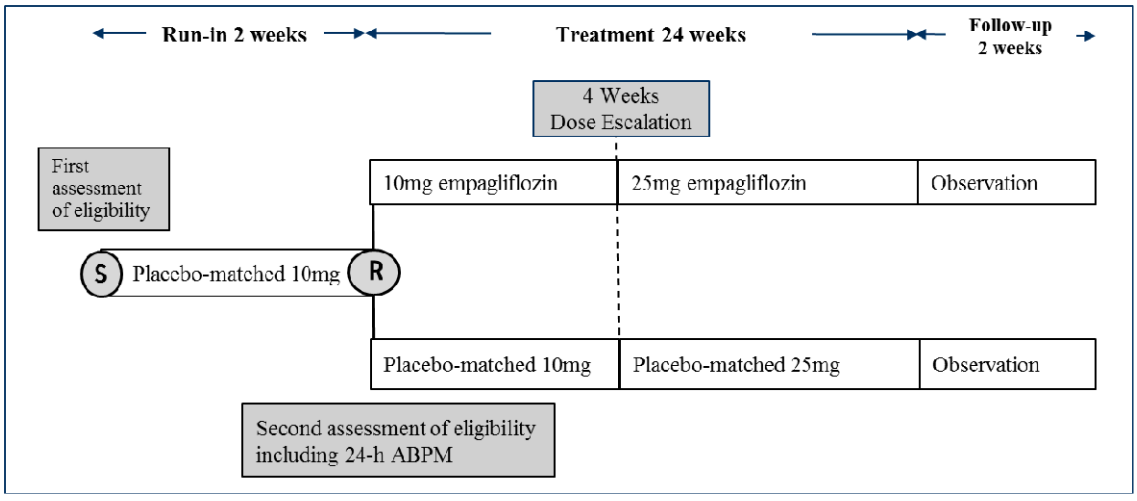


Figure 3.1:1: 1245.29 Trial design

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

BI will appoint a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial, ensures appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management and Statistical evaluation will be done by BI according to BI SOPs. For these activities, a Trial Data Manager and a Trial Statistician will be appointed.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons will be given in the Trial Master File (TMF) document.

The organisation of the trial in the participating countries will be done by the respective local BI operative unit (OPU) or a by a Contract Research organization (CRO) with which the responsibilities and tasks have been agreed and a written contract has been filed before initiation of the clinical trial. In each local OPU participating in this study, a CML will be appointed responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU.

A Co-ordinating Investigator will be nominated to coordinate investigators at different sites participating in this multicenter trial. Tasks and responsibilities for the coordinating Investigator will be defined in a contract filed before initiation of the trial.

Documents on participating (Principal) investigators and other important participants, especially their curricula vitae, will be filed in the TMF document.

Details on handling of the trial supplies including responsible institutions are given in Section 4 of this protocol.

The Investigator Site File (ISF) document will be kept in print-out version at the sites as far as required by local regulation and BI SOPs. A copy of the ISF documents will be kept as an electronic TMF document according to BI SOPs.

3.1.1.1 Hepatic External Adjudication

Certain hepatic events will be adjudicated / assessed by external independent experts. The events which will be reviewed will be defined in a charter for hepatic events. Events may be defined as abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for hepatic injury events, including liver enzyme elevations.

For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested including lab values, histological analysis, results of ultrasound, cat scan (CT), magnetic resonance imaging **(**MRI**)**, scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion. The assessments will be analysed on project level.

3.1.1.2 Clinical Event Committee for Diabetic ketoacidosis (DKA)

An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see Section 5.2.2.1). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met. For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication.

The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.

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

Empagliflozin used at both 10 mg and 25 mg dose has been shown to reduce seated SBP in patients with T2DM (1245.20) and to reduced hourly mean SBP and DBP (ABPM) including daytime and night time SBP and DBP in patients with T2DM and hypertension (1245.48) [c01678844]. Subgroup analysis of the data from the 1245.48 study show clinically meaningful changes in HbA1c after 12 weeks of treatment with both doses of empagliflozin in the black/African American subgroup; the low percentage of black/African Americans (5% of all patients) in that study did not allow for reliable results for SBP and DBP (ABPM). For this study, patients will enter on the basis of insufficient BP and glycemic control despite current therapy.

Metformin therapy represents the drug of choice unless contraindicated in patients newly diagnosed with type 2 diabetes mellitus with an HbA1c > 7.0% and should be titrated to a maximum tolerated dose which is generally greater than 1500 mg/day. Therefore, patients with current metformin treatment represent an important proportion of patient population with type 2 diabetes mellitus.

Sulfonylureas (SU) and Dipeptidyl peptidase-4 (DPP-4**)** inhibitors can be used as monotherapy but are frequently added to metformin when patients are not at goal with metformin. Sulfonylureas (eg. Glimiperide, glyburide, glipizide) and DPP-4 inhibitors (eg. sitagliptin, linagliptin, saxagliptin, alogliptin) are important alternative monotherapies when metformin is not used and more importantly when used in combination with metformin. Therefore patients with current sulfonylurea or DPP-4 inhibitor treatment represent an important proportion of the patient population with type 2 diabetes.

Phase III studies have shown that treatment with empagliflozin 10 mg or 25 mg for up to 24-weeks results in a reduction of HbA1c up to 0.85%, body weight up to 2.2kg and SBP up to 4.8 mmHg compared to placebo. This was observed with empagliflozin monotherapy, add on to metformin, to metformin plus sulfonylurea, to pioglitazone with or without metformin, and to basal insulin with metformin and/or sulfonylurea [c01678844]. Since the observed effect on BP is greater with 25 mg compared with 10 mg empagliflozin, the study design will include a dose escalation from a starting dose of 10mg to 25 mg empagliflozin 4 weeks after the start of treatment. The placebo-controlled design is considered ethically acceptable on the basis of appropriate criteria for patient discontinuation, relatively short study duration and criteria for rescue therapy as defined in the relevant guidelines (e.g. FDA Guidance for Industry for developing drugs in diabetes) (refer to Section 2.3).

This study will also provide a better understanding of the effect of empagliflozin on the circadian patterns of 24-hour BP control in hypertensive black/African American patients with T2DM. ABPM is considered a gold standard in BP measurement and a better predictor of cardiovascular risk than clinic BP (P13-12437). The use of ABPM has been integrated in major hypertension guidelines such as JNC8 (R14-0310) and European Society of Hypertension / European Society of Hypertension (P13-12437) and the American Heart Association (P08-03352). While slight differences exist among these guidelines there is agreement that ABPM provides a more accurate measurement of BP and correlates with hypertension related organ damage more closely than office BP, provides a more accurate evaluation of "white coat" as well as masked hypertension and a more accurate assessment of patients with drug resistance and hypotensive symptoms (P08-03352, P13-12437).

The randomised period is planned for 24 weeks to reflect both changes in HbA1c (primary endpoint) and ABPM and body weight (key secondary endpoints). The two-week follow-up period is considered to be sufficient, as previous studies with empagliflozin have shown that the pharmacodynamic effect of empagliflozin only extends to about 3 days after the last dose.

The rationale for dose and dose-interval selection is described in Section 4.1.3.

3.3 SELECTION OF TRIAL POPULATION

Approximately 700 patients will be screened for the trial in US. About 85 trial centres will be participating to ensure that approximately 154 patients are randomised to trial treatment (77 to each treatment group). The intention is that at least 2 patients should be randomised at each trial centre. Investigators who fail to screen at least one patient in the first 6 weeks of the trial may be re-evaluated for further participation. If enrolment is delayed, additional centres may be recruited.

Permission to randomise more than 8 patients per site must be obtained from the TCM at Boehringer Ingelheim. This will only be allowed after a careful review of the enrolment status.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all centres when such a number of patients has been screened and it is anticipated that a

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

The check for patient eligibility will be based upon a complete medical history including a physical examination and clinical laboratory tests. Judgement of the clinical relevance of a concomitant disease is at the discretion of the investigator. Conditions under therapy are always clinically relevant.

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

3.3.1 Main diagnosis for study entry

The study will be performed in black/African American patients (defined as a person having origins in any of the black racial groups of Africa as self-identified by the patient) with T2DM and hypertension that have insufficient glycaemic and BP control despite diet and exercise.

3.3.2 Inclusion criteria

1. Diagnosis of T2DM prior to informed consent.

   Note: Documentation should be available before randomization at latest. Confirmation can be in the form of formal documents or by verbal communication of the date of diagnosis from a patient or from their primary care physician (if records are not available). It is up to the medical judgment of the Investigator to deem if the information is accurate.

2. Male and female black/African American patients on diet and exercise regimen who are EITHER

   drug-naïve (defined as absence of any oral antidiabetic therapy, glucagon like peptide-1 **(**GLP-1**)** analog or insulin for 12 weeks, 16 weeks for pioglitazone prior to randomisation)

   OR

   pre-treated with stable dose of

   - Metformin only, or
   - Sulfonylurea only, or
   - DPP-4 inhibitor only, or
   - metformin plus sulfonylurea, or

- metformin plus DPP-4 inhibitor.

Treatment has to be unchanged for a minimum of 12 weeks prior to randomization.

Dose for metformin: maximum tolerated dose

The maximum daily dose of SU or DPP-4 inhibitor should not exceed that stated in the local label.

3. HbA1c of ≥ 7.0% (53 mmol/mol) and ≤ 11.0% (97 mmol/mol) at Visit 1 (screening).
4. Mean seated SBP 140-180 mmHg at Visit 1 (screening).
5. Successful completion of baseline ABPM testing with a mean SBP 135-175 mmHg prior to randomisation.
6. Treatment with stable doses of at least one but not more than 4 antihypertensive medication ≥ 4 weeks prior to randomisation.
7. Age ≥ 18 years at Visit 1 (screening)
8. Signed and dated written informed consent by date of Visit 1 in accordance with Good Clinical Practice **(**GCP**)** and local legislation

3.3.3 Exclusion criteria

1. Uncontrolled hyperglycemia with a glucose level >270 mg/dl (>15.0 mmol/L) after an overnight fast during placebo run-in (includes Visit 2.1) and confirmed by a second measurement (not on the same day).
2. Exposure to any other antidiabetic medication within 12 weeks prior to randomisation other than metformin, sulfonylurea, DPP-4 inhibitor, metformin plus sulfonylurea or metformin plus DPP-4 inhibitor.
3. Current hypertension treatment with oral Minoxidil (topical minoxidil for hair growth is allowed).
4. Mean seated SBP ≥181 mmHg during placebo run-in visit and confirmed by a second measurement (not on the same day) preferably within one day.
5. Upper arm circumference that exceeds the upper circumference level of the cuff size of either ABPM and/or BP measurement device used in the study.
6. Night shift workers who routinely sleep during the daytime and/or whose work hours include midnight.
7. Diagnosis of autoimmune diabetes/Type I diabetes mellitus, monogenic (neonatal or maturity onset diabetes of the young (MODY)) diabetes or Type I diabetes in adults/ latent autoimmune diabetes of adults (LADA) per investigator or patient medical history at the time of Visit 1 (screening).
8. Known or suspected secondary hypertension (e.g. renal artery stenosis, phaeochromocytoma, Cushing's disease).

9. History or evidence of hypertensive retinopathy (Keith-Wagener grade III or IV) and/or hypertensive encephalopathy.
10. Clinically significant valvular heart disease or severe aortic stenosis in the opinion of the investigator.
11. Acute coronary syndrome (non- ST wave elevated myocardial infarction (STEMI), STEMI and unstable angina pectoris), stroke or transient ischemic attack within 3 months prior to informed consent.
12. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined during screening and/or run-in phase.
13. Impaired renal function, defined as eGFR< 45 ml/min/1.73m^2 (moderate renal impairment, chronic kidney disease epidemiology collaboration CKD-EPI formula) as determined during screening and/or run-in phase.
14. Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption.
15. Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years.
16. Blood dyscrasias or any disorders causing hemolysis or unstable Red Blood Cells (e.g. malaria, babesiosis, haemolytic anaemia, thalassemia, sickle cell anaemia (sickle cell trait is allowed)).
17. Medical history and signs and symptoms of diabetic autonomic neuropathy.
18. Treatment with anti-obesity drugs 3 months prior to randomisation (i.e. surgery, aggressive diet regimen, etc.) leading to unstable body weight.
19. Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM in the opinion of the investigator.
20. Pre-menopausal women (last menstruation ≤ 1 year prior to informed consent) who:
    - are nursing or pregnant or
    - are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial. Acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems (IUDs/IUSs), oral, implantable or injectable contraceptives, complete sexual abstinence (if acceptable by local authorities), double barrier method and vasectomised partner.
21. Alcohol, drug or confectionary liquorice abuse within the 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake in the investigator's opinion.

22. Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial; or participating in another trial (involving an investigational drug and/or follow-up) after discontinuing medication in that trial.
23. Any other clinical condition that would jeopardize patient's safety while participating in this clinical trial in the opinion of the investigator.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from the trial if:

- The patient withdraws consent, without the need to justify the decision.
- If a patient becomes pregnant during the trial. The patient will be followed up until birth or otherwise termination of the pregnancy.

Treatment with study drugs should be discontinued if:

- The patient needs to take concomitant drugs that interfere with the investigational product or other study medications(s).
- The patient is no longer able to participate for other medical reasons (e.g. surgery, AEs, or other diseases).
- Introduction of rescue therapy due to hyperglycemia, high HbA1c or hypertension as described in Section 4.2.1 does not lead to sufficient treatment efficacy (rescue criteria still met). In this case, the reason for study drug discontinuation will be classified as "lack of efficacy".
- Occurrence of hypoglycemia (e.g. repeated hypoglycaemic episodes) or DKA that may put the patient at risk with continued participation. Patients should be assessed for ketoacidosis immediately if symptoms occur, regardless of blood glucose level. Discontinuation or temporary interruption of study medication should be considered, until the situation is clarified.

Patients who discontinue treatment prematurely will be followed up until the end of the study (for further details please see Sections 6.2.2 and 6.2.3).

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

Patients who drop out during the screening phase prior to randomisation (Visit 3) will be considered screening failures. They have to be recorded as screening failure in eCRFs and no further follow-up is required.

Patients who discontinue from treatment or withdraw from the study after randomisation (Visit 3) will be considered as "early discontinuations" and the reason for premature discontinuation must be recorded in the eCRFs. The data will be included in the trial database

and will be reported. If determined by investigator as necessary for patient safety, new antidiabetic medication regimen can be started immediately after discontinuation and must be recorded in eCRFs.

For the analysis of this trial it is absolutely crucial that all planned assessments are done as planned, even if patients discontinue trial treatment. All patients who discontinue from treatment after randomisation (Visit 3 and beyond) and who do not withdraw consent will be followed up for the intended regular treatment period. All assessments related to the primary and secondary endpoints must be performed as if the patient would have remained on treatment. Details of procedures to be followed for patients prematurely terminating the trial treatment can be found in Section 6.2.3).

If a patient withdraws consent, participation in the study will end, the study medication will be stopped and the study staff will try to arrange tests for end of treatment procedures and a follow-up visit (Visit 8 procedures) with the patient for the patient's safety (For further details please see Section 6.2.3). All used medication kit boxes and remaining study medication should be returned. Patients who withdraw consent will not be contacted any more about the study.

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

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site,

2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial and/or invalidate the earlier positive benefit-risk-assessment,

3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

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

3.3.5 Re-screening

Re-screening is permitted for the following categories of screen failed patients only:

- Patients who were screen failed due to exclusionary background anti-diabetic therapies (sulfonylurea, DPP4-inhibitor, metformin + sulfonylurea, metformin +DPP4-inhibitor) according to prior versions of the protocol.

- Patients who were screen failed due to exclusionary HbA1c 7.0% (53 mmol/mol) - 7.4% (57 mmol/mol) at Visit 1 according to prior versions of the protocol. Patients

who were screen failed due to exclusionary HbA1c below 7.0% or above 11.0% cannot be re-screened.

- Patients who were screen failed due to exclusionary mean seated DBP (Visit 1) according to prior versions of the protocol. However, mean seated SBP (Visit 1) must have been 140-180 mmHg at the previous screening.
- Patients who were screen failed due to taking 4 antihypertensive medications (≥ 4 weeks prior to randomization) according to prior versions of the protocol.
- Patients who were screen failed due to out-of-window visits prior to ABPM testing (Visit 2.2). If ABPM testing has commenced, no re-screening is permitted.

A patient who was screen failed due to any of the above screen failure reasons is permitted to be re-screened once only. A new patient number should be assigned to the re-screened patient who should be re-consented. Rationale for re-screening must be document in source documents.

Re-screening is not permitted for patients who were screen failed due to other reasons.

3.3.6 Repeat test

HbA1c test (Visit 1) may be repeated once if the test result from the central lab is exclusionary but the most recent test result from a local lab (taken before Visit 1 but not older than one month), if any, falls within the acceptable range.

ABPM test (Visit 2.2) may be repeated once if the first attempt is unsuccessful. Refer to Footnote B and Footnote I of the Flow Chart, as well as Section 5.1.2 and Section 6.2.1 for additional details on repeat ABPM.

Rationale for all repeat tests must be documented in source documents.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The study medication will be provided by Boehringer Ingelheim.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product one are below.

Substance:	empagliflozin
Pharmaceutical form:	tablet
Source:	Boehringer Ingelheim
Unit Strength:	10 mg
Route of administration:	p.o., once daily

The characteristics of the test product two are below.

Substance:	empagliflozin
Pharmaceutical form:	tablet
Source:	Boehringer Ingelheim
Unit Strength:	25 mg
Route of administration:	p.o., once daily

The characteristics of the reference product are below.

Substance:	placebo matching empagliflozin 10 mg
Pharmaceutical form:	tablet
Source:	Boehringer Ingelheim
Unit Strength:	-
Route of administration:	p.o., once daily

The characteristics of the reference product are below.

Substance:	placebo matching empagliflozin 25 mg
Pharmaceutical form:	tablet
Source:	Boehringer Ingelheim
Unit Strength:	-
Route of administration:	p.o., once daily

4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into the randomised double-blind treatment period, treatment assignment will be by means of a third-party phone/web-based randomisation at Visit 3. This will involve the use of an interactive response technologies **(**IRT**)** system. To facilitate the use of the IRT system, the Investigator will receive an IRT system manual including all necessary instructions for using the IRT system. A copy of the manual will be available in the ISF.

Patients will be randomly assigned to empagliflozin 10 mg or placebo in a balanced 1:1 ratio. For further details (e.g. stratification) please refer to Section 7.5.

Patient assignment to the treatment groups will be determined by a computer generated random sequence. Access to the randomisation code will be controlled and documented – for further details please refer to Sections 4.1.5.1 and 4.1.5.2.

The assigned medication number will be entered in the eCRF, and the corresponding medication kit should be given to the patient. Using this procedure, relevant parties will be blinded to the treatment group assignment.

Kit numbers must be checked carefully before dispensing to patients. Dispensing the proper medication kit to a patient is important to avoid unintentional switching of treatments during a patient's trial participation. If an error in dispensing kits is discovered, the site must contact the affected patient(s) immediately to have them come in for a new kit(s). The drug administration pages in remote data capture **(**RDC**)** should reflect the actual kits taken by the patients.

4.1.3 Selection of doses in the trial

Empagliflozin will be administered in a starting dose of 10 mg once daily. At Visit 4, patients will be dose escalated to a dose of 25 mg once daily. These doses were selected based on the results from previous dose-finding studies (please refer to Section 1.2 and to the current version of the IB, c01678844), are currently used in the phase III program and one or both doses are expected to be the approved dose(s).

4.1.4 Drug assignment and administration of doses for each patient

Medication will be dispensed in a double-blind and single-dummy manner.

All patients will be assigned a placebo run-in kit at the beginning of the placebo run-in period (Visit 2.1), and dispensing will occur just once. Dispensing of kits for the double-blind treatment period will begin at Visit 3. Dispensing will occur on 3 occasions over a period of 24 weeks. For further details regarding packaging (e.g. number of tablets per kit box) please refer to Section 4.1.6.

