Clinical Trial Protocol

	Document Number:	**c26980387-02**
BI Trial No.	1245-0191	
BI Investigational Medicinal Product(s)	Jardiance®, Empagliflozin BI 10773	
Title	A phase III, randomised, double-blind, placebo-controlled, parallel group study of Empagliflozin (10 mg and 25 mg) administered orally once daily in combination with insulin with or without up to two oral anti-diabetic agents for 24 weeks in Chinese type 2 diabetic patients with insufficient glycemic control.	
Lay Title	A study to test how well empagliflozin works in Chinese patients with type 2 diabetes who already take insulin	
Clinical Phase	III	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	A revised protocol based on the first global amendment	
Version and Date	**Version:** 2.0	**Date:** 20 Apr 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	20 Apr 2021
Revision date	N/A
BI trial number	1245-0191
Title of trial	A phase III, randomised, double-blind, placebo-controlled, parallel group study of Empagliflozin (10 mg and 25 mg) administered orally once daily in combination with insulin with or without up to two oral anti-diabetic agents for 24 weeks in Chinese type 2 diabetic patients with insufficient glycemic control.
Coordinating Investigator	[redacted]
Trial site(s)	Multi-center trial conducted in China
Clinical phase	III
Trial rationale	In China, more than 33% of adults with type 2 diabetes receive insulin therapy (basal or premixed), but only 26% of those have adequate glycemic control. Empagliflozin was approved in China in 2017 for the treatment of T2DM as an adjunct to diet and exercise and in combination with various oral anti-diabetic therapies. However, using Empagliflozin in combination with insulin has not been investigated in Chinese patients with T2DM. The aim of this study is to evaluate efficacy and safety over 24 weeks of Empagliflozin therapy in Chinese T2DM patients whose glycemia is inadequately controlled despite background treatment on a stable dose of basal or premixed insulin, with or without other oral antihyperglycemic drugs.
Trial objective(s)	To determine the efficacy and safety of Empagliflozin added to insulin-treated type 2 diabetes patients.
Trial endpoints	The primary endpoint is: • Change from baseline in glycosylated haemoglobin A_{1c} (HbA_{1c}) after 24 weeks of treatment. Secondary efficacy endpoints are: • Percentage of patients with HbA_{1c}<7.0% after 24 weeks of treatment • Change in Body Weight from Baseline to Week 24 • Change in Systolic Blood Pressure (SBP) from Baseline to Week 24 • Change in Diastolic Blood Pressure (DBP) from Baseline to Week 24 • Change in Fasting Plasma Glucose (FPG) from Baseline to Week 24 • Change in 2-hour Post-prandial Glucose (PPG) from Baseline to Week 24 Secondary safety endpoints are: • Occurrence of hypoglycemic events • Occurrence of adjudicated diabetic ketoacidosis (DKA) events
Trial design	Randomised, double-blind, multi-center, placebo-controlled, parallel group study compares Empagliflozin (10 mg or 25 mg) to placebo as add-on therapy to stable insulin with or without up to two oral antidiabetic drugs.
Total number of patients randomised	Approximately 216
Number of patients on each treatment	Approximately 72
Diagnosis	The study will be performed in Chinese patients with T2DM who have insufficient glycemic control despite diet and exercise and receiving insulin alone or in combination with other Oral Antidiabetic Drugs (OADs).

Main in- and exclusion criteria	**Inclusion criteria** 1. Age ≥18 years and ≤75 years old at Visit 1; 2. Chinese patient with diagnosis of Type 2 diabetes prior to Visit 1; 3. A stable treatment with premixed Insulin (≥ 20IU/day) or basal insulin (≥ 16 IU/day) for at least 12 weeks prior to enrolment with or without up to two OADs - With maximum insulin dose of ≤ 1 unit/kg/day. Acceptable basal insulins should have duration of action up to 24 h such as insulin degludec, insulin glargin, insulin detemir or NPH (neutral protamine hagedorn) insulin; Acceptable pre-mixed insulins could be once or twice daily posology only.The total insulin dose should not be changed by more than 20% of the baseline value within the 12 weeks prior to randomisation (Visit 3). Both human insulin and insulin analogue are acceptable; - If the patient is taking OADs, regimen has to be unchanged for at least