Patients will be dose escalated at Visit 4/Week 4 to 25 mg empagliflozin. If it is in the investigator's opinion that the patient cannot tolerate either 10 mg or 25 mg doses, the investigator should refer to Section 3.3.4.1 for withdrawal of patient from the study.

Table 4.1.4: 1 empagliflozin, placebo, oral administration per dose group and day

Dose group	Treatment	total units per dose	timing
Placebo run-in period:			
All patients	placebo	1 tablet	once daily, morning
Treatment period (e.g. double-blind, single-dummy):			
10 mg empagliflozin	active drug	1 tablet	once daily, morning
Placebo-matched 10 mg empagliflozin	matching placebo	1 tablet	once daily, morning
Treatment period-Dose escalation (e.g. double-blind, single-dummy):			
25 mg empagliflozin	active drug	1 tablet	once daily, morning
Placebo-matched 25 mg empagliflozin	matching placebo	1 tablet	once daily, morning

From the start of the placebo run-in period (Visit 2.1), patients should be instructed to take their trial medication once daily with water. To ensure a dose interval of about 24 hours, the medication should be taken at approximately the same time every day. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. On days before the next visit, the dose should be taken 22-26 hours before the planned dose at the visit. No double doses should be taken, and dose reductions are not permitted. Empagliflozin can be taken with or without food.

Patients should be instructed not to take their trial medication on the morning of study visits as they will be dosed whilst in the clinic. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day. Visits should be routinely scheduled in the morning, at approximately the same time of day (07:00 AM to 11:00 AM) for each visit. The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF. Study medication administration should follow physical and laboratory assessments.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Placebo for the run-in period from screening to randomization will be open label.

After randomisation at Visit 3, patients, investigators and everyone involved in analysing or with an interest in this double-blind study will remain blinded with regard to the randomised treatment assignments until after database lock. However, due to the requirements to report Serious Unexpected Suspected Adverse Reactions (SUSARs), it may be necessary for a representative from BI's pharmacovigilance group to access the randomisation code for individual patients during study conduct. In such cases, access to the code will only be permitted by authorised pharmacovigilance representatives. Access to the code will be via an IRT system.

The randomisation code will be kept secret by Clinical Trial Support at BI up to database lock. Please refer to Section 4.1.5.2 for the rules regarding breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Procedures for emergency unblinding

In this blinded trial an emergency unblinding will be available to the Investigator via an IRT system. Treatment unblinding may only be allowed in emergency situations when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. If patient treatment is unblinded, the Sponsor must be informed immediately. The reason for treatment unblinding, together with the date, must be documented on the appropriate eCRF page.

4.1.6 Packaging, labelling, and re-supply

Study medication (empagliflozin and placebo) will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The study medication will consist of boxes labelled with the trial identification and medication kit number. Each box will contain an appropriate number of empagliflozin tablets or matching empagliflozin placebo with some reserve (see below), for dosing until the next scheduled visit.

Within each kit box, tablets will be packaged in blisters which will contain one tablet in 7 rows for a 7-day supply (total of seven tablets per blister), according to Table 4.1.4: 1. For each dose patients must take one tablet from one row. Blisters will be packaged in medication kit boxes labelled with the trial identification and medication kit number.

The placebo run-in kit, assigned to all patients successfully completing Visit 2.1, will contain 21 tablets in 3 blisters (i.e. sufficient supply for 2 weeks, with 1-week in reserve).

Double-blind treatment period kit, dispensed at Visit 3, will contain 35 tablets in 5 blisters (i.e. sufficient supply for 4 weeks, with 1-week in reserve). At Visit 3, one kit will be dispensed per patient. The total number of tablets dispensed to a patient during the treatment period will therefore be 35.

Each double-blind treatment period dose escalation kit, dispensed starting at Visits 4 and 5.2, will contain 35 tablets in 5 blisters (i.e. sufficient supply for 4 weeks, with 1-week in reserve). Two kits will be dispensed at Visit 4 per patient and three kits will be dispensed at Visit 5.2 per patient. The total number of tablets dispensed to a patient during the treatment period will therefore be 175.

Supply and re-supply will be managed by an IRT system.

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

4.1.7 Storage conditions

The trial medication (empagliflozin and placebo) must be kept in its tightly closed original packaging under the recommended storage conditions indicated on the label. The minimum/maximum storage temperature must be measured and documented at least weekly by the Investigator / pharmacist / investigational drug storage manager in accordance with BI (or designated CRO) SOPs. If storage conditions are found to be outside the specified range, site personnel should immediately contact the CML via the list of contacts in the ISF.

4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor and/or a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the Institutional Review Board **(**IRB**)** / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,

- availability of a signed and dated clinical trial protocol (CTP) or immediately imminent signing of the CTP(in exceptional cases, medication could already be sent to the site, before its activation via an IRT system)
- if applicable, availability of the proof of a medical licence for the principal investigator,
- for USA, availability of the Form 1572.

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

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

There are no non-investigational medicinal products (NIMPs) defined for this trial.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Details of all concomitant therapy during the clinical trial will be recorded on the appropriate pages of the eCRFs. Patients who are treated with contraindicated medication should not be enrolled into the study.

4.2.1 Rescue medication, emergency procedures, and additional treatments

Throughout the duration of the trial, patients should continue to take their current therapy, the dose of which should remain unchanged if at all possible (for further details see below). This medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

Rescue medication, for the treatment of hyperglycemia, can be initiated during the double-blind treatment period of the trial (i.e. from Visits 3-7.2) and during follow up period but only if the criteria below are met:

- Week 1 – 12 (i.e. up to and including the result from Visit 5.2):
  The patient has a glucose level > 270 mg/dl (> 15.0 mmol/l) after an overnight fast

- Week >12 – 26 (i.e. from the day after Visit 5.2 onwards):
  The patient has a glucose level > 200 mg/dl (> 11.1 mmol/l) after an overnight fast

The above results should be confirmed, meaning that there is a minimum of two measurements, at least one of which should be performed after an overnight fast at the investigational site, and on a different day to the initial (overnight fast) measurement.

A FPG and an HbA1c sample should be taken before initiation of rescue therapy and sent to central lab for analysis. The HbA1c sample is not required if a sample has been taken and sent to the central lab for analysis within the last 4 weeks.

Special attention must be paid to monitor for instances of DKA. All patients must be made aware of this potential risk and need to be instructed to contact the Investigator or other healthcare professional in case of symptoms of DKA. For further details see Section 2.3.

In case of a suspected DKA the Investigator should ensure that appropriate tests are performed at the earliest opportunity according to local guidelines, such as a blood gas test (i.e. pH, bicarbonate; the results will be collected on the relevant page of the eCRF) and that the patient is appropriately treated (i.e. hospitalized or referred to emergency treatment) according to local treatment guidelines.

Rescue medication, for the treatment of hypertension, can be initiated during the double-blind treatment period of the trial (i.e. from Visits 3-7.2) and during follow up period but only if the criteria below are met:

- Week 1 – 4 (i.e. up to and including the result from Visit 4.0):
  The patient has a mean seated SBP level ≥180 mm Hg and/or mean seated DBP level ≥110 mm Hg at the clinic visit

- Week 4 – 26 (i.e. from the day after Visit 4.0 onwards):
  The patient has a mean seated SBP level ≥160 mm Hg and/or mean seated DBP level ≥100 mm Hg at the clinic visit

The above results should be confirmed, meaning that there is a minimum of two seated blood pressure measurements (second measurement at the investigational site on a different day to the initial measurement).

If the above criteria are met, the initiation of rescue medication is at the Investigator's discretion, based on the patient's current clinical condition (e.g. ongoing illness etc.). The choice of rescue medication will depend upon the current medication. Adjustment of the current therapy or addition of another antidiabetic and/or antihypertensive medication would be appropriate. Rescue medication and its dosage will be left to the discretion of the Investigator and the administration of rescue medication is to be conducted according to GCP with the exception of the following:

- Due to their known effect on blood pressure, thiazolidinediones (eg pioglitazone) and GLP-1 analogs must not be used as rescue medication for hyperglycemia.

- Any SGLT-2 inhibitor that is or may become available during the conduct of this trial must not be used as rescue medication.

Regardless of the choice made, rescue medication should be taken in accordance with the local prescribing information of that respective medication, taking into account potential contraindications. Rescue medication can be used from when it is initiated until the end of the trial.

In the case of hypoglycemia and/or hypotension that may put the patient at risk (e.g. repeated symptomatic hypoglycemia or severe hypoglycemia, repeated syncope), appropriate adjustment of oral antidiabetic and/or antihypertensive therapy such as a dose reduction / discontinuation of ongoing rescue medication or existing therapy should be initiated. Reduction or discontinuation of ongoing rescue medication should be considered before a reduction in the dose of existing therapy.

If, in the Investigator's clinical opinion, no further effect from the rescue medication is anticipated, and the patient's hyper- or hypoglycemia, and/or hyper- or hypotension cannot be controlled, the patient should discontinue the trial medication as specified in Section 3.3.4.

Any rescue medication will be recorded in the source documents and on the appropriate pages of the eCRF.

Rescue medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

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

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In any situation other than rescue conditions, the use of other antidiabetic and antihypertensive agents will be prohibited during the course of the study except for existing current therapy and, if applicable, the ongoing rescue medication.

- Pioglitazone and GLP-1 analogs must not be used as rescue medication for hyperglycemia.

- Any SGLT-2 inhibitor that is or may become available during the conduct of this trial must not be used as rescue medication.

Short-term use of additional prandial/intravenous insulin will be permitted (only in the event of an emergency situation and/or hospitalisation) based on clinical judgement of the Investigator or treating physician. Prolongation of additional prandial/intravenous insulin treatment over more than 2 weeks vs. treatment discontinuation should be discussed on a

case-by-case basis between the Investigator and the CML/TCM. Please also refer to Section 3.3.3 regarding the permitted use of antidiabetic agents pre-trial.

Additionally, treatment with anti-obesity drugs or systemic steroids will be prohibited due to their influence on glucose metabolism. However, one-off or short-term use (i.e. ≤ 1 week duration) of systemic steroids will be permitted as well as therapy with non-systemic steroids such as inhaled or local steroids. Furthermore, for patients taking thyroid hormones, any change in the dose should be avoided. If dose changes do occur, then they should be recorded in the source documents and in the eCRF.

For patients receiving metformin, in case a vascular administration of iodine containing contrast agent is required, metformin should be temporarily discontinued at the time of or before the contrast agent is given and resumed not earlier than 48 hours after administration.

4.2.2.2 Restrictions on diet and life style

At the beginning of the Run-in period, patients will receive diet and exercise counselling by a diet specialist or trained staff member. The counselling will be based on local diet recommendations and should include a food log/intake booklet. The patients will be reminded to follow the agreed diet and exercise plan at every visit. A food intake booklet will be provided as a tool but site specific tools could also be used. Record of the actual food intake over a time of three consecutive days before the clinic visit is requested at regular intervals as indicated in the Flow chart. The food intake booklet will remain with the patient and no data will be transferred to the eCRF. The respective procedure for illiterate patients (if included) is described in Appendix 10.1.

Women of child-bearing potential must continue to practice an acceptable method of birth control (in accordance with the trial exclusion criteria Section 3.3.3) throughout the duration of the study.

Patients should also not take an investigational drug in another trial within 30 days prior to intake of study medication in this trial.

There are no other restrictions on diet and lifestyle.

4.3 TREATMENT COMPLIANCE

Patients will be asked to bring all trial medication containers (with or without any remaining tablets) with them to each trial visit. The tablets will be counted by the Investigator or study nurse and compliance will be calculated according to the formula:

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

Compliance during the placebo run-in period should be between 80% and 120%. If compliance is outside this range, the patient should be carefully interviewed and, if necessary,

re-informed about the purpose and the conduct of the trial. Unreliable patients should not be randomised at the discretion of the Investigator.

Compliance during the double-blind treatment period should also be between 80% and 120%. Patients who are not compliant according to this definition should be carefully interviewed and re-informed about the purpose and the conduct of the trial.

A comment should be registered in the eCRF (Study medication compliance page) for any patient that has taken <80% study medication or who has not taken study medication since the last visit. Any time a patient is off study medication for > 7 consecutive days this should be also registered in the eCRF on the Study Med Stop page. Starting and stopping study medication is allowed in this trial.

Patients who forget to return trial medication and empty containers should be reminded to bring them to their next visit. Compliance for patients who forget to return trial medication in two consecutive visits should be calculated per the discretion of the Investigator and this should be reflected on the clinical history.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

The primary endpoint in this study is change from baseline in HbA1c at 24 weeks of treatment. Throughout the study protocol, the term ''baseline'' refers to the last observation prior to randomisation of the patient.

Key secondary endpoints:

- Change from baseline in mean 24-hour ambulatory SBP at 12 weeks of treatment.
- Change from baseline in mean trough ambulatory SBP at 12 weeks of treatment.
- Change from baseline in body weight at 24 weeks of treatment
- Change from baseline in trough seated SBP at 12 weeks of treatment.

Other secondary endpoints are:

- Change from baseline in mean 24-hour ambulatory DBP at 12 weeks of treatment.
- Change from baseline in trough seated SBP at 24 weeks of treatment
- Change from baseline in mean 24-hour ambulatory SBP at 24 weeks of treatment.
- Change from baseline in mean 24-hour ambulatory DBP at 24 weeks of treatment.
- Change from baseline in trough seated DBP at 12 weeks of treatment
- Change from baseline in trough seated DBP at 24 weeks of treatment

[redacted]

[redacted]

5.1.2 Assessment of efficacy

HbA1c

Blood samples for the determination of HbA1c at the central laboratory will be taken. At the screening Visit 1, the blood sample can be taken at any time during the visit. At all other Visits, the blood samples should be drawn before breakfast and before trial drug administration. The samples will be analysed at a central laboratory or its affiliates having a National Glycohaemoglobin Standardisation Program Level I certificate. Further details about sample handling, shipment, and assay procedures can be found in the ISF (Lab manual).

Fasting plasma glucose

Blood samples for the determination of FPG at the central laboratory will be taken after an overnight fast. The samples should be taken before breakfast and before trial drug administration. The samples will be measured at a central laboratory using validated assays. Further details about sample handling and shipment can be found in the ISF (Lab manual).

Ambulatory blood pressure monitoring (ABPM)

ABPM will be performed in parallel using the ABPM device. A blood pressure monitoring device will be provided for ABPM recordings.

On the mornings when the ABPM device will be applied (Visits 2.2, 5.1 and 7.1), patients should arrive at approximately half an hour prior to medication intake to allow additional time for ABPM procedures, so that dosing of medication occurs as close as possible to patient daily dosing time. It is important that the dosing time for the baseline ABPM (Visit 2.2) is the same as the dosing time for the 12 and 24 week ABPM (Visits 5.1 and 7.1). In addition, for collection of Visit 2.2, 5.1 and 7.1 ABPM, the daytime and night time activities of the patient during the 24 hours should be similar. For example, if the baseline ABPM falls on a normal workday, then the final ABPM measurement should be scheduled for a normal workday, not a weekend or vacation day. Measurements of BP using the monitor should be taken from the same arm that is used to measure seated BP.

The ABPM device will be programmed to measure blood pressure every 20 minutes throughout the day and night to measure BP. Patients should be advised not to move the arm during each blood pressure measurement and will also be given instructions concerning interruption of measurement in case of malfunction of the device or repositioning of the cuff if it slips.

At each ABPM visit (Visits 2.2, 5.1 and 7.1), patients are to come to the clinic fasting and the following procedure will be performed. The ABPM device will be attached to the patient and test readings will be taken to check if the device is working properly prior to medication intake. The first test reading is the Beginning of Test reading. Once it has been confirmed that the monitor is properly functioning, study medication will be administered. Record the time the medication was administered and the time the monitor was prompted to take the Beginning of Test reading. The next day when the patient returns to the clinic, the monitor will be prompted to take a Conclusion of Test reading. The device will then be removed and the time of the Conclusion of Test will be recorded. This should be done within 23:30-24 hours of starting monitor.

After each ABPM session, the data from the device is to be downloaded and assessed to determine if the session was successful.

At Visit 2.2 only, if the first session does not pass quality criteria or the mean ABPM SBP is outside the required range , the session should be repeated. Only one repeat session will be permitted. It is important to remember to record the 24-hour mean SBP which is displayed at the bottom of the quality compliance (QC) results. The 24-hour mean SBP at this visit together with a successful session determines eligibility for randomization.

After the removal of the monitor and prior to study medication intake, the patient will be allowed rest for 15 minutes and a seated BP measurement (trough BP) will be taken. The patient will then be given study medication. The time for each of the seated BP measurement, medication intake, and the beginning and conclusion of the 24 hours ABPM readings must be recorded.

Further details on the procedure for BP measurement utilizing ABPM device can be found in the ISF.

Blood pressure (seated SBP and DBP)

SBPand DBP as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 2 minutes of rest in the seated position. The BP measurement should be performed three times at each time point and the mean value of these measurements will be calculated by RDC. Further details on the procedure for BP measurements are given in Appendix 10.2.

Trough mean BP value is the mean of these three measurements on the day of the clinic visit before study drug intake.

[redacted]

Weight [redacted]

Weight measurements should always be done on the same scales for one patient. In order to get comparable body weight values, it should be performed in the following way:

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

[redacted]

[redacted]

5.2 SAFETY

5.2.1 Endpoints of safety

- Adverse events
- Hypoglycaemic events
- Adverse events of special interest (AESI)
- Changes from baseline in clinical laboratory values
- Positive orthostatic blood pressure test after 12 weeks of treatment

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient in a clinical investigation who was 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.

Adverse reaction

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

Serious adverse event

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

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

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

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

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above. The latest list of "Always Serious AEs" can be found in the RDC system. These events should always be reported as SAEs as described in Section 5.2.2.2.

Adverse Events of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.2.2.2. The following events are defined as 'adverse events of special interest (AESI)':

- Hepatic injury defined by the following alterations of liver parameters after randomisation at Visit 3:
    - an elevation of AST and/or ALT ≥ 3-fold ULN combined with an elevation of bilirubin ≥ 2-fold ULN measured in the same blood draw sample.
    - An isolated elevation of AST and /or ALT ≥ 5 fold ULN irrespective of any bilirubin elevation

Patients showing these lab abnormalities need to be followed up according to Appendix 10.4.2 of this CTP and the "DILI checklist" provided in RDC/ISF

- Decreased renal function: creatinine value shows a ≥ 2 fold increase from baseline and is above the upper limit of normal (ULN)

- Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

  In case of metabolic acidosis, ketoacidosis and DKA further investigations should be done according to the medical judgment and the clinical course until a diagnosis is made and/or the patient is recovered.

  DKA is defined by the diagnostic criteria in Table 5.2.2.1: 1 below, and as defined by the American Diabetes Association (ADA) (R14-5435).
  Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgment should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in Table 5.2.2.1: 1 below (see Section 2.3 for further details).

  In case of a suspected DKA the Investigator should ensure that appropriate tests are performed locally at the earliest opportunity according to local guidelines, such as a blood gas test (pH, bicarbonate) and that the patient is appropriately treated (i.e. hospitalized or referred to emergency treatment) according to local treatment guidelines.

Table 5.2.2.1: 1 Diagnostic criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma Glucose (mg/dl)	>250	>250	>250
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum bicarbonate (mEg/L)	15-18	10-<15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

* Nitroprusside reaction method
** Calculation: 2[measured Na (mEq/L) + glucose (mg/dl)/18]
*** Calculation: (Na^+)-$(Cl^- + HCO_3^-)$ (mEq/L)

Patients with AESI need to be followed up appropriately. The investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per investigator discretion.

These lab findings constitute a hepatic injury alert and the patients showing the above alterations in liver parameters or hepatic (S)AEs should be followed up according to Section 10.4 of this CTP and the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure 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.

For any of these AESI adverse events the central lab will alert the investigator and the investigator should report the event to the Pharmacovigilance centre immediately (within 24 hours of being informed, and without waiting for confirmation of the results via a second measurement) being documented on an SAE form, even if they do not meet any of the seriousness criteria – for details please see Section 5.2.2.2. The investigator shall collect a respective trough pharmacokinetics **(**PK**)** sample and an unscheduled lab sample for creatinine or hepatic enzymes as soon as possible (see Section 5.5.1) and initiate follow-up laboratory test of creatinine according to medical judgement and hepatic enzymes according to Section 10.5.2.

Intensity of adverse event

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

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

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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. preexisting 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 diminished).

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

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

5.2.2.2 Adverse event and serious adverse event collection and reporting

<u>AE Collection</u>
The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate eCRF by the Investigator:

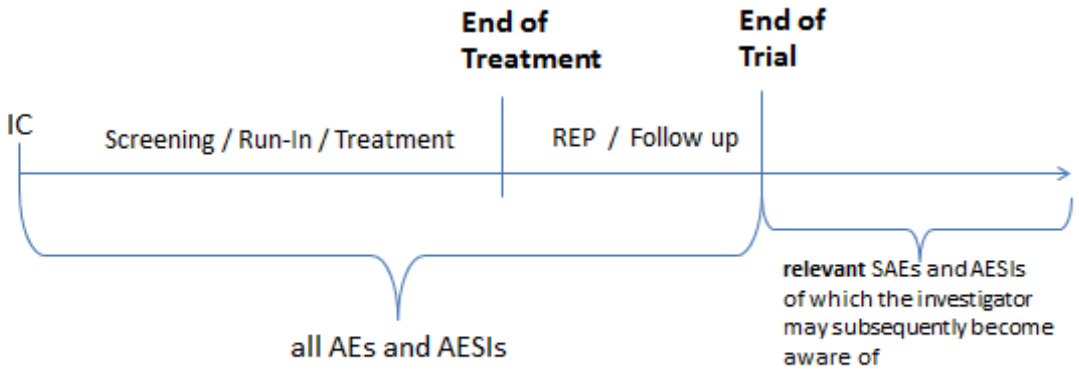
From signing the informed consent onwards through the Residual Effect Period (REP) until trial completion (individual patient's End of Trial):

- all AEs (serious and non-serious), and AESIs. This also applies to patients who prematurely discontinue from the study.

  If an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual patient's End of Trial contact, the Investigator must report all AEs (serious and non-serious) and AESIs.

After the individual patient's end of trial:

- The Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.



The REP is defined as ≤ 7 days following last intake of trial medication. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.3. Events which occurred after the REP will be considered as post treatment events.

AE Reporting to Sponsor and Timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

Information required

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

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

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

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

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

Pregnancy

In the rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the clinical trial after having taken trial medication, the investigator must report any potential drug exposure during pregnancy which occurred in a female subject or in a partner to a male subject to the Sponsor immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF).

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).

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.

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

5.2.3 Assessment of safety laboratory parameters

All safety laboratory samples (except at Visit 1) will be collected after a full overnight fast (nothing to eat or drink except water for at least 10 hours) and before investigational drug as described in the Flow Chart and Section 6. The blood sample at Visit 1 (screening visit) can be taken with the patient in a fasted or non-fasted state.

All parameters that will be determined during the trial conduct are listed in Table 5.2.3:1 and 5.2.3:2. The analysis will be performed by a central laboratory. The respective reference range and details about sample handling and shipment will be provided in the ISF (Lab Manual).

Reduced safety lab panels excluding urinalysis are planned for the following visits:

- For the screening Visit 1, laboratory only includes liver transaminases, alkaline phosphatase, serum creatinine, TSH and urinalysis
- For the first visit after randomisation (4 weeks), only ~~fasting plasma glucose~~ **FPG** will be determined (see Flow Chart).

The following safety lab parameters will only be determined at each of the following study visit:

- Lipid fractions: planned at V3, V5.2, V7.2 and V8
- TSH: planned at V1
- Albumin (urine) at V3, V5.2, V7.2 and V8
- BNP at V3, V5.2 and V7.2

Table 5.2.3: 1 Safety laboratory parameters – whole blood, serum or plasma

Haematology

- Haematocrit
- Haemoglobin
  - Reticulocyte Count (reflex test if Hb outside normal range)
- Red Blood Cells (RBC) / Erythrocytes
- WBC / Leukocytes
- Platelet Count / Thrombocytes
- Differential Automatic (relative and absolute count):
  Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes

Table 5.2.3: 1 Safety laboratory parameters – whole blood, serum or plasma (continued)

Clinical chemistry

- Albumin
- Alkaline phosphatase
  - γ-GT (gamma-glutamyl transferase)
    (reflex test triggered by elevated alkaline phosphatase on two sequential measures)
- ALT (alanine aminotransaminase, SGPT)
- AST (aspartate aminotransaminase, SGOT)
- Bicarbonate
- Bilirubin total, fractionated if increased
- Calcium
- Chloride
- Creatinine
- Creatine kinase (CK)
- CK-MB, troponin (reflex tests if CK is elevated)
- Cystatin C
- hsCRP
- Lactate dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- Urea (BUN)
- Uric acid

Lipids (only selected visits)

- Cholesterol (total)
- HDL cholesterol
- Calculated LDL cholesterol
- Triglycerides (reflex test for direct LDL cholesterol triggered if triglycerides are > 400 mg/dl or 4.52 mmol/l)

Table 5.2.3: 2 Safety laboratory parameters - urine

Urinalysis

Semi quantitative (dipstick)
- Nitrite*
- Protein
- Ketone
- Urine pH
- Leukocyte Esterase (for WBC)*

Quantitative
- Albumin
- Creatinine

Microscopic analysis
-will be performed as reflex test if any of semi-quantitative tests/dipstick is abnormal:
- Urine RBC/Erythrocyte
- Urine WBC/Leukocytes*
- Urine sediment microscopic examination
- Urine culture:
  Reflex test triggered by positive Leucocyte Esterase (for WBC) and/or nitrite in the semi quantitative test/dipstick

* Nitrite and leucocyte esterase (for WBC) will be determined both locally on site (not recorded in CRF) and via central lab. A positive result at site triggers the sampling of mid-stream urine for urine culture.

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

The GFR will be derived from serum creatinine values based on the CKD-EPI formula as expressed below:

Black Female
If serum creatinine <= 0.7

$$eGFR = 166 \times (\text{serum creatinine} /0.7)^{-0.329} \times 0.993^{Age}$$

If serum creatinine > 0.7

$$eGFR = 166 \times (\text{serum creatinine} /0.7)^{-1.209} \times 0.993^{Age}$$

Black male
If serum creatinine <= 0.9

$$eGFR = 163 \times (\text{serum creatinine} /0.9)^{-0.411} \times 0.993^{Age}$$

If serum creatinine > 0.9

$$eGFR = 163 \times (\text{serum creatinine} /0.9)^{-1.209} \times 0.993^{Age}$$

where serum creatinine is measured in mg/dl.

Renal function impairment will be classified in the following way:

- eGFR ≥ 120 ml/min/1.73m^2;
- eGFR 120-60 ml/min/1.73m^2;
- eGFR ≤ 60 ml/min/1.73m^2

These 3 classes of renal impairment will be the basis for stratification at randomisation [redacted]

Empagliflozin influences hepatic glucose output and hepatic triglyceride mobilization which could theoretically reduce fat stores in the liver. This may improve liver function and reduce the burden of NAFLD. NAFLD fibrosis score will be used to assess changes in the status of NAFLD.

NAFLD fibrosis score will be calculated in-house:

> NAFLD Fibrosis Score = -1.675 + 0.037 x age (yr) + 0.094 x BMI (kg/m^2) + 1.13 x IFG/diabetes mellitus (yes = 1, no = 0) + 0.99 x AST/ALT ratio - 0.013 x platelet (x109/L) - 0.66 x albumin (g/dl)

Pregnancy testing (urine) will be performed in female patients of child-bearing potential only according to the time points indicated in the Flow Chart.

Criteria for hypoglycaemic events

Every episode of plasma glucose ≤ 70 mg/dl (3.9 mmol/l) should be documented in the eCRF with the respective time and date of occurrence. Any hypoglycemia with glucose values < 54 mg/dl (< 3.0 mmol/l) and all symptomatic and severe hypoglycemias should be documented as an AE "hypoglycaemic event".

For the analysis, all hypoglycemias will be classified according to the following criteria:

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

Follow-up on suspicion for urinary tract infections

Patients having a history of chronic/recurrent UTI or genital infection or an acute episode of UTI or genital infection at screening will be identified and this condition has to be documented as medical history or baseline condition in the eCRF, respectively.

For documentation of acute urinary tract infections during trial conduct, the following measures have to be taken:

- In any case of suspected UTI (symptomatic or asymptomatic) a urine culture sample has to be taken and sent to central lab for confirmation of the diagnosis.

- To be able to identify asymptomatic UTIs immediately, a dipstick-test (leucocyte esterase [for WBC] and Nitrite) will be performed at the site at each safety visit with urinalysis. In case of a positive result at site, a urine culture sample has to be taken and sent to central lab for confirmation of the diagnosis. A negative urine dipstick does not require a midstream urine culture sample to be sent to central lab, unless UTI is suspected.

- If there is negative dipstick at site, but the dipstick performed at the central lab is positive, a mid-stream urine sample should be collected from the patient only if the investigator has a suspicion of a UTI.

5.2.4 Electrocardiogram

At start of run-in and end of treatment, a complete physical examination will be performed by the investigator or qualified designee (see Flow Chart). Documentation of, and findings from the physical examination, must be part of the source documents available at the site.

Printed paper traces from 12-lead ECGs (I, II, III ,aVR, aVL, aVF, V1-V6) will be collected at screening. ECG traces on thermopaper should be copied to normal paper to avoid fading. In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischemia), an additional ECG will be recorded. All ECGs will be evaluated, (signed, dated and commented upon) by the treating physician/investigator and stored locally. Any clinically relevant changes in the ECG will be reported as AEs and followed up and/or treated locally until normal or stable condition. Any ECG abnormalities will be carefully monitored and if necessary the patient will be removed from the trial and medically treated.

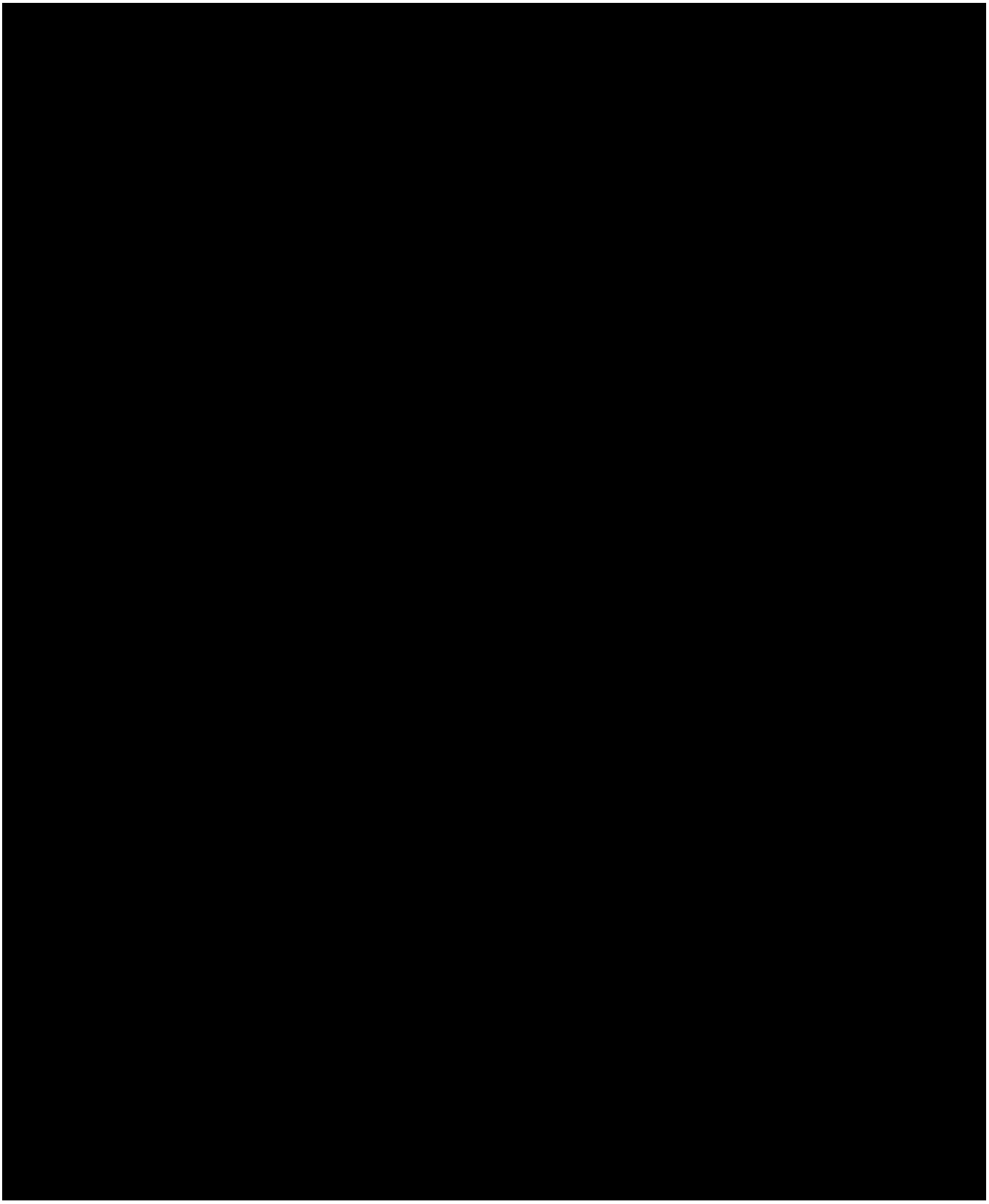
5.2.5 Assessment of other safety parameters

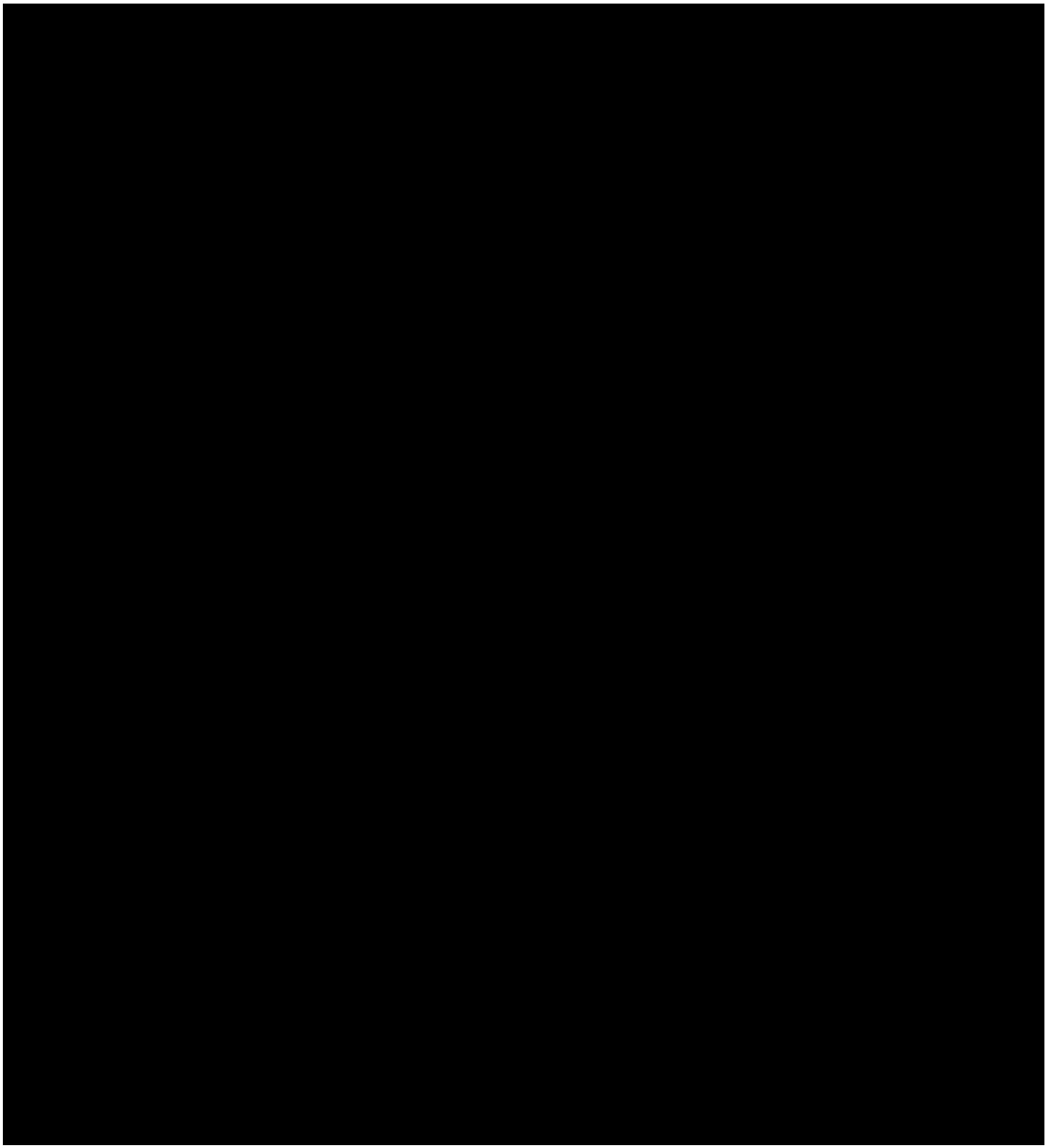
All patients will be provided with HBGM equipment and supplies for use at home during the 2-week Run-In Period. Instruction on the proper use of the HBGM will be provided by the study staff. The patient will be asked to record the results of the HBGM test on a HBGM Testing Log that will be included in the patients source document file. Only in the case of linked adverse events or of hypoglycemia, the single HBGM values will be recorded in the CRF. The respective procedure for illiterate patients (if included) is described in the Appendix 10.1. Even though review of the HBGM log is required, electronic review of the

glucometer is not required. If a patient forgets to return their Log, they should be reminded to record HBGM values on the Log and return it at the next visit.

During Run-In and Follow-up, HBGM testing should be performed once daily in the fasted state and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycemia. If during Run-in, results of a HBGM test reveal blood glucose of >270 mg/dl (>15.0 mmol/L) after an overnight fast the patient should contact the site. Patient should also eat or drink something immediately and contact the site in the event that blood glucose level drops below 54 mg/dl (3.0 mmol/l). The investigator should then decide about start of the randomised period or further patient participation in the trial based on fasted plasma glucose determinations according to the inclusion and exclusion criteria as outlined in Section 3.3.

During the randomised treatment period, HBGM testing should be performed once weekly (more frequently if required by local authorities) and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycemia. If during this period, results of a fasting HBGM test reveal blood glucose levels meeting rescue criteria (see Section 4.2.1), the patient should contact the site and the investigator should follow the instructions given in Section 4.2.1.





6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits with the exception of ABPM visits should be routinely scheduled in the morning, at approximately the same time of day (07:00 AM to 11:00 AM). For ABPM visits, patients should arrive at approximately half an hour prior to medication intake to allow additional time for ABPM procedures, so that dosing of medication occurs as close as possible to patient daily dosing time. If a patient mistakenly takes trial medication on the morning of a visit before attending the clinic (excluding visits starting before randomisation) or comes in non-fasted where a fasting condition is required (all visits except screening), the visit should be rescheduled for another day as soon as possible reminding the patient about the expected conditions. The rescheduled visit must take place in a short enough time-frame so that the patient has sufficient trial medication available. Fasting visits should take place at a minimum of 10 hours after the end of the patient's last meal.

Patients who are fasting (e.g. for religious or cultural reasons) should be instructed to perform HBGM tests regularly and to contact the site in case of signs/symptoms or values suggestive hypoglycemia.

All patients are to adhere to the visit schedule as specified in the Flow Chart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. The trial medication packs contain sufficient medication to allow for these time windows.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart. Additional details regarding visit procedures are provided below. All visits, except Visit 1, must be performed in fasted state (10 hours without food and only water).

6.2.1 Screening and run-in period

Visit 1 (Screening)

- The screening visit is the only visit in this study that does not need to be done fasting.
- No trial procedures should be done unless the patient has consented to taking part in the trial. Patient identification numbers are available in the RDC system. If a patient is re-screened, a new patient identification number should be assigned.
- Once they have consented, the patient is considered to be enrolled in the trial and to have started screening. The patient should be recorded on the enrolment log and registered in the IRT system as a screened patient.
- BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, please see Appendix 10.3.
- Once Visit 1 procedures are complete and laboratory results are received, inclusion/exclusion criteria must be reviewed. If the patient meets inclusion/exclusion criteria, the patient should be contacted to schedule next visit. If the patient does not meet

inclusion/exclusion criteria the patient must be recorded in CRFs and registered in the IRT system as a Screen failure.

Visit 2.1 (Run-in period)

- From this visit onwards, patients should be fasting (no food or drinks, water only for at least 10 hours) prior to each visit.
- Inclusion/exclusion criteria must be reviewed at this visit
- BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, please see Appendix 10.3.
- Collection of urine and blood for laboratory testing must be performed prior to administration of study medication.
- Provide patient with diet and exercise counseling. Patients should be given a food log to be completed for three consecutive days prior to Visit 3 as indicated in the Flow Chart.
- Provide HBGM equipment/supplies and instruct patient on the correct use of HBGM.
- Instruct patient to perform a HBGM once daily during the run-in period in the fasted state and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper or hypoglycemia. Instruct patient to contact site immediately if blood glucose reaches the limit described in Section 4.2.1.
- Once all visit procedures are conducted, contact the IRT system to obtain run-in medication kit number and dispense the medication to the patient.
- Administer dose of medication.
- Remind the patient to arrive half an hour earlier for the next scheduled visit (Visit 2.2).
- Instruct patients NOT to take study medication on the morning of the next trial visit.

Visit 2.2 (Baseline ABPM visit)

- ABPM should be done during the run-in period within 7 days prior to Visit 3.
- The ABPM device is attached to the patient and proper operation of the device should be ensured.
- Record the time the medication was administered and the time the monitor was prompted to take the Beginning of Test reading.
- Instruct the patient on the proper use of the ABPM device . The monitor should remain on the patient for at least 24 hours. The patient should be instructed to not remove the monitor and schedule a visit for the next day for removal of the monitor if possible. Patient should arrive early again for the visit on the next day.
- The next day when the patient returns to the clinic (within 23:30-24 hours of the beginning of the test), prompt the monitor to take a Conclusion of Test reading. If an invalid reading occurs for the Conclusion of Test reading, continue to trigger a manual reading until a valid reading is registered. The monitor will then be removed and the time of the Conclusion of Test will be recorded.
- Once the data from the session is downloaded, review the QC results to determine if the session was technically successful. Remember to record the 24-hour mean SBP displayed

at the bottom of the QC results. The 24-hour mean SBP at this visit together with a successful session determines eligibility for randomization.

- If the first ABPM attempt was unsuccessful (failed QC and/or the mean ABPM SBP is outside the required range), repeat it within 2 days. Patients having two unsuccessful baseline ABPM sessions should not be randomised and must be discontinued.
- If ABPM was successful**,** the patient is eligible for randomization and procedures for Visit 3 can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken. If conducted on the same day, procedures for Visit 3 should be done prior to administrating study medication.
- Allow the patient to rest for at least 15 minutes after the monitor is removed. Then take a seated blood pressure measurement. Record the time of this measurement. This should be done prior to administering study medication.
- For further instructions for ABPM measurements, please see Section 5.1.2**.**
- Instruct patients NOT to take study medication on the morning of the next trial visit.

Patients who fail the run-in period following Visit 2 procedures should be registered as a screen failure in the IRT system.

6.2.2 Treatment period

The treatment period is from Visit 3 to Visit 7.2. Patients will be dispensed medication at Visits 3, 4, and 5.2. Patients will receive a new kit number through the IRT system on each occasion. Assessments should be performed as mentioned in the Flow Chart and the respective protocol sections.

Throughout the treatment period, BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, please see Appendix 10.3.

Visit 3 (Randomisation visit)

- Inclusion/exclusion criteria must be reviewed prior to randomization
- BP measurement and orthostatic blood pressure test should always be done before taking any blood sample.
- Collection of urine and blood for laboratory testing must be performed prior to administration of study medication.
- Collect returned run-in medication.
- Collect blood sample for PG evaluation after obtaining separate informed consent. PG sample should be collected for randomised patients only.
- Patients should be reminded about the importance of following the agreed diet and exercise plan. Patients should be given a food log to be completed for three consecutive days prior to Visit 4 as indicated in the Flow Chart.
- Provide HBGM equipment/supplies and instruct patient on the correct use of HBGM.

- Instruct patient to perform a HBGM once weekly during the treatment period (more frequently if required by local authorities) in the fasted state and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper or hypoglycemia. Instruct patient to contact site immediately if blood glucose reaches the limit described in Section 4.2.1.
- Once all visit procedures are conducted, contact the IRT system to randomise the patient and obtain medication kit numbers and dispense the medication to the patient.
- Administration first dose of study medication.
- Instruct patients NOT to take study medication on the morning of the next trial visit.

Visit 4

- BP should always be measured before taking any blood samples.
- Collection of urine and blood for laboratory testing must be performed prior to administration of study medication at each visit.
- Collect returned medication.
- New medication kit must be dispensed according to the Flow Chart, and the IRT system must be contacted to obtain medication kit numbers to be dispensed.
- Patients should be reminded about the importance of following the agreed diet and exercise plan. Patients should be given a food log to be completed for three consecutive days prior to Visit 5.2 as indicated in the Flow Chart.
- Provide HBGM equipment/supplies and instruct patient on the correct use of HBGM.
- Instruct patient to perform a HBGM once weekly during the treatment period (more frequently if required by local authorities) in the fasted state and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper or hypoglycemia. Instruct patient to contact site immediately if blood glucose reaches the limit described in Section 4.2.1..
- Once all visit procedures are conducted, contact the IRT system to obtain medication kit numbers (Dose escalation kit) and dispense the medication to the patient. Administer dose of study medication.
- Remind the patient to arrive half an hour earlier for the next scheduled visit (Visit 5.1).
- Instruct patients NOT to take study medication on the morning of the next trial visit.

Visit 5.1 (Week 12 ABPM visit)

- ABPM should be done within 7 to 2 days prior to Visit 5.2.
- Attach ABPM device to the patient and initiate the test readings to ensure the monitor is operating properly.
- Administer study medication on the morning of the study visit after the test readings have confirmed that the device is operating properly. Record the time the medication was administered and the time the monitor was prompted to take the Beginning of Test reading.
- Instruct the patient on the proper use of the monitor. The ABPM device should remain on the patient for at least 24 hours. The patient should be instructed not to remove the

monitor and schedule a visit for the next day for removal of the monitor. Patient should arrive early again for the visit on the next day.

- The next day when the patient returns to the clinic (within 23:30-24 hours of the beginning of the test), prompt the monitor to take a Conclusion of Test reading. If an invalid reading occurs for the Conclusion of Test reading, continue to trigger a manual reading until a valid reading is registered. The monitor will then be removed and the time of the Conclusion of Test will be recorded.
- If ABPM was successful, procedures for Visit 5.2 can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken. If conducted on the same day, procedures for Visit 5.2 should be done prior to administrating study medication.
- If the first ABPM attempt was unsuccessful (failed QC), a repeat reading should be taken within 2 days. Patient having two technically unsuccessful ABPM sessions may continue with Visit 5.2. Procedures for Visit 5.2 can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken.
- Allow the patient to rest for at least 15 minutes after the monitor is removed. Then take a seated blood pressure measurement. Record the time of this measurement. This should be done prior to administering study medication.
- Administer dose of study medication.
- For further instructions for ABPM measurements, please see Section 5.1.2.
- Instruct patients NOT to take study medication on the morning of the next trial visit.

Visit 5.2

- BP and orthostatic blood pressure test should always be done before taking any blood samples.
- Collection of urine and blood for laboratory testing must be performed prior to administration of study medication at each visit.
- PK trough sample should be collected within 30 minutes prior to intake of study medication.
- Collect returned medication.
- New medication kit must be dispensed according to the Flow Chart, and the IRT system must be contacted to obtain medication kit numbers to be dispensed.
- Patients should be reminded about the importance of following the agreed diet and exercise plan. Patients should be given a food log to be completed for three consecutive days prior to Visit 7.2 as indicated in the Flow Chart.
- Provide HBGM equipment/supplies and instruct patient on the correct use of HBGM.
- Instruct patient to perform a HBGM once weekly (more frequently if required by local authorities) in the fasted state and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper or hypoglycemia. Instruct patient to contact site immediately if blood glucose reaches the limit described in Section 4.2.1.
- Once all visit procedures are conducted, contact the IRT system to obtain medication kit numbers (Dose escalation kit) and dispense the medication to the patient. Administer dose of study medication.

- Instruct patients NOT to take study medication on the morning of the next trial visit.

Visit 6 (Phone visit)

- Remind the patient to arrive half an hour earlier for the next scheduled visit (Visit 7.1).
- Instruct patients NOT to take study medication on the morning of the next trial visit.

Visit 7.1

- ABPM should be done within 7 to 2 days prior to visit 7.2.
- Attach ABPM device to the patient and initiate the test readings to ensure the device is operating properly.
- Administer study medication on the morning of the study visit after the test readings have confirmed that the device is operating properly. Record the time the medication was administered and the time the monitor was prompted to take the Beginning of Test reading.
- The ABPM device should remain on the patient for at least 24 hours.
- Instruct the patient on the proper use of the monitor. The patient should be instructed not to remove the monitor and schedule a visit for the next day for it removal. Patient should arrive early again for the visit on the next day.
- The next day when the patient returns to the clinic (within 23:30-24 hours of the beginning of the test), prompt the monitor to take a Conclusion of Test reading. If an invalid reading occurs for the Conclusion of Test reading, continue to trigger a manual reading until a valid reading is registered. The device will then be removed and the time of the Conclusion of Test will be recorded.
- If ABPM was successful, procedures for Visit 7.2 can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken. If done on the same day, procedures for Visit 7.2 should be done prior to administrating study medication.
- If the first ABPM attempt was unsuccessful (failed QC), a repeat reading should be taken within 2 days. Patient having two technically unsuccessful ABPM sessions may continue with Visit 7.2. Procedures for Visit 7.2 can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken.
- Allow the patient to rest for at least 15 minutes after the monitor is removed. Then take a seated blood pressure measurement. Record the time of this measurement. This should be done prior to administering study medication.
- Administer dose of study medication.
- For further instructions for ABPM measurements, please see Section 5.1.2.
- Instruct patients NOT to take study medication on the morning of the next trial visit.

Visit 7.2 (end of treatment)

- BP measurement and orthostatic blood pressure test should always be done before taking any blood samples.

- Collection of urine and blood for laboratory testing.
- PK trough sample should be collected.
- Collect returned medication.
- Patients should be reminded about the importance of following the agreed diet and exercise plan.
- Provide HBGM equipment/supplies and instruct patient on the correct use of HBGM.
- Instruct patient to perform a HBGM test at least once daily during the follow up period. Instruct patient to immediately perform a blood glucose test if they experience signs/symptoms of hypo- or hyperglycemia. Instruct patient to contact site immediately if blood glucose reaches limit described in Section 4.2.1.
- Visit 7.2 is the last visit of the treatment period after ABPM is done. No study medication is administered at this visit.
- Instruct patient to continue to take the current therapy as usual. Additional antidiabetic medication can be started after the follow-up visit, in case there is no medical need for rescue medication before that.

6.2.3 End of trial and follow-up period

For all patients who successfully complete the study according to the protocol a follow-up visit (Visit 8) with the patient should be done by the investigator at the end of the follow-up period of 14 days.

Visit 8 (follow-up visit)

- Vital signs
- Body weight measurement
- BP measurement and orthostatic blood pressure test should always be done before taking any blood samples.
- Collection of urine and blood for laboratory testing.
- Home blood glucose monitoring
- Documentation of any adverse events.
- Documentation of concomitant therapies

Patients discontinuing trial medication early from the trial

In general patients should be encouraged to re-start study medication in case of temporary treatment interruptions. If the duration of interruption is more than 7 days, this should be recorded in the “Study Medication Temporary Discontinued/re-started" eCRF.

For the analysis of this trial it is absolutely crucial that all planned assessments are done as planned, even if patients discontinue trial treatment. Patients who discontinue treatment prematurely and who do not withdraw their informed consent must therefore be followed up for the intended regular treatment period. All assessments related to the primary and secondary endpoints must be performed as if the patient would have remained on treatment.

For patients who stop study medication permanently prior to completion of 24 weeks of treatment and who are willing to be followed up, the following should be performed whenever possible:

- Premature treatment discontinuation (PTD) visit should be performed within 7 days of last intake of study drug or as soon as possible including all examinations and assessments that are part of the Visit 7.2. If the PTD visit occurs within the time window of a scheduled visit, the PTD visit will replace the scheduled visit.

- Subsequently, a follow-up visit (Visit 8 procedures) should be conducted within 14 days of the PTD visit that replaces the next visit according to the visit schedule.

- Thereafter, patients would be followed up according to the visit schedule.

- Visit 7.2 will be the last visit for these patients. Follow-up Visit 8 does not need to be performed.

The last per study contact should be at Visit 7.2. If determined by investigator as necessary for patient safety, new antidiabetic medication regimen can be started immediately after discontinuation and must be recorded in eCRFs.

If a patient is not able to attend a study visit, the study staff should contact him/her (or someone designated – e.g. family member or personal physician) to inquire about medical information pertaining to adverse events, particularly primary and key secondary outcome events, and/or mortality, until the end of the study. Alternatively, data should be collected from medical records.

For patients who discontinue treatment prematurely but do not wish to follow the visit schedule, the following should be performed whenever possible:

- Visit 7.2 should be performed within 7 days of last intake of study drug.

- Subsequently, a follow-up visit (Visit 8 procedures) should be conducted within 14 days of the premature discontinuation visit.

If this patient withdraws consent, then the last per study contact will be Visit 8.

Patients who withdraw consent

Patients who withdraw consent during the trial should perform Visit 7.2 within 7 days of last intake of study drug. A follow-up visit (Visit 8 procedures) should be conducted within 14 days of the premature discontinuation for their safety.

The following procedures should be performed at Visit 8.

- Vital signs

- Body weight measurement
- BP measurement and orthostatic blood pressure test should always be done before taking any blood samples.
- Collection of blood and urine samples for safety laboratory evaluation.
- Documentation of any adverse events.
- Documentation of concomitant therapies

A patient who reverses the decision to withdraw consent should be re-consented with the latest version and will continue the visit schedule according to the date of randomisation.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a multi-centre, multi-national, randomised, parallel-group, double-blind, placebo-controlled trial to investigate the effect of (10 mg/25 mg) of empagliflozin and placebo after 24 weeks treatment on glucose control, BP and body weight in hypertensive black/African American patients with T2DM. The randomisation will be performed stratified by screening HbA1c values (<8.5%, ≥8.5%), renal function at screening (eGFR ≥120 ml/min/1.73m^2,eGFR 120-60ml/min/1.73m^2, eGFR ≤60 ml/min/1.73m^2) and pretreatment with Metformin at screening (yes/no).

Based on experiences with the primary endpoints in other trials and based on literature data, the HbA1c change from baseline, and change from baseline in BP are regarded as normally distributed. Therefore, a restricted maximum likelihood estimation based on mixed-effect model for repeated measures analysis or an analysis of covariance **(**ANCOVA**)** approach can be used.

With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to administration of any randomised study medication.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Primary Hypotheses

The confirmatory analyses will compare empagliflozin to placebo. The following hierarchical multiple testing procedure will be used to evaluate superiority for the primary endpoint followed by the evaluation of superiority of the key secondary endpoints, while maintaining the overall probability of a type I error at 0.05. The primary endpoint of change from baseline to 24 weeks in HbA1c along with the key secondary endpoints change from baseline in mean 24-hour ambulatory SBP at 12 weeks of treatment, change from baseline in mean trough ambulatory SBP at 12 weeks of treatment, change from baseline in body weight in kg at week 24 of treatment, and change from baseline in trough seated SBP at 12 weeks of treatment, will be tested in the following pre-specified hierarchical sequence, to address issues of multiplicity. Proceeding onto the next step in the sequence relies upon rejecting H_0 in the previous step, a ‘success’. Each step will only be considered confirmatory if all previous steps were ‘successful’. If any of the previous steps were not successful, the tests of the subsequent steps have to be interpreted in an exploratory sense. This procedure allows testing each step at the two-sided alpha-level of 5%:

1. change from baseline in HbA1c at 24 weeks of treatment
2. change from baseline in mean 24-hour ambulatory SBP at 12 weeks of treatment
3. change from baseline in mean trough ambulatory SBP at 12 weeks of treatment
4. change from baseline in body weight in kg at week 24 of treatment
5. change from baseline in trough seated SBP at 12 weeks of treatment

At each of the 5 stages of the hierarchical sequence the hypotheses will be tested as described below:

$H_{0,1}$: No difference in mean endpoint between empagliflozin and placebo

$H_{1,1}$: A difference in mean endpoint between empagliflozin and placebo

7.3 PLANNED ANALYSES

The statistical analysis will be based on the following populations.

Treated Set

The treated set will consist of all patients who were randomised and treated with at least one dose of trial medication.

Full Analysis Set

The full analysis set (FAS) will consist of all randomised patients who were treated with at least one dose of study drug and had a baseline and at least one on-treatment HbA1c measurement

Per Protocol Set

The per-protocol set (PPS) will consist of all randomised patients who are part of the FAS but who do not have any important protocol violations (IPV) leading to exclusion. Further details on the definition of the PPS and the definition of IPVs will be provided in the TSAP.

7.3.1 Primary analyses

Mean changes from baseline for HbA1c up to 24 weeks of treatment will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach on the FAS data set. Patients will be analysed according to the treatment group they are randomised to. Analyses will include the fixed, categorical effects of treatment, pre-treatment with Metformin at screening, renal function at baseline, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline HbA1c and baseline HbA1c -by-visit interaction. An unstructured (co)variance structure will be used to model the within patient measurements. If the model first fails to converge using an unstructured (co)variance structure, then a hierarchical approach is applied until a (co)variance structure is obtained where the model converges. Therefore the following (co)variance structures are tested according to the pre-specified order: (1) unstructured, (2) Toeplitz, (3) variance components, (4) compound symmetry. As soon as one model converges this will be the final model used, therefore no further testing of subsequent (co)variance structures is required. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95%

confidence intervals). The primary treatment comparisons will be the contrast between treatments at the endpoint visit at 24 weeks of treatment.

For the key secondary endpoint change from baseline in mean 24-hour ambulatory SBP at 12 weeks of treatment an ANCOVA comparing the change from baseline in mean 24-hour ambulatory SBP at 12 weeks of treatment will be used as primary analysis on the FAS using last observation carried forward **(**LOCF**)** for missing ABPM assessments.

The statistical model will be the following:

change from baseline in 24-hour ambulatory SBP at 12 weeks =

overall mean + baseline 24-hour ambulatory SBP + treatment + pre-treatment with Metformin + renal function + HbA1c + random error

'Treatment', 'pre-treatment with Metformin', and 'renal function' are fixed classification effects and 'baseline 24-hour ambulatory SBP' and 'HbA1c' are fixed covariates. The random error is assumed to be normally distributed with mean 0 and unknown variance σ^2.

A similar ANCOVA model~~s~~ on the FAS using LOCF for missing ABPM assessments will be performed for the change from baseline in mean trough ambulatory SBP at 12 weeks of treatment just replacing the relevant key secondary endpoint**'s** baseline and 12 week assessments in the model.

For the key secondary endpoints change from baseline in body weight in kg at week 24 of treatment and change from baseline in trough seated SBP at 12 weeks of treatment a restricted maximum likelihood estimation based on mixed-effect model for repeated measures for mean changes from baseline will be used on the FAS observed case [redacted] analysis set to obtain adjusted means for the treatment effects. These model**s** will include the same discrete fixed effects as the model for the primary endpoint and baseline HbA1c as a continuous fixed effect. Furthermore these models will include the interaction between visit and treatment, and an interaction between visit and baseline measurement of the key secondary endpoint as well as the corresponding baseline measurements of the key secondary endpoint as continuous fixed effect. The covariance approach for this model will be the same as for the primary endpoint. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The primary treatment comparisons will be the contrast between treatments at the 12 week visit for trough seated SBP and 24 week visit for the body weight and significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

All analyses will be implemented using SAS®.

7.3.2 Secondary analyses

[redacted]

The primary endpoint analysis method as detailed in Section 7.3.1 will be repeated for the PPS.

The primary endpoint will as well be analysed using an ANCOVA model in the FAS. The model will include randomised treatment, pre-treatment with Metformin, and renal function at baseline as categorical fixed effects, and baseline HbA1c as continuous covariate. Missing HbA1c data will be imputed using the LOCF approach.

The term "baseline HbA1c" refers to the last assessment prior to the administration of any randomised study medication.

The model for the primary endpoint is as follows:

HbA1c change from baseline at week 24 = overall mean

+ HbA1c at baseline
+ treatment
+ renal function
+ pretreatment with Metformin
+ random error

This model includes effects accounting for the following sources of variation: 'HbA1c at baseline', 'renal function' at baseline, 'pretreatment with Metformin' at screening, and 'treatment'. 'Treatment', 'renal function', and 'pretreatment with Metformin' are fixed classification effects and 'HbA1c baseline' is a linear covariate. The random error is assumed to be normally distributed with mean 0 and variance σ^2. This secondary analysis will be performed on the FAS with treatment assignment as randomised. Missing data will be imputed using the LOCF approach.

For the key secondary endpoints change from baseline in body weight in kg at week 24 of treatment and change from baseline in trough seated SBP at 12 weeks as well an ANCOVA model will be calculated on the FAS. The model for the change from baseline includes 'treatment', 'renal function' at baseline, 'pretreatment with Metformin' at screening as fixed categorical effects, and HbA1c at baseline, and baseline trough seated SBP or baseline body weight in kg respectively, as linear covariate. Missing data will be imputed using the LOCF approach.

The other continuous secondary endpoints as listed in Section 5.1.1 will be analysed on the FAS as follows:

The continuous secondary endpoints will be analysed using similar models as used for the primary analyses for the key secondary endpoints. [redacted]

[redacted]

7.3.3 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of ≤ 7 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. The REP is defined as ≤ 7 days following last intake of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values. Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.4 Interim analyses

No interim analyses are planned.

[redacted]

7.3.6 Pharmacodynamic analyses

Not applicable.

7.3.7 Pharmacogenomic analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

Mixed Model Repeated Measures (MMRM) models and ANCOVA models including a LOCF imputation of missing data are used like discussed above in Section 7.3.1 and Section 7.3.2. The mixed effect model
will handle missing data based on a likelihood method under the "missing at random assumption". Efficacy data will be censored at the date of first intake of antidiabetic rescue medication for all analyses, i.e., will be set to missing, if not explicitly stated otherwise.

Blood pressure data will additionally be censored from the day of change in antihypertensive therapy.

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

Further details will be provided in the TSAP.

7.5 RANDOMISATION

The trial will be performed as a double-blind design with respect to study medication. Patients will be randomised to the two study treatments in a 1:1 ratio. The randomisation will be performed in blocks. The block size will be reported in the Clinical Trial Report (CTR). The randomisation will be stratified by the following factors:

- screening HbA1c value (<8.5%, ≥8.5%)
- renal function at screening (eGFR ≥120 ml/min/1.73m^2,eGFR 120-60ml/min/1.73m^2, eGFR≤ 60 ml/min/1.73m^2)
- pretreatment with Metformin at screening (yes/no)

The randomisation of patients to the treatment groups will be performed via an IRT system. BI will arrange for the randomisation as well as packaging and labelling of study medication. The randomisation list will be generated using a validated system, which involves a pseudorandom number generator and a supplied seed number so that the resulting allocation of medication numbers to treatment is both reproducible and non-predictable.

7.6 DETERMINATION OF SAMPLE SIZE

In order to ensure that each comparisons of empagliflozin and placebo with respect to HbA1c, mean systolic ABPM blood pressure and body weight have a power of at least 80%, 64 patients plus an additional 20% drop-out rate, resulting in 77 patients per arm are required per treatment group. This is derived from the assumption that the difference in change from baseline compared to placebo in 24-hour SBP is 5 mmHg with a standard deviation of 10

mmHg (resulting in a power of 80%), and the difference in body weight is 2 kg with a standard deviation of 2.3kg (resulting in a power of 99%). With this sample size the power to detect a 0.6% difference in HbA1c with a standard deviation of 1.1% will be >85%.

The planned treatment group sizes are considered as sufficient for the confirmatory evaluation of efficacy and the descriptive assessment for safety, tolerability and PK.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

The respective procedure for illiterate patients (if included) is described in the Appendix 10.1.

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

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

8.2 DATA QUALITY ASSURANCE

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

- central lab analysis of efficacy endpoints, biomarkers and safety lab
- central IRT system for stratification, randomisation and kit allocation at each visit
- Central hepatic adjudication assessment

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan available in TMF.

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

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via RDC. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the empagliflozin this is: the current version of the IB c01678844. The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for matching placebo.

8.4.2 Expedited reporting to health authorities

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R05-0939 Wright EM, Turk E. The sodium/glucose cotransport family SLC5. Pfluegers Arch 447 (5), 510 - 518 (2004).

R14-0310 James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507-20

R14-5435 American Diabetes Association. Hyperglycemic crises in diabetes. Diabetes Care 27 (Suppl 1), S94 - S102 (2004)

9.2 UNPUBLISHED REFERENCES

c01678844 BI 10773 Investigator's Brochure.

10. APPENDICES

10.1 INCLUSION OF ILLITERATE PATIENTS

10.1.1 Home blood glucose monitoring

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

- At Visit 2.1, the person assisting the patient with this process (e.g. the patient's caregiver or relative) will attend the clinic together with the patient.

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

- The site staff should then train both the patient and above-mentioned individual with respect to the correct use of the HBGM equipment during each period of the trial. This will include the use of the glucose meter itself and the test strips, lancet device and control solution(s).

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

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

10.1.2 Patient information and informed consent (including pharmacogenetics)

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

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

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

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

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

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

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

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

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

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

- The same process as outlined above will be followed for obtaining consent for the optional pharmacogenetic aspect of the trial.

10.1.3 Food intake diary recording

For illiterate patients, the recording in the food intake diary will be assisted by the person who attended the clinic with the patient and who was also briefed by the site staff on how to complete the food intake diary.

10.2 BLOOD PRESSURE MEASUREMENT PROCEDURE

Blood pressure measurements are to be made per the Flow Chart.

The preferred method for blood pressure measurement is standard mercury sphygmomanometry. If a standard mercury sphygmomanometer is not available, it is suggested that the investigator use http://www.dableducational.org to determine if the device is recommended.

Initially, blood pressure should be taken 3 times in both arms. If the mean pressures differ by more than 10 mmHg, the arm with the higher pressure (systolic or – if needed, diastolic)

should be used for subsequent measurements. If the pressures are ≤10mmHg, the non-dominant arm should be used for subsequent measurements.

Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The same method and type of device should be used throughout the trial, for a given patient. All blood pressure measurements should be performed approximately at the same time, i.e. in the morning prior to any blood being drawn or any study medication being taken.

After patients have rested quietly, in the seated position for two minutes, three blood pressure measurements will be taken approximately two minutes apart. The seated pulse rate will be taken during the two-minute interval between the second and third blood pressure reading.

Blood pressure measurements should be recorded to the nearest 2 mmHg only when measured with a manual sphygmomanometer; when digital devices are used the value from the device should be recorded to the nearest 1 mmHg and the pulse rate from the second measurement should be used.

For calculation of mean values, decimal places should be rounded to integers (e.g. a DBP of 94.5 would be rounded to 95 mmHg and a DBP of 109.4 would be rounded to 109 mmHg).

10.3 ORTHOSTATIC BLOOD PRESSURE MEASUREMENT PROCEDURE

Orthostatic blood pressure measurements should be performed on the same arm as BP and ABPM and, if possible, by the same person. The same method and device must be used throughout the trial, for a given patient. All blood pressure measurements should be performed approximately at the same time, i.e. in the morning prior to any blood being drawn or any study medication being taken.

Procedure for Orthostatic Blood pressure:

1. Obtain the patient's pulse rate and BP while supine for 5 minutes
2. Record the readings
3. Have the patient stand.
4. Obtain the patient's pulse rate and BP every minute during the first 3 minutes while standing (1, 2 and 3 minutes)
5. Record the readings

If any one of the three pulse rate**s** has increased by 20 BPM from the supine pulse rate or any one of the three systolic blood pressures has decreased by 20 mmHg from supine SBP, or any one of the three DBPs has decreased by 10 mmHg from supine DBP**,** orthostatic BP test is considered positive.

If the patient is unable to stand, orthostatic BP test may be taken while the patient is sitting with feet dangling. If positive orthostatic BP test changes occur while sitting, DO NOT continue in the standing position.

Document the time and vital signs for supine and standing positions after 1, 2 and 3 minutes.

10.4 CLINICAL EVALUATION OF LIVER INJURY

10.4.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 , AESI, and hepatic SAEs are to be further evaluated using the following procedures:

10.4.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by local laboratory and results are made available to the investigator and to BI as soon as possible. If in such a case ALT and/or AST $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN or an isolated elevation of AST and/or ALT $\geq$ 5 fold ULN (without an elevation of total bilirubin $\geq$ 2 fold ULN) are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the “DILI checklist” provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the “DILI checklist” provided in the ISF;

and report these via the CRF and/or the “DILI checklist”.

The following laboratory tests should be performed:

Clinical chemistry
alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology
Hepatitis A (Anti-IgM, Hep A total), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Hep D Antibody), Hepatitis E (Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody

Hormones, tumor marker
TSH

Haematology
Thrombocytes, eosinophils

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

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and GCP.

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1 CHANGES

Number of global amendment		1.0
Date of CTP revision		*16Dec2014*
EudraCT number		*N/A*
BI Trial number		*1245.29*
BI Investigational Product(s)		*empagliflozin*
Title of protocol		A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus
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	1	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		1. Diagnosis of T2DM prior to informed consent.

Number of global amendment		1.0
		Note: Documentation should be available before randomization at latest. Confirmation can be in the form of formal documents or by verbal communication of the date of diagnosis from a patient or from their primary care physician (if records are not available). It is up to the medical judgment of the Investigator to deem if the information is accurate.
Rationale for change		Clarification of this inclusion criteria
Section to be changed	2	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		2. Male and female black/African American patients on diet and exercise regimen alone or who are: drug-naïve (defined as absence of any oral antidiabetic therapy , GLP-1 analog or insulin for 12 weeks, 16 weeks for pioglitazone prior to randomisation) or pre-treated with stable dose of metformin at a minimum dose of ≥ 1500 mg/day **or maximum tolerated dose unchanged** for 12 weeks prior to randomisation.
Rationale for change		Some patients are not on or able to tolerate a Metformin dose of 1500mg/day. This change will allow entry of patients who are on a lower or maximum tolerate stable dose of Metformin into the study.
Section to be changed	3	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		6. Treatment with stable doses of **at least one but not more than 3** ~~≤ 3~~ antihypertensive medication ≥ 4 weeks prior to randomisation.
Rationale for change		Clarification on number of stable anti-hypertensive medication.
Section to be changed	4	Synopsis: Criteria for safety
Description of change		All adverse events including hypoglycaemic events and ~~protocol specified~~ adverse events of special interest (AESI) ~~cardiovascular events (Clinical Event Committee adjudication results), changes from baseline in electrocardiogram (ECG)~~ and clinical laboratory values
Rationale for change		Removed reference to CEC and ECG

Number of global amendment		1.0
Section to be changed	5	Synopsis: Statistical methods; 7.1 Statistical Design-model; 7.3.1 Primary analysis; 7.3.2 Secondary analysis; 7.5 Randomisation
Description of change		~~background medication of~~ **pretreatment with** Metformin
Rationale for change		Correcting reference to metformin as pretreatment.
Section to be changed	6	Flowchart
Description of change		1. Visit window for visit 2.2 adjusted from -6 to **+6**. 2. Visit window for visit 5.2 adjusted from -2/+7 to **-1**/+7. 3. Added check for food log completion. 4. Foot note "N" combined with "B"; Foot note "N" removed. Added: **ABPM visits should not overlap with subsequent visits**. 5. Fasting blood **and urine** samples **to be collected**~~,~~ for central lab**s at each visit indicated (refer to Lab manual).** ~~except: u~~**A u**rine dipstick to be done locally~~,~~; upon positive result at site for leukocyte esterase (WBC) or nitrites a midstream urine sample ~~for urine culture (central lab analysis)~~ should be taken **and sent for urine culture analysis (central lab)**. 6. **At the conclusion of each attempt, patient should be allowed to rest for at least 15 minutes after removal of the ABPM and a trough seated blood pressure measurement should be taken prior to intake of study medication.** 7. **/PWA** 8. At these visits samples **for** liver fibrosis, inflammation and/or steatosis will be collected.
Rationale for change		1. Correction of window 2. Correction of window to avoid overlap of visits 3. Correction. 4. Clarification 5. Clarification of safety labs to be collected at each visit 6. Adjustment of footnotes 7. Clarification *8.* Clarification to specify PWA measurements 9. Clerical correction
Section to be changed	7	Abbreviations
Description of change		**DEDP Drug Exposure During Pregnancy** ~~DMC Data Monitoring Committee~~
Rationale for change		Added new term Removed reference to DMC

Number of global amendment		1.0
Section to be changed	8	3.1 Overall Trial Design and Plan
Description of change		The Residual Effect Period (REP), that is, the time period, for which adverse events will still be considered "on-treatment" is ≤ 7 days following last intake of trial medication. **Events which occurred after the REP will be considered as post treatment events.** All AEs, including those persisting after trial completion must be ~~tracked~~ **followed up** until **they have** resol**ved** ~~ution~~**, have been sufficiency characterized,** or ~~until the site confirms that~~ no further information can be obtained.
Rationale for change		Clarification on the definition of adverse events occurring within the REP and follow up activities.
Section to be changed	9	3.1.1 Administrative structure of the trial
Description of change		~~Clinical Event Committee~~ ~~An independent external committee (Clinical Event Committee (CEC)) will be established to adjudicate centrally and in a blinded fashion events suspect of stroke, myocardial ischemia (incl. myocardial infarction), cardiovascular death and other relevant events based on the FDA guideline [R09-2151]. The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.~~ ~~For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as ECGs, laboratory values, angiography, echocardiography reports, CAT scan (CT) and or Magnetic Resonance Imaging (MRI) scans, discharge summaries, and autopsy reports to support the external event adjudication.~~ ~~The tasks and responsibilities of the CEC will be filed in a contract before initiation of the trial and will contain written operating procedures. The CEC will maintain the adjudication results in writing. Details will be described in a specific charter.~~
Rationale for change		Data from this study will not be adjudicated for cardiac events.
Section to be changed	10	3.3.3 Exclusion criteria
Description of change		~~18. Systolic blood pressure difference of >10 mmHg between the arms at screening.~~
Rationale for change		Not required for safety reasons per consultation with co-ordinating investigator. This exclusion criteria was also in conflict with

Number of global amendment		1.0
		instructions for measuring BP in Appendix.
Section to be changed	11	3.3.4 Removal of patients from therapy or assessment
Description of change		All patients who discontinue from treatment after randomisation (Visit 3 and beyond) will be followed up until the end of the study. It is very important that patients who discontinue treatment after randomisation **conduct a premature discontinuation visit (Visit 7.2 procedures) and also a follow-up visit (Visit 8 procedures). After these procedures, the patient should return to complete the remainder of the scheduled visits** ~~are followed up using the same visit schedule~~ ~~until the end of the trial~~ (For further details please see Section 6.2.2). **The last per study contact for these patients should be at Visit 7.2; Visit 8 will not need to be done at this point.** If a patient is not able to attend a study visit, the study staff should contact him/her (or someone designated – e.g. family member or personal physician) to inquire about medical information pertaining to adverse events, particularly primary and key secondary outcome events, and/or mortality, until the end of the study. Alternatively, data should be collected from medical records. Additionally the investigator will ask patients who discontinued the study drug to actively contact the site in case of a cardiovascular outcome event that may qualify as a primary or key secondary endpoint (i.e. Non-fatal MI, non-fatal stroke, hospitalization for unstable angina). If a patient withdraws consent, participation in the study will end, the study medication will be stopped and the study staff will try to arrange ~~the End of Study~~ ~~tests and procedures~~ **tests for premature discontinuation procedures and a follow-up visit (Visit 8 procedures)** with the patient for the patient's safety. All used medication kit boxes and remaining study medication should be returned. Patients who withdraw consent will not be contacted any more about the study.
Rationale for change		Clarification of study procedures and visits for patients who prematurely discontinue study medication.
Section to be changed	12	4.2.1 Rescue medication, emergency procedures and additional treatments;
Description of change		Adjustment of the ~~background~~ **current** therapy or addition of another antidiabetic and/or antihypertensive medication would be appropriate.
Rationale for change		Clarified reference to background medication as current therapy.

Number of global amendment		1.0
Section to be changed	13	4.2.2.1 Restrictions regarding concomitant treatment
Description of change		In any situation other than rescue conditions, the use of other antidiabetic and antihypertensive agents will be prohibited during the course of the study except for ~~background~~ **existing current** therapy and, if applicable, the ongoing rescue medication.
Rationale for change		Clarified reference to background medication as existing current therapy.
Section to be	14	5.1.1 Endpoints of efficacy

[redacted]

Number of global amendment		1.0
change		clarification.

[redacted]

Number of global amendment		1.0
		• **Change from baseline** [redacted]
[redacted]		
Section to be changed	19	5.1.2 Assessment of efficacy
Description of change		At each ABPM~~/PWA~~ visit (Visits 2.2, 5.1 and 7.1), patients are to come to the clinic fasting and the following procedure will be performed. The ABPM~~/PWA~~ monitor will be attached to the patient and **test readings will be taken to** check~~ed to see~~ if **the device** ~~it~~ is working properly prior to medication intake. **The first test reading is the Beginning of Test reading.** Once it has been confirmed that the monitor is properly functioning, study medication will be administered ~~followed by prompting of the monitor to take the Beginning of Test reading~~. Record the time the medication was administered and the time the monitor was prompted to take the Beginning of Test reading. The next day when the patient returns to the clinic, the monitor will be prompted to take a Conclusion of Test reading. The device will then be removed and the time of the Conclusion of Test will be recorded. This should be done within ~~22~~ **23:30**-24 hours of starting monitor.
Rationale for change		Clarification on the Beginning of Test ABPM reading and time frame for Conclusion of Test.
Section to be	20	[redacted]
[redacted]		

Number of global amendment		1.0
		[redacted]
[redacted]		[redacted]
Section to be changed	21	5.2.1 Endpoints of safety
Description of change		• ~~Protocol-specified a~~**A**dverse events of special interest (AESI)
Rationale for change		Updating name for adverse events of special interest
Section to be changed	22	5.2.2.1 Definitions of adverse events (Adverse event)
Description of change		**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.**
Rationale for change		Clarification of AE definition
Section to be changed	23	5.2.2.1 Definitions of adverse events (Serious adverse event)
Description of change		A serious adverse event (SAE) is defined as any AE which results in death, is ~~immediately~~ life-threatening, results in persistent or significant disability / incapacity, requires ~~or prolongs~~ **in**patient hospitalisation **or prolongation of existing hospitalization**, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. **Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.** **Every new occurrence of cancer will be reported as a SAE**

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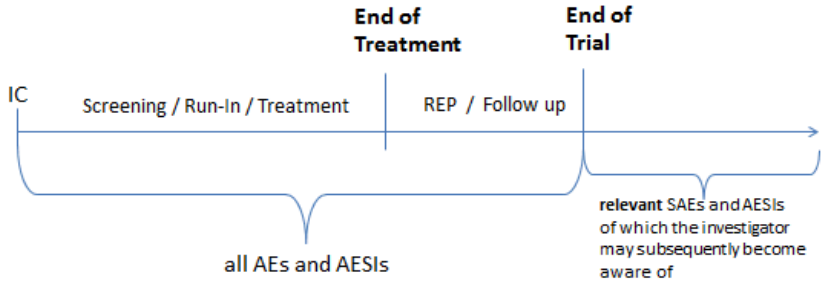
		regardless of the duration between discontinuation of the drug and the occurrence of the cancer. ~~Cancers with new histology or exacerbation of an existing cancer are always considered serious.~~
Rationale for change		Updated definition of SAE.
Section to be changed	24	5.2.2.1 Definitions of adverse events (Causal relationship of adverse event)
Description of change		Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms. Yes: There is a reasonable causal relationship between the investigational product administered and the AE. No: There is no reasonable causal relationship between the investigational product administered and the AE. ~~If a SAE is reported from a still blinded trial, t~~**T**he causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (~~i.e.~~ **such as** any active comparator or placebo and for ~~according to the~~ trial **procedure**~~design~~). **The reason for the decision on causal relationship needs to be provided on the SAE form (if applicable).**
Rationale for change		Updating language for causality of AEs.
Section to be changed	25	5.2.2.1 Definitions of adverse events
Description of change		**<u>AEs considered "Always Serious"</u>** **In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above. In order to support the investigator with the identification of these "always serious adverse events", if a**

Number of global amendment		1.0
		non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked. These events should always be reported as SAEs as described in section 5.2.2.2. **The latest list of "Always Serious AEs" can be found in the RDC system.**
Rationale for change		Updated description of how to manage BI always serious adverse events.
Section to be changed	26	5.2.2.1 Definitions of adverse events
Description of change		~~Protocol Specified~~ Adverse Events of Special Interest (AESI) • **The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE.** ~~The term~~ AESI are events of medical concern requiring monitoring and rapid communication and can be classified as either serious or non-serious. • ~~In addition~~ **These lab findings constitute a hepatic injury alert** and the patients showing the above alterations in liver parameters or hepatic (S)AEs should be followed up according to Section 10.5.2 of this CTP and the "DILI checklist" provided in the ISF. **In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure 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.**
Rationale for		Clarification of definition and instructions for AESI with updated

Number of global amendment		1.0
change		language.
Section to be changed	27	5.2.2.2 Adverse event and serious adverse event reporting
Description of change		All AEs, serious and non-serious, occurring during the course of the clinical trial ~~(i.e., from signing the informed consent onwards through the Follow-up period)~~ will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF. **AE Collection** The following must be collected and documented on the appropriate eCRF by the Investigator: **From signing the informed consent onwards until trial completion (End of Trial) or last per protocol contact, all AEs (serious and non-serious), and AESIs. This also applies to patients who prematurely discontinue from the study.**  For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1. The Residual Effect Period (REP), that is, the time period, for which adverse events will still be considered "on-treatment" is ≤ 7 days following last intake of trial medication. **Events which occurred after the REP will be considered as post treatment events.** Post Study: **After the last per protocol contact,** ~~T~~the investigator does not need to actively monitor patients for **AEs** ~~adverse events once the clinical trial has ended~~. However, if the investigator

Number of global amendment		1.0
		becomes aware of an SAE(s) **or AESI** that occurred after the **last per protocol contact** ~~patient has completed the clinical trial~~ (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF. ~~BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.~~ ~~The list of these adverse events can be found via the RDC-system.~~ With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs, AESI and non-serious AEs must include a causal relationship assessment made by the investigator. The SAE form is to be forwarded immediately (within 24 hours ~~of awareness~~) to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the ISF) or by using the electronic submission process. This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. **In specific occasions the Investigator could inform the Sponsor upfront via telephone; however, this does not replace the requirement to complete and submit the BI SAE form.** It also applies if new information to existing SAEs, AESI or non-serious AEs relevant to the SAE or AESI becomes available. <u>Pregnancy</u> In **the** rare case **that a female subject participating in this clinical trial becomes pregnant** ~~s, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial,~~ after having taken study medication, the investigator must report immediately **(within 24 hours)** ~~any~~ **the** drug exposure during pregnancy **(DEDP)** to the sponsor**'s**~~. Drug exposure during pregnancy has to be reported immediately (within 24 hours of awareness to the defined~~ unique entry point ~~for SAE forms of the~~

Number of global amendment		1.0
		~~respective BI OPU~~ (country-specific contact details will be provided in the ISF). **The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.** 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).** In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. **If there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.**
Rationale for change		Clarification on the instructions for reporting AEs and SAE with updated language.
Section to be changed	28	5.2.4 Electrocardiogram
Description of change		At start of run-in and end of treatment, a complete physical examination will be performed by the investigator **or qualified designee** (see Flow Chart). Documentation of, and findings from the physical examination, must be part of the source documents available at the site.
Rationale for change		Added allowance for qualified designee to perform physical exams
Section to be changed	29	6.2.1 Screening and run-in period; Visit 2.2 (Baseline ABPM visit)
Description of change		• The next day when the patient returns to the clinic (within ~~22~~ **23:30**-24 hours of the beginning of the test), prompt the monitor to take a Conclusion of Test reading. The monitor will then be removed and **the time of the Conclusion of Test will be recorded**. • Allow the patient to rest for **at least** 15 minutes after the monitor is removed. Then take a seated blood pressure measurement. Record the time of this measurement. **This should be done prior to administering study medication.**
Rationale for change		Clarification on the time frame for Conclusion of Test and rest time after removal of monitor at Visit 2.2. and
Section to be changed	30	6.2.2 Treatment period; Visit 5.1 (Week 12 ABPM visit) and Visit

Number of global amendment		1.0
		7.1
Description of change		• Attach ABPM/PWA monitor to the patient and **initiate the test readings to** ensure the monitor is operating properly. • Administer study medication on the morning of the study visit **after the test readings have confirmed that the device is operating properly** ~~prior to starting the monitor~~. **Record the time the medication was administered and the time the monitor was prompted to take the Beginning of Test reading.** • The next day when the patient returns to the clinic (within ~~22~~ **23:30**-24 hours of the beginning of the test), prompt the monitor to take a Conclusion of Test reading. The monitor will then be removed and **the time of the Conclusion of Test will be recorded**. • Allow the patient to rest for **at least** 15 minutes after the monitor is removed. Then take a seated blood pressure measurement. Record the time of this measurement. **This should be done prior to administering study medication.**
Rationale for change		Clarification on timing and procedure for staring ABPM readings, the time frame for Conclusion of Test and rest time after removal of the monitor at Visits 5.1 and 7.1.
Section to be changed	31	6.2.3 End of trial and follow-up period
Description of change		The next day when the patient returns to the clinic (within ~~22~~ **23:30**-24 hours of the beginning of the test), prompt the monitor to take a Conclusion of Test reading. The monitor will then be removed and **the time of the Conclusion of Test will be recorded**. Patients discontinuing trial medication early from the trial ~~Patients who stop study medication for more than 7 consecutive days during the trial should have the discontinuation recorded in the eCRFs.~~ **In general patients should be encouraged to re-start study medication in case of temporary treatment interruptions. If the duration of interruption is more than 7 days, this should be recorded in the "Study Medication Temporary Discontinued/re-started" eCRF.** **For patients who stop study medication permanently**, **a premature discontinuation visit (Visit 7.2 procedures) and also a follow-up visit (Visit 8 procedures) should be conducted.** The patient should **then** continue **with** ~~to follow~~ the study visit schedule per the Flow Chart **with the exception of the follow up visit which will not be required. The last per study contact should be at Visit 7.2.** If determined by investigator as necessary for patient safety, new antidiabetic medication regimen can be started immediately after

Number of global amendment		1.0
		discontinuation and must be recorded in eCRFs. Patients who withdraw consent Patients who withdraw consent during the trial will be asked to complete **premature discontinuation procedures and a follow-up visit (Visit 8 procedures)** ~~Final Visit and Follow up procedures,~~ for their safety. A patient who reverses the decision to withdraw consent should be re-consented with the latest version and will continue the visit schedule according to the date of randomization. In case of premature discontinuation from the 24 week treatment period, ~~a~~ Visit 7.2 **procedures** should be performed and the patient should return to Visit 8 (14 days after Visit 7.2). The following procedures should be performed at Visit 8.
Rationale for change		Provide clarification on procedures and study visit to be conducted for patients who prematurely discontinue treatment or withdraw consent.
Section to be changed	32	7.3 PLANNED ANALYSIS
Description of change		**Full Analysis Set** The full analysis set (FAS) will consist of all randomised patients who were treated with at least one dose of study drug and had a baseline and **at least** one ~~follow-up~~ **on-treatment** HbA1c measurement
Rationale for change		Correction on definition of full analysis set to clearly state that the HbA1c measurement after baseline needs to be an on-treatment measurement.
Section to be changed	33	7.3 PLANNED ANALYSIS
Description of change		**Per Protocol Set** Further details on the definition of the PPS will be provided in the ~~Trial Statistical Analysis Plan (~~TSAP~~)~~.
Rationale for change		Corrected for document formatting.
Section to be changed	34	7.3.3 Safety analyses

Number of global amendment		1.0
Description of change		Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). Adverse events occurring prior to the first drug administration will be assigned to the screening period while all other adverse events, if within 7 days of the last study medication intake, will be assigned to the treatment period for evaluation**. Events which occurred after the REP will be considered as post treatment events**.
Rationale for change		Clarification on AEs after the REP.
Section to be changed	35	8.2 Data Quality Assurance
Description of change		In order to achieve a high level of standardised processes, data collection of efficacy and safety endpoints is coordinated centrally: • central lab analysis of efficacy endpoints, biomarkers and safety lab • ~~central ECG collection (for clinically relevant ECG changes documented as an AE or suspected clinically relevant ECG changes)~~ • central IRT system for stratification, randomisation and kit allocation at each visit • Central hepatic adjudication and malignancy assessment
Rationale for change		Removed reference to ECG collection and adjudication.
Section to be changed	36	9.1 Published References
Description of change		~~R09-2151 FDA Guidance for Industry - Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes~~
Rationale for change		CEC will not be utilized in the study. Removed reference.
Section to be changed	37	10.3 Blood pressure measurement procedures
Description of change		The preferred method for blood pressure measurement is standard mercury sphygmomanometry. If a standard mercury sphygmomanometer is not available**, it**. ~~It~~ is suggested that the investigator use **http://www.dableducational.org/** ~~www.dsbleducational.org~~ to determine if the device is recommended.

Number of global amendment		1.0
Rationale for change		Corrected link to webpage.

11.2 GLOBAL AMENDMENT 2 CHANGES

Number of global amendment		2.0
Date of CTP revision		*12Aug2015*
EudraCT number		*N/A*
BI Trial number		*1245.29*
BI Investigational Product(s)		*empagliflozin*
Title of protocol		A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus
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	1	Synopsis: No. of patients; 3.1 Overall trial design and plan; 3.3

Number of global amendment		2.0
changed		Selection of trial population
Description of change		Total no. of sites: ~~70~~ **85** Total no. of patients screened: ~~560~~ **385** Total no/ of patients entered: ~~280~~ **154** No. of patients in each treatment group: ~~140~~ **77** No. of patients at each site: ~~4~~ 2
Rationale for change		Patient numbers adjusted according to a decrease in statistical power determined for the study.
Section to be changed	2	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		2. Male and female black/African American patients on diet and exercise regimen who are: drug-naïve (defined as absence of any oral antidiabetic therapy , glucagon like peptide-1 (GLP-1) analog or insulin for 12 weeks, 16 weeks for pioglitazone prior to randomisation) or pre-treated with stable dose of metformin**, sulfonylurea (SU), DPP-4 inhibitor, metformin plus sulfonylurea or metformin plus DPP-4 inhibitor**. **Treatment has to be unchanged for a minimum of 12 weeks prior to randomisation** **Minimum dose for metformin: - 1500 mg/day or** **- maximum tolerated dose** **The maximum daily dose of SU or DPP-4 inhibitor should not exceed that stated in the local label** ~~at a minimum dose of ≥ 1500 mg/day or maximum tolerated dose unchanged for 12 weeks prior to randomization.~~ **note: Patients who were screen failed due to exclusionary anti-diabetic background medication according to versions of the protocol prior to Version 3 (SU, SU+Met, DPP-4 inhibitor, DPP-4 inhibitor +Met) are allowed to be re-screened.**
Rationale for change		Allow inclusion of patients currently treated with sulfonylurea, DPP-4 inhibitor.
Section to be changed	3	Synopsis: Criteria for efficacy; 2.1 Rational for performing the trial; 2.2 Trial Objectives; 5.1.1 Endpoints of efficacy; 7.2 Null and alternative hypothesis
Description of		Added to key secondary endpoint: change from baseline in body

Number of global amendment		2.0
change		weight in kilograms (kg) at 24 weeks of treatment Removed from key secondary endpoint: change from baseline in mean 24-hr ambulatory diastolic blood pressure (DBP) at 12 weeks.
Rationale for change		Readjustment of key secondary endpoints to include body weight. Mean 24-hr DBP at 12 weeks moved from key secondary endpoint to secondary endpoint section.
Section to be changed	4	Synopsis: Statistical methods
Description of change		For the change from baseline in trough seated SBP up to 12 weeks of treatment **and the change from baseline in body weight in kg at 24 weeks** as well a restricted maximum likelihood estimation based on mixed-effect model**s** for repeated measures analysis will be used to obtain adjusted means for the treatment effects on the full analysis set (FAS). Th**ese**~~is~~ model**s** will include the same discrete fixed effects as the model for the primary endpoint and baseline HbA1c as continuous fixed effect, as well as interaction between visit and treatment, and interaction between visit and baseline measurement of the key secondary endpoint, as well as the corresponding baseline measurements of the key secondary endpoint as continuous effect . The primary treatment comparisons will be the contrast between treatments at the 12 week visit **for seated SBP and 24 week visit for body weight**. The key secondary endpoint change from baseline in 24-hour ambulatory SBP ~~and DBP at 12 weeks~~, and change from mean trough ambulatory SBP at 12 weeks will be analyzed by using an analysis of covariance (ANCOVA) approach in the FAS with last observation carried forward (LOCF) for missing data. The model will include randomised treatment, renal function at baseline, pretreatment with Metformin at screening as discrete fixed effects and the baseline of the key secondary endpoint and HbA1c at baseline as continuous fixed effects. The overall type I error across the hypotheses tests in the confirmatory analysis will be maintained at a level of $\alpha \leq 0.05$ using a hierarchical testing sequence. The sample size of ~~140~~ **154** patients per group was derived **(assuming n=64 per groups plus a 20% drop-out rate)** based on the requirement that the comparisons of empagliflozin versus placebo with respect to the HbA1c**.** ~~and~~ BP **and body weight**

Number of global amendment		2.0
		should have a power of at least ~~9~~**8**0% at the two-sided α level of 5%.
Rationale for change		Inclusion of body weight as a key secondary endpoints; sample size reduced according to recalculation of statistical power for the study.
Section to be changed	5	Flowchart
Description of change		1. Added column for PTD visit and footnote S added 2. Visit window for visit 2.2 adjusted from +6 to +7. 3. Visit window for visit 5.1 adjusted from -5 to +7. 4. Visit window for visit 5.2 adjusted from -1/+7 to -7/+7. 5. Visit window for visit 7.1 adjusted from +5 to +14. 6. Footnote R added 7. Footnote "B"; Removed: sentences stating that ABPM visits should not overlap with subsequent visits and added **If the ABPM testing is successful, procedures for the subsequent visit can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken.** 8. Footnote "J"; added: **At Visit 7.2 patients should not intake study medication after collection of PK sample.**
Rationale for change		1. Clarify PTD visit procedures and timing. 2. Allow following visit procedures to be conducted after successful completion of ABPM session. 3. Allow following visit procedures to be conducted after successful completion of ABPM session. 4. Allow following visit procedures to be conducted after successful completion of ABPM session. 5. Allow following visit procedures to be conducted after successful completion of ABPM session. 6. Clarification *7.* Allow following visit procedures to be conducted after successful completion of ABPM session. 8. Clarification
Section to be changed	6	Entire Document
Description of change		References to pulse wave assessment (PWA) removed from body of document.
Rationale for change		PWA will be removed as a study procedure and data will no longer be collected.
Section to be	7	Abbreviations

Number of global amendment		2.0
changed		
Description of change		**Cl^- Chloride** **DKA Diabetic Ketoacidosis** **HCO_3^- Bicarbonate** **mEq/L milliequivalents per litre** **mg/dl milligrams per decilitre** ~~PWA Pulse Wave Analysis~~
Rationale for change		Added new terms and removed reference to PWA
Section to be changed	8	2.3 Benefit - Risk Assessment
Description of change		**Special attention will be paid to monitor for diabetic ketoacidosis (DKA). A potential risk for DKA has been reported by the FDA in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dl).** **The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. In addition it needs to be taken into account that, due to the insulin independent mode of action, there is a possibility that ketoacidosis in patients treated with SGLT2 inhibitors is not accompanied by typical hyperglycemia as usually expected for DKA.** **Patients who may be at higher risk of DKA while taking SGLT2 inhibitors include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), severely dehydrated patients, and patients with a history of ketoacidosis or who are known to have a low beta-cell function reserve.**
Rationale for change		Added information on DKA class effect and risks of DKA with empagliflozin.
Section to be changed	9	3.1.1 Administrative structure of the trial and 8.2 Data Quality assurance
Description of change		Section 3.1.1. Hepatic External Adjudication ~~and Cancer Assessments~~

Number of global amendment		2.0
		Certain ~~events of cancer and certain~~ hepatic events will be adjudicated / assessed by external independent experts. The events which will be reviewed will be defined in ~~two~~ **a** charter~~s~~, ~~one~~ for hepatic events ~~and one for malignancies~~. Events may be defined as abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for ~~events of malignancies and~~ hepatic injury events, including liver enzyme elevations. Section 8.2. Central hepatic adjudication ~~and malignancy~~ assessment
Rationale for change		Within the huge clinical trial program there is no evidence that empagliflozin treatment is associated with an increased risk of cancer. Therefore no further cancer assessments are deemed necessary.
Section to be changed	10	3.2 Discussion of trial design, including the choice of control group
Description of change		**Sulfonylureas and DPP-4 inhibitors can be used as monotherapy but are frequently added to metformin when patients are not at goal with metformin. Sulfonylureas (eg. Glimiperide, glyburide, glipizide) and DPP-4 inhibitors (eg. sitagliptin, linagliptin, saxagliptin, alogliptin) are important alternative monotherapies when metformin is not used and more importantly when used in combination with metformin. Therefore patients with current sulfonylurea or DPP-4 inhibitor treatment represent an important proportion of the patient population with type 2 diabetes.**
Rationale for change		Added information on patients treated with SU and DPP-4 inhibitor; these patients are eligible for the study.
Section to be changed	11	3.3.3 Exclusion criteria
Description of change		**Exposure to a**~~A~~ny other antidiabetic medication within 12 weeks prior to randomisation other than metformin**, sulfonylurea, DPP-4 inhibitor, metformin plus sulfonylurea or metformin plus DPP-4 inhibitor.**
Rationale for change		Adjusted to permit entry of patient treated with monotherapy SU or DPP-4 inhibitor or in combination with metformin.
Section to be changed	12	3.3.3 Exclusion criteria

Number of global amendment		2.0
Description of change		11. Acute coronary syndrome (non- ST wave elevated myocardial infarction (STEMI), STEMI and unstable angina pectoris), stroke or trans**ient** ischemic attack within 3 months prior to informed consent. 22. Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial; or participating in another trial (involving an investigational drug and/or follow-up) after discontinuing medication in **that** ~~this~~ trial.
Rationale for change		Correction of clerical errors.
Section to be changed	13	3.3.4 Removal of patients from therapy or assessment
Description of change		1) Occurrence of hypoglycemia **(e.g. repeated hypoglycaemic episodes) or DKA** that may put the patient at risk with continued participation. ~~(e.g. repeated hypoglycaemic episodes) as assessed by the investigator~~**. Patients should be assessed for ketoacidosis immediately if symptoms occur, regardless of blood glucose level. Discontinuation or temporary interruption of study medication should be considered, until the situation is clarified.** 2) Patients who drop out during the screening phase prior to randomisation (Visit 3) will be considered screening failures. They have to be recorded as screening failure in eCRFs and no further follow-up is required. ~~SAEs occurring in patients after having discontinued in the study due to screening failures and who did not receive any study medication, should be reported if the investigator considers the SAE to be related to the screening procedure.~~ 3) **For the analysis of this trial it is absolutely crucial that all planned assessments are done as planned, even if patients discontinue trial treatment.** All patients who discontinue from treatment after randomisation (Visit 3 and beyond) **and who do not withdraw consent** will be followed up **for the intended regular treatment period** ~~until the end of the study~~. **All assessments related to the primary and secondary endpoints must be performed as if the patient would have remained on treatment.** ~~It is very important that patients who discontinue treatment after randomization conduct a premature discontinuation~~

Number of global amendment		2.0
		~~visit (Visit 7.2 procedures) and also a follow-up visit (Visit 8 procedures). After these procedures, the patient should return to complete the remainder of the scheduled visits (For further details please see~~ **Details of procedures to be followed for patients prematurely terminating the trial treatment can be found in** Section 6.2.3). ~~The last per study contact for these patients should be at Visit 7.2; Visit 8 will not need to be done at this point. If a patient is not able to attend a study visit, the study staff should contact him/her (or someone designated – e.g. family member or personal physician) to inquire about medical information pertaining to adverse events, particularly primary and key secondary outcome events, and/or mortality, until the end of the study. Alternatively, data should be collected from medical records. Additionally the investigator will ask patients who discontinued the study drug to actively contact the site in case of a cardiovascular outcome event that may qualify as a primary or key secondary endpoint (i.e. Non-fatal MI, non-fatal stroke, hospitalization for unstable angina).~~ If a patient withdraws consent, participation in the study will end, the study medication will be stopped and the study staff will try to arrange tests for **end of treatment** ~~premature discontinuation~~ procedures and a follow-up visit (Visit 8 procedures) with the patient for the patient's safety **(For further details please see Section 6.2.3).** All used medication kit boxes and remaining study medication should be returned. Patients who withdraw consent will not be contacted any more about the study.
Rationale for change		1) Included guidance for cases of DKA. 2) Removed reference to SAE reporting; detailed in section 5.2.2 3) Clarification of follow up procedures for patients who prematurely discontinue from the study.
Section to be changed	14	4.2 Concomitant therapy, restrictions, and rescue treatment
Description of change		**Patients who are treated with contraindicated medication should not be enrolled into the study.**
Rationale for change		Added as a reminder to not enrol patients on contra-indicated medication.
Section to be changed	15	4.2.1 Rescue medication, emergency procedures, and additional treatments
Description of		**Special attention must be paid to monitor for instances of**

Number of global amendment		2.0
change		**DKA. All patients must be made aware of this risk and need to be instructed to contact the Investigator or other healthcare professional in case of symptoms of DKA. For further details see Section 2.3.** **In case of a suspected DKA the Investigator should ensure that appropriate tests are performed at the earliest opportunity according to local guidelines, such as a blood gas test (i.e. pH, bicarbonate; the results will be collected on the relevant page of the eCRF) and that the patient is appropriately treated (i.e. hospitalized or referred to emergency treatment) according to local treatment guidelines.**
Rationale for change		To provide guidance on managing cases of DKA.

[redacted]

Number of global amendment		2.0
		[redacted]
[redacted]		[redacted]
Section to be changed	18	5.2.2 Assessment of adverse events
Description of change		1) Adjusted language for definitions of adverse events, residual effect period, AE reporting, and pregnancy and restructured section. 2) **Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)** **In case of metabolic acidosis, ketoacidosis and DKA further investigations should be done according to the medical judgment and the clinical course until a diagnosis is made and/or the patient is recovered.** **DKA is defined by the diagnostic criteria in Table 5.2.2.1: 1 below, and as defined by the American Diabetes Association (ADA) [R14-5435].** **Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgment should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in Table 5.2.2.1: 1 below (see Section 2.3 for further details).** **In case of a suspected DKA the Investigator should ensure that appropriate tests are performed locally at the earliest opportunity according to local guidelines, such as a blood gas test (pH, bicarbonate) and that the patient is appropriately treated (i.e. hospitalized or referred to emergency treatment) according to local**

<table>
<tr><td>Number of global amendment</td><td></td><td>2.0</td></tr>
<tr><td></td><td></td><td>treatment guidelines.

Table 5.2.2.1: 1 Diagnostic criteria for DKA
<table>
<tr><td></td><td colspan="3">DKA</td></tr>
<tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>Plasma Glucose (mg/dl)</td><td>>250</td><td>>250</td><td>>250</td></tr>
<tr><td>Arterial pH</td><td>7.25-7.30</td><td>7.00-7.24</td><td><7.00</td></tr>
<tr><td>Serum bicarbonate (mEg/L)</td><td>15-18</td><td>10-<15</td><td><10</td></tr>
<tr><td>Urine ketones*</td><td>Positive</td><td>Positive</td><td>Positive</td></tr>
<tr><td>Serum ketones*</td><td>Positive</td><td>Positive</td><td>Positive</td></tr>
<tr><td>Effective serum osmolality (mOsm/kg)**</td><td>Variable</td><td>Variable</td><td>Variable</td></tr>
<tr><td>Anion gap***</td><td>>10</td><td>>12</td><td>>12</td></tr>
<tr><td>Alteration in sensoria or mental obtundation</td><td>Alert</td><td>Alert/drowsy</td><td>Stupor/ coma</td></tr>
</table>
* Nitroprusside reaction method
** Calculation: 2[measured Na (mEq/L) + glucose (mg/dl)/18]
*** Calculation: (Na^+)-$(Cl^- + HCO_3^-)$ (mEq/L)</td></tr>
<tr><td>Rationale for change</td><td></td><td>1) Update based on new template
2) Inclusion of DKA as AESI</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Section to be changed</td><td>19</td><td>5.2.3 Assessment of safety laboratory parameters</td></tr>
<tr><td>Description of change</td><td></td><td>1) For the first visit after randomisation (4 weeks), only fasting plasma glucose ~~and lipid status~~ will be determined (see Flow Chart).
2) NAFLD fibrosis score will be calculated in-house ~~at the central labs based on the following formula~~:</td></tr>
<tr><td>Rationale for change</td><td></td><td>1) Lipids will not be assessed at this visit, correction
2) Clarification on where scores will be calculated</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Section to be changed</td><td>20</td><td>[redacted]</td></tr>
</table>

[redacted]

Number of global amendment		2.0
[redacted]		
Section to be changed	21	6.2.1 Screening and run-in period (Visit 2.2); 6.2.2 Treatment period (Visit 5.1 and 7.1)
Description of change		1. Added, "**If an invalid reading occurs for the Conclusion of Test reading, continue to trigger a manual reading until a valid reading is registered."** 2. (Visit 2.2 only) added word to, "Patients having two technically unsuccessful baseline ABPM~~/PWA~~ sessions should not be randomized and **must** be discontinued." 3. Updated and added language to allow for procedures for next visits to be done on the same day as the return ABPM session if the ABPM reading is successful.
Rationale for change		1. Added procedure to ensure that the accurate conclusion of test (COT) is recorded on the device. Only a valid reading will trigger the COT; otherwise the last valid reading will be used as the COT. 2. To emphasize that patients cannot be randomised if they do not achieve a successful baseline ABPM read. 3. Allowance provided for those patients who cannot take multiple days off in close succession.
Section to be changed	22	6.2.3 End of trial and follow-up period
Description of change		For all patients **who successfully** complete~~ing~~ the study according to the protocol a follow-up visit (Visit 8) with the patient should be done by the investigator at the end of the follow-up period of 14 days. <u>Visit 8 (follow-up visit)</u> • **Vital signs** • **Body weight measurement** • BP measurement and orthostatic blood pressure test should always be done before taking any blood samples. • Collection of urine and blood for laboratory testing.

Number of global amendment		2.0
		• **Documentation of any adverse events.** • **Documentation of concomitant therapies**
Rationale for change		Administrative change to clarify Visit 8 procedures and to include body weight data since this is now a key secondary endpoint.
Section to be changed	23	6.2.3 End of trial and follow-up period
Description of change		Patients discontinuing trial medication early from the trial In general patients should be encouraged to re-start study medication in case of temporary treatment interruptions. If the duration of interruption is more than 7 days, this should be recorded in the "Study Medication Temporary Discontinued/re-started" eCRF. **For the analysis of this trial it is absolutely crucial that all planned assessments are done as planned, even if patients discontinue trial treatment. Patients who discontinue treatment prematurely and who do not withdraw their informed consent must therefore be followed up for the intended regular treatment period. All assessments related to the primary and secondary endpoints must be performed as if the patient would have remained on treatment.** For patients who stop study medication permanently **prior to completion of 24 weeks of treatment and who are willing to be followed up, the following should be performed whenever possible:** • **Premature treatment discontinuation (PTD) visit should be performed within 7 days of last intake of study drug or as soon as possible including all examinations and assessments that are part of the Visit 7.2. If the PTD visit occurs within the time window of a scheduled visit, the PTD visit will replace the scheduled visit.** • **Subsequently, a follow-up visit (Visit 8 procedures) should be conducted within 14 days of the PTD on visit that replaces the next visit according to the visit schedule.**

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		• **Thereafter, patients would be followed up according to the visit schedule.** • **Visit 7.2 will be the last visit for these patients. Follow-up Visit 8 does not need to be performed.** ~~, a premature discontinuation visit (Visit 7.2 procedures) and also a follow-up visit (Visit 8 procedures) should be conducted. The patient should then continue with the study visit schedule per the Flow Chart with the exception of the follow up visit which will not be required.~~ The last per study contact should be at Visit 7.2. If determined by investigator as necessary for patient safety, new antidiabetic medication regimen can be started immediately after discontinuation and must be recorded in eCRFs. **If a patient is not able to attend a study visit, the study staff should contact him/her (or someone designated – e.g. family member or personal physician) to inquire about medical information pertaining to adverse events, particularly primary and key secondary outcome events, and/or mortality, until the end of the study. Alternatively, data should be collected from medical records.** **For patients who discontinue treatment prematurely <u>but do not wish to follow the visit schedule,</u> the following should be performed whenever possible:** • **<u>Visit 7.2</u> should be performed within 7 days of last intake of study drug.** • **Subsequently, a follow-up visit (Visit 8 procedures) should be conducted within 14 days of the premature discontinuation visit.** **If this patient withdraws consent, then the last per study contact will be Visit 8.** <u>Patients who withdraw consent</u> Patients who withdraw consent during the trial ~~they~~ **should perform** ~~will be asked to complete premature discontinuation~~ **Visit 7.2** ~~procedures~~ **within 7 days of last intake of study drug.** ~~and a~~ **A** follow-up visit (Visit 8 procedures) **should be**

Number of global amendment		2.0
		conducted within 14 days of the premature discontinuation for their safety. **The following procedures should be performed at Visit 8.** • **Vital signs** • **Body weight measurement** • **BP measurement and orthostatic blood pressure test should always be done before taking any blood samples.** • **Collection of blood and urine samples for safety laboratory evaluation.** • **Documentation of any adverse events.** • **Documentation of concomitant therapies** A patient who reverses the decision to withdraw consent should be re-consented with the latest version and will continue the visit schedule according to the date of randomisation. ~~In case of premature discontinuation from the 24 week treatment period, Visit 7.2 procedures should be performed~~ and ~~the patient should return to Visit 8 (14 days after Visit 7.2). The following procedures should be performed at Visit 8.~~ ~~• Vital signs~~ ~~• Collection of blood and urine samples for safety laboratory evaluation.~~ ~~• Documentation of any adverse events.~~ ~~Documentation of concomitant therapies~~
Rationale for change		To clarify and distinguish the expectations for follow up of patients that prematurely discontinue treatment who agree to be followed up, who do not want to be followed up, and who withdraw consent.
Section to be changed	24	7.1 Statistical design - model
Description of change		This is a multi-centre, multi-national, randomised, parallel-group, double-blind, placebo-controlled trial to investigate the effect of (10 mg/25 mg) of empagliflozin and placebo after 24 weeks treatment on glucose control, ~~and~~ BP **and body weight** in

Number of global amendment		2.0
		hypertensive black/African American patients with T2DM.
Rationale for change		Changed to include body weight.
Section to be changed	25	7.3 Planned analyses
Description of change		**Per Protocol Set** The per-protocol set (PPS) will consist of all randomised patients who **are part of the FAS but who do not have any important protocol violations (IPV) leading to exclusion.** ~~o Were treated for 24 weeks with the study medication~~ ~~o Had an overall study treatment compliance between 80% and 120% (inclusive)~~ ~~o Received only the study treatment that they were randomised to~~ ~~o Had a week 24 HbA1c assessment within 161 to 175 days (inclusive) from Study Day1.~~ ~~o Had stable on-study antihypertensive and antidiabetic background therapy~~ ~~o Were NOT prematurely unblinded by the investigator.~~ Further details on the definition of the PPS **and the definition of IPVs** will be provided in the TSAP.
Rationale for change		FAS definition changed to be in line with current internal project standard. Detailed FAS definition will be found in TSAP where IPVs are defined as well.
Section to be changed	26	7.3.1 Primary analyses
Description of change		1. Mean changes from baseline for HbA1c up to 24 weeks of treatment will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach on the FAS data set. Patients will be analysed according to the treatment group they are randomized to. Analyses will include the fixed, categorical effects of treatment, pretreatment with Metformin at screening, renal function at baseline, visit, and treatment-by-visit interaction, as

Number of global amendment		2.0
		well as the continuous, fixed covariate~~s~~ of baseline HbA1c and baseline HbA1c -by-visit interaction. An unstructured (co)variance structure will be used to model the within patient measurements. ~~If this analysis fails to converge, the following covariance structures will be tested: AR (1), Toeplitz and compound symmetry.~~ **If the model first fails to converge using an unstructured (co)variance structure, then a hierarchical approach is applied until a (co)variance structure is obtained where the model converges. Therefore the following (co)variance structures are tested according to the pre-specified order: (1) unstructured, (2) Toeplitz, (3) variance components, (4) compound symmetry. As soon as one model converges this will be the final model used, therefore no further testing of subsequent (co)variance structures is required.** ~~If the analysis with unstructured (co)variance structure fails, the covariance structures AR (1), Toeplitz and compound symmetry are tested and the covariance structure converging to the best fit, as determined by Akaike' s information criterion, will be used as the primary analysis.~~ 2. A s~~S~~imilar ANCOVA model~~s~~ on the FAS using LOCF for missing ABPM assessments will be performed for the change from baseline in mean trough ambulatory SBP at 12 weeks of treatment ~~and for change from baseline in mean 24-hour ambulatory DBP at 12 weeks of treatment~~ just replacing the relevant key secondary endpoint**'s** baseline and 12 week assessments in the model. 3. For the key secondary endpoint**s change from baseline in body weight in kg at week 24 of treatment and** change from baseline in trough seated SBP at 12 weeks of treatment a restricted maximum likelihood estimation based on mixed-effect model for repeated measures for mean changes from baseline ~~in trough seated SBP up to week 12~~ will be used on the FAS observed case (OC) analysis set to obtain adjusted means for the treatment effects. Th**ese**~~is~~ model**s** will include the same discrete fixed effects as the model for the primary endpoint and baseline HbA1c as a continuous fixed effect. **Furthermore** ~~T~~**these** models will include the interaction between visit and treatment, and an interaction between visit and baseline measurement of the key secondary

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		endpoint as well as the corresponding baseline measurements of the key secondary endpoint as continuous fixed effect. The covariance approach for this model will be the same as for the primary endpoint. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The primary treatment comparisons will be the contrast between treatments at the 12 week visit **for trough seated SBP and 24 week visit for the body weight** and significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).
Rationale for change		1. Covariance structure in combination with model selection for MMRM model was changed to ensure type I error control for model selection using a hierarchical model selection approach. 2. & 3. Analysis section adjusted for new key secondary endpoint change from baseline in body weight in kg at week 24 of treatment and deletion of parts on old key secondary endpoint change from baseline in mean 24-hour ambulatory DBP at 12 weeks Further editorial changes were performed in this Section, e.g. medication of Metformin was replaced by pre-treatment with Metformin as this was missed to be updated in the last protocol amendment.
Section to be changed	27	7.3.2 Secondary analyses
Description of change		1. The primary endpoint will as well be analysed using an analysis of covariance model (ANCOVA) in the FAS. The model will include randomised treatment, **pre-treatment** with Metformin, and renal function at baseline as categorical fixed effects, and baseline HbA1c as continuous covariate. Missing HbA1c data will be imputed using the LOCF approach. The term "baseline HbA1c" refer**s** to the last assessment prior to the administration of any randomised study medication. 2. For the key secondary **endpoints change from baseline in body weight in kg at week 24 of treatment and**

Number of global amendment		2.0
		change from baseline in trough seated SBP at 12 weeks as well an ANCOVA model will be calculated on the FAS. The model for the change from baseline includes 'treatment', 'renal function' at baseline, 'pretreatment with Metformin' at screening as fixed categorical effects, and HbA1c at baseline, and baseline trough seated SBP **or baseline body weight in kg respectively,** as linear covariate. Missing data will be imputed using the LOCF approach.
Rationale for change		Paragraph adjusted for new key secondary endpoint and reference to metformin as pre-treatment was corrected.
Section to be changed	28	7.3.3 Safety analyses
Description of change		**Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of ≤ 7 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.** **All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as ≤ 7 days following last intake of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).** **Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and**

Number of global amendment		2.0
		percentage of patients with abnormal values or clinically relevant abnormal values. Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment. ~~Standard safety analyses will be performed on the TS.~~ ~~The empagliflozin treatment group will be compared with the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to summarise continuous (quantitative) data.~~ ~~Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). Adverse events occurring prior to the first drug administration will be assigned to the screening period while all other adverse events, if within 7 days of the last study medication intake, will be assigned to the treatment period for evaluation. Events which occurred after the REP will be considered as post treatment events.~~ ~~Independent of this rule, the relationship of an adverse event to the study drug will be assessed by the investigator. The evaluation of adverse events will comprise various frequency tabulations.~~ ~~Descriptive statistics will be presented for the tolerability parameters.~~ ~~Descriptive statistics of laboratory values over time and for the difference from baseline will be provided. Frequency tables of changes with respect to the reference range between baseline and last value on treatment will also be presented.~~ ~~Reasons for discontinuation and use of post-baseline concomitant medications will be tabulated.~~ ~~The details of the analysis will be specified in the TSAP.~~
Rationale for change		This section was changed to reflect new project standard for safety analyses. Analysis details will be described in TSAP.
Section to be changed	29	7.6 Determination of sample size

<table>
<tr><td>Number of global amendment</td><td></td><td>2.0</td></tr>
<tr><td>Description of change</td><td></td><td>In order to ensure that each comparison~~s~~ of empagliflozin and placebo with respect to HbA1c**,** ~~and~~ mean **systolic** ABPM blood pressure **and body weight** have a power of at least ~~90~~**80**%, ~~140 are required per treatment group~~ **64 patients plus an additional 20% drop-out rate, resulting in 77 patients per arm are required per treatment group**. This is derived from the assumption that the difference in change from baseline **compared to placebo** in 24-hour SBP is ~~4~~ **5** mmHg with a standard deviation of 10 mmHg **(resulting in a power of 80%),** and the difference in ~~DBP~~ **body weight** is 2 **kg**~~mmHg~~ with a standard deviation of ~~5 mmHg~~ **2.3kg (resulting in a power of 99%)**. With this sample size the power to detect a 0.**6**~~5~~% difference in HbA1c with a standard deviation of 1.1% will be >**85**~~95~~%.

The planned treatment group sizes are considered as sufficient for the confirmatory evaluation of efficacy and the descriptive assessment for safety, tolerability and pharmacokinetics.

~~For blood pressure scenarios see sample size calculations in table below.~~

<table>
<tr><td>~~Scenario~~</td><td>~~**1**~~</td><td>~~2~~</td><td>~~3~~</td><td>~~4~~</td><td>~~5~~</td><td>~~**6**~~</td><td>~~7~~</td><td>~~8~~</td><td>~~9~~</td><td>~~10~~</td></tr>
<tr><td>~~SBP/ DBP~~</td><td>~~**S B P**~~</td><td>~~SB P~~</td><td>~~SB P~~</td><td>~~SB P~~</td><td>~~S B P~~</td><td>~~**D BP**~~</td><td>~~D BP~~</td><td>~~D BP~~</td><td>~~DB P~~</td><td>~~DB P~~</td></tr>
<tr><td>~~Mean change from baseline~~</td><td>~~**4**~~</td><td>~~4~~</td><td>~~4~~</td><td>~~3.7~~</td><td>~~3. 4~~</td><td>~~**2**~~</td><td>~~2~~</td><td>~~2~~</td><td>~~1.9~~</td><td>~~1.8~~</td></tr>
</table>
</td></tr>
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Number of global amendment		2.0
		~~Standard deviation~~ ~~**10**~~ ~~10~~ ~~10~~ ~~11~~ ~~10~~ ~~**5**~~ ~~5~~ ~~5~~ ~~5.6~~ ~~5.3~~ ~~Sample size (both groups)~~ ~~**280**~~ ~~252 (10 % off from 280)~~ ~~266 (5 % off from 280)~~ ~~280~~ ~~280~~ ~~**280**~~ ~~252 (10 % off from 280)~~ ~~266 (5 % off from 280)~~ ~~280~~ ~~280~~ ~~Power~~ ~~**92**~~ ~~89~~ ~~90~~ ~~80~~ ~~81~~ ~~**92**~~ ~~89~~ ~~90~~ ~~81~~ ~~81~~
Rationale for change		Power and patient numbers adjusted due to new underlying assumptions made to reflect realistic assumptions for this specific trial population, to avoid overpowering and to be able to finalize this trial in a reasonable time period with low recruitment rates occurring.
Section to be changed	20	9. References
Description of change		• **R14-5435 American Diabetes Association. Hyperglycemic crises in diabetes. Diabetes Care 27 (Suppl 1), S94 - S102 (2004)** • ~~U06-1897-08~~ **c01838761** [redacted] BI 10773 Investigator's Brochure BI 10773 in type 2 diabetes mellitus, current version **12. 15 July 2015**.
Rationale for change		1. Added new reference for DKA management 2. Update to Investigator Brochure version.

11.3 GLOBAL AMENDMENT 3 CHANGES

Number of global amendment		3.0
Date of CTP revision		*14April2015*
EudraCT number		*N/A*
BI Trial number		*1245.29*
BI Investigational Product(s)		*empagliflozin*
Title of protocol		A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus
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	1	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		2. Male and female black/African American patients on diet and exercise regimen who are: drug-naïve (defined as absence of any oral antidiabetic therapy , glucagon like peptide-1 (GLP-1) analog or insulin for 12 weeks, 16 weeks for pioglitazone prior to randomisation)

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		or pre-treated with stable dose of metformin, sulfonylurea (SU), DPP-4 inhibitor, metformin plus sulfonylurea or metformin plus DPP-4 inhibitor. Treatment has to be unchanged for a minimum of 12 weeks prior to randomisation ~~Minimum d~~**D**ose for metformin: ~~- 1500 mg/day or~~ - maximum tolerated dose The maximum daily dose of SU or DPP-4 inhibitor should not exceed that stated in the local label note: Patients who were screen failed due to exclusionary anti-diabetic background medication according to versions of the protocol prior to Version 3 (SU, SU+Met, DPP-4 inhibitor, DPP-4 inhibitor +Met) are allowed to be re-screened.
Rationale for change		Clarification on the dose for metformin
Section to be changed	2	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		3. HbA1c of ≥ 7.**0**~~5~~% (5**3**~~8~~ mmol/mol) and ≤ 11.0% (97 mmol/mol) at Visit 1 (screening)
Rationale for change		Adjustment of lower limit for HbA1c to allow for entry of patients with HbA1c between 7.0% and 7.4%.
Section to be changed	3	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		4. Mean seated SBP 140-180 mmHg ~~and DBP 90-110 mmHg~~ at Visit 1 (screening)
Rationale for change		Removed mean seated DBP criteria to allow for entry of patients with isolated systolic hypertension.
Section to be changed	4	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		6. Treatment with stable doses of at least one but no more than ~~3~~**4** antihypertensive medication ≥ 4 weeks prior to randomisation.
Rationale for change		Increased number of permitted background antihypertensive medications to permit entry of patients on 4 antihypertensive therapy. Patients with severe hypertension will still be excluded by upper limit for mean seated SBP in inclusion criteria 4.
Section to be	5	Flowchart- Footnote B

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changed		
Description of change		Patients will undergo 24-hour ABPM testing. If **patients fail the test** ~~testing is unsuccessful~~, this procedure should be repeated.
Rationale for change		Administrative clarification on ABPM testing outcome.
Section to be changed	6	Abbreviations and Entire Document
Description of change		Updated list of abbreviations and corrected text in document accordingly.
Rationale for change		Administrative change.
Section to be changed	7	Entire Document and Section 9.2 Unpublished References
Description of change		1. ~~c01838761~~ **c01678844** 2. ~~c01838761~~ **c01678844** [redacted] BI 10773 Investigator's Brochure ~~BI 10773 in type 2 diabetes mellitus~~, current version **13. 11 Feb 2016**. 3. ~~R09-1164 Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 39(1)193] (2009).~~
Rationale for change		Replace link to reference and undated reference to Investigator Brochure. Removed reference.
Section to be changed	8	3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		**For information regarding Adverse event and serious adverse event reporting, please refer to Section 5.2.2.2** ~~The Residual Effect Period (REP), that is, the time period, for which adverse events will still be considered "on-treatment" is ≤ 7 days following last intake of trial medication. Events which occurred after the REP will be considered as post treatment events. All AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiency characterized, or no further information can be obtained. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial~~

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		~~(including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator. Such reports should contain an assessment of causality with regard to the trial treatment~~
Rationale for change		Administrative change
Section to be changed	9	3.1.1.2 Clinical Event Committee for Diabetic ketoacidosis (DKA)
Description of change		**An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see Section 5.2.2.1). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met. For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication.** **The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.**
Rationale for change		New adjudication process for diabetic ketoacidosis was added to trial.
Section to be changed	10	3.3 Selection of Trial Population
Description of change		Approximately up to ~~385~~ **620** patients will be screened for the trial in US. About 85 trial centres will be participating to ensure that approximately 154 patients are randomised to trial treatment (77 to each treatment group).
Rationale for change		Increased number of patients expected to be screened to reflect a higher screen failure rate.
Section to be changed	11	3.3.3 Exclusion criteria
Description of change		4. Mean seated SBP ≥181 mmHg ~~and/or mean seated DBP≥111 mmHg~~ during placebo run-in visit and confirmed by a second measurement (not on the same day) preferably within one day.
Rationale for change		Removed mean seated DBP to align with changes to inclusion criteria 4.

Number of global amendment		3.0
Section to be changed	12	5.1.2 Assessment of efficacy- *Ambulatory blood pressure monitoring (ABPM)*
Description of change		**After each ABPM session, the data from the device is to be downloaded and assessed for quality to determine if the session was technically successful. If the first session does not pass quality criteria or the mean ABPM SBP is below the required threshold, the session should be repeated. Only one repeat session will be permitted. At Visit 2.2 only, it is important to remember to record the 24-hour mean systolic blood pressure which is displayed at the bottom of the QC results. The mean systolic BP at this visit together with a technically successful session determines eligibility for randomization.**
Rationale for change		To provide clarification on ABPM testing process.
Section to be changed	13	5.2.2.1 Definitions of adverse events-Adverse reaction
Description of change		**<u>Adverse reaction</u>** **An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.**
Rationale for change		Addition of new definition of Adverse Reaction
Section to be changed	14	5.2.2.1 Definitions of adverse events- Serious adverse events
Description of change		**Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any**

Number of global amendment		3.0
		suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
Rationale for change		Administrative addition to provide further guidance on assessment of serious adverse events or adverse reactions.
Section to be changed	15	5.2.2.1 Definitions of adverse events- Causal relationship of adverse event
Description of change		**The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.** 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. preexisting 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 diminished).** **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**

Number of global amendment		3.0
		time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned) **• Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).** **Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.** **• Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).** **• Disappearance of the event even though the study drug treatment continues or remains unchanged.** ~~Yes: There is a reasonable causal relationship between the investigational product administered and the AE.~~ ~~No: There is no reasonable causal relationship between the investigational product administered and the AE.~~
Rationale for change		Administrative changes to provide guidance on causality assessment.
Section to be changed	16	5.2.2.2 Adverse event and serious adverse event reporting-AE collection
Description of change		1. From signing the informed consent onwards **through the Residual Effect Period (REP)** until trial completion (**individual patient's** End of Trial) ~~or last per protocol contact,~~: • all AEs (serious and non-serious), and AESIs. This also applies to patients who prematurely discontinue from the study. **If an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual patient's End of Trial contact, the Investigator must report all AEs (serious and non-serious) and AESIs.**

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		After the individual patient's end of trial: • **The Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.** 2. ~~Post Study: After the last per protocol contact, the investigator does not need to actively monitor patients for AEs. However, if the investigator becomes aware of an SAE(s) or AESI that occurred after the last per protocol contact (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.~~
Rationale for change		Administrative changes to provide clarification on expectations for adverse event report at specific time points.
Section to be changed	17	5.2.3 Assessment of safety laboratory parameters
Description of change		The following safety lab parameters will **only be** ~~not~~ be determined at each **of the following** study visit: • **Lipid fractions: planned at V3, V5.2, V7.2 and V8** • TSH: planned at V1 • Albumin (urine) at V3, V5.2, V7.2 and V8 • ~~Brain natriuretic peptide (~~BNP~~)~~ at V3, V5.2 and V7.2
Rationale for change		Administrative change to clarify tests that will only be collected at specific visits.
Section to be changed	18	5.6.1 [redacted]

[redacted]

Number of global amendment	[redacted]
[redacted]	
Section to be changed	19	6.2.1 Visit 2.1 (Run-in period); 6.2.2 Visit 3 (Randomisation visit)
Description of change		**Inclusion/exclusion criteria must be reviewed prior to randomization**
Rationale for change		Administrative change to clarify that patient eligibility must be reviewed at these visits.
Section to be changed	20	6.2.1 Visit 2.2 (Run-in period)
Description of change		• **Once the data from the session is downloaded, review the QC results to determine if the session was technically successful. Remember to record the 24-hour mean systolic BP displayed at the bottom of the QC results. The mean systolic BP at this visit together with a technically successful session determines eligibility for randomization.** • If **the first** ABPM **attempt** was ~~technically~~ unsuccessful **(failed QC and/or the mean ABPM SBP is below the required threshold)**, repeat it within 2 days. Patients having two ~~technically~~ unsuccessful baseline ABPM sessions should

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		not be randomised and must be discontinued. • If ABPM was ~~technically~~ successful**, the patient is eligible for randomization and** procedures for Visit 3 can be conducted on the same day after the ABPM device is removed and trough seated blood pressure measurement is taken. If conducted on the same day, procedures for Visit 3 should be done prior to administrating study medication.
Rationale for change		To provide clarification on ABPM testing process and determination of eligibility for randomization.
Section to be changed	21	6.2.2 Visit 5.1 (Week 12 ABPM visit); Visit 7.1
Description of change		• Removed the word technically from these sections. • If **the first** ABPM **attempt** was ~~technically~~ unsuccessful **(failed QC)**, a repeat reading should be taken within 2 days.
Rationale for change		To provide clarification on ABPM testing process and determination of eligibility for randomization.
Section to be changed	22	6.2.3 End of trial and follow-up period
Description of change		Visit 8 (follow-up visit) • Vital signs • Body weight measurement • BP measurement and orthostatic blood pressure test should always be done before taking any blood samples. • Collection of urine and blood for laboratory testing. • **Home blood glucose monitoring** • Documentation of any adverse events. • Documentation of concomitant therapies
Rationale for change		To correct omission of home blood glucose monitoring at this visit to align with flow chart.
Section to be changed	23	8.4.1 Listedness
Description of change		To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the empagliflozin this is: the current version of the IB (~~c01838761~~ **c01678844**). The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for matching placebo~~, study~~

Number of global amendment		3.0
		~~design, or invasive procedures~~.
Rationale for change		Administrative correction
Section to be	24	[redacted]
[redacted]		
Rationale for change		Removed [redacted] This information is in Section 5.3.3.1.
Section to be changed	25	10.3 Blood Pressure Measurement Procedure
Description of change		Initially, blood pressure should be taken 3 times in both arms. If the **mean** pressures differ by more than 10 mmHg, the arm with the higher pressure (systolic or – if needed, diastolic) should be used for subsequent measurements. If the pressures are ~~<~~≤10mmHg, the non-dominant arm should be used for
Rationale for change		Administrative clarification.
Section to be changed	26	10.4 [redacted]
[redacted]		

Number of global		[redacted]
[redacted]		

11.4 GLOBAL AMENDMENT 4 CHANGES

Number of global amendment		4.0
Date of CTP revision		*18 July 2016*
EudraCT number		*N/A*
BI Trial number		*1245.29*
BI Investigational Product(s)		*empagliflozin*
Title of protocol		A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus
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		☐

Number of global amendment		4.0
Section to be changed	1	Synopsis; Main criteria for inclusion and 3.3.2 Inclusion criteria
Description of change		Male and female black/African American patients on diet and exercise regimen ~~alone,~~ ~~or~~ who are **EITHER** drug-naïve (defined as absence of any oral antidiabetic therapy, glucagon like peptide-1 **(**GLP-1**)** analog or insulin for 12 weeks, 16 weeks for pioglitazone prior to randomisation) **OR** pre-treated with stable dose of • Metformin **only, or** • Sulfonylurea **only, or** • DPP-4 inhibitor **only, or** • metformin plus sulfonylurea, or • metformin plus DPP-4 inhibitor. Treatment has to be unchanged for a minimum of 12 weeks prior to randomization. Dose for metformin: maximum tolerated dose The maximum daily dose of SU or DPP-4 inhibitor should not exceed that stated in the local label ~~note: Patients who were screen failed due to exclusionary anti-diabetic background medication according to versions of the protocol prior to Version 3 (SU, SU+Met, DPP-4 inhibitor, DPP-4 inhibitor+Met) are allowed to be re-screened.~~
Rationale for change		Administrative clarification, and to maintain consistency of information within the document. Screen failure instructions moved to new section (3.3.5)

Section to be changed	2	3.3 Selection of Trial Population
Description of change		Approximately ~~up to 620~~ **700** patients will be screened for the trial in US.
Rationale for change		Increased number of patients expected to be screened to reflect a higher screen failure rate.

Section to be changed	3	3.3.5 Re-screening
Description of change		**Re-screening is permitted for the following categories of screen failed patients only:**

		• **Patients who were screen failed due to exclusionary background anti-diabetic therapies (sulfonylurea, DPP4-inhibitor, metformin + sulfonylurea, metformin +DPP4-inhibitor) according to prior versions of the protocol.** • **Patients who were screen failed due to exclusionary HbA1c 7.0% (53 mmol/mol) -7.4% (57 mmol/mol) at Visit 1 according to prior versions of the protocol. Patients who were screen failed due to exclusionary HbA1c below 7.0% or above 11.0% cannot be re-screened.** • **Patients who were screen failed due to exclusionary mean seated DBP (Visit 1) according to prior versions of the protocol. However, mean seated SBP (Visit 1) must have been 140-180 mmHg at the previous screening.** • **Patients who were screen failed due to taking 4 antihypertensive medications (≥ 4 weeks prior to randomization) according to prior versions of the protocol.** • **Patients who were screen failed due to out-of-window visits prior to ABPM testing (Visit 2.2). If ABPM testing has commenced, no re-screening is permitted.** **A patient who was screen failed due to any of the above screen failure reasons is permitted to be re-screened once only. A new patient number should be assigned to the re-screened patient who should be re-consented. Rationale for re-screening must be document in source documents.** **Re-screening is not permitted for patients who were screen failed due to other reasons.**
Rationale for change		Added subsection to allow re-screen of patients who were screen failed based on the earlier versions of the protocol but would be eligible based on the revised inclusion/exclusion criteria in the subsequent protocol versions.

Section to be changed	4	3.3.6 Repeat test
Description of change		**HbA1c test (Visit 1) may be repeated once if the test result from the central lab is exclusionary but the most recent test result from a local lab (taken before Visit 1 but not older than**

		one month), if any, falls within the acceptable range. **ABPM test (Visit 2.2) may be repeated once if the first attempt is unsuccessful. Refer to Footnote B and Footnote I of the Flow Chart, as well as Section 5.1.2 and Section 6.2.1 for additional details on repeat ABPM.** **Rationale for all repeat tests must be documented in source documents.**
Rationale for change		To allow confirmatory testing of HbA1c if there is a discrepancy of values between central and local lab results. ABPM re-test is not new. It is repeated in this section for completeness of information.

Section to be changed	5	5.1.1 Endpoints of efficacy
Description of change		Change from baseline in mean **seated** trough heart rate at 12 weeks of treatment
Rationale for change		Administrative clarification.

Section to be changed	6	5.1.2 Assessment of efficacy
Description of change		After each ABPM session, the data from the device is to be downloaded and assessed ~~for quality~~ to determine if the session was ~~technically~~ successful. **At Visit 2,2 only,** ~~I~~if the first session does not pass quality criteria or the mean ABPM SBP is ~~below~~ **outside** the required **range** ~~threshold~~, the session should be repeated. Only one repeat session will be permitted. ~~At Visit 2.2 only, i~~**I**t is important to remember to record the 24-hour mean SBP which is displayed at the bottom of the quality compliance (QC) results. The 24-hour mean SBP at this visit together with a ~~technically~~ successful session determines eligibility for randomization
Rationale for change		Administrative clarification and to maintain consistency of information within the document.

Section to be changed	7	5.2.2.2 Adverse event and serious adverse event **collection and** reporting
Description of change		Added the words “collection and” to the sub title.
Rationale for change		Administrative clarification.

Section to be	8	[redacted]

[redacted]

Section to be changed	9	6.2.1 Screening and run-in period
Description of change		Visit 1 (Screening) • The screening visit is the only visit in this study that does not need to be done fasting. • No trial procedures should be done unless the patient has consented to taking part in the trial. **Patient identification numbers are available in the RDC system. If a patient is re-screened, a new patient identification number should be assigned.**
Rationale for		Added information on patient identification numbers.

change		

Section to be changed	10	6.2.1 Screening and run-in period
Description of change		Visit 2.2 (Baseline ABPM visit) • Once the data from the session is downloaded, review the QC results to determine if the session was technically successful. Remember to record the 24-hour mean SBP displayed at the bottom of the QC results. The 24-hour mean SBP at this visit together with a ~~technically~~ successful session determines eligibility for randomization. If the first ABPM attempt was unsuccessful (failed QC and/or the mean ABPM SBP is ~~below~~ **outside** the required **range** ~~threshold~~), repeat it within 2 days. Patients having two unsuccessful baseline ABPM sessions should not be randomised and must be discontinued.
Rationale for change		Administrative clarification on ABPM repeat, and to maintain consistency of information within the document.

Section to be changed	11	8.4.2
Description of change		**Expedited reporting to health authorities ~~and IECs/IRBs~~** **BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP**. ~~Expedited reporting of serious adverse events, e.g. SUSARs to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF~~
Rationale for change		To fulfil both global and local regulatory reporting obligations.

Section to be changed	12	10 Appendices
Description of change		Re-numbring of the following appendices 10.3 re-numbered to **10.2** 10.4 re-numbered to **10.3** 10.5 re-numbered to **10.4**
Rationale for change		Administrative corrections.

APPROVAL / SIGNATURE PAGE

Document Number: c01945509 **Technical Version Number:7.0**

Document Name: clinical-trial-protocol

Title: A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	19 Jul 2016 21:54 CEST
Approval-Medical [redacted]		20 Jul 2016 04:20 CEST
Author-Trial Statistician		20 Jul 2016 08:52 CEST
Approval-Team Member Medicine		20 Jul 2016 09:23 CEST
Approval-Clinical Pharmacokinetics		20 Jul 2016 13:13 CEST
Approval-Therapeutic Area [redacted]		22 Jul 2016 14:52 CEST
Verification-Paper Signature Completion		22 Jul 2016 15:44 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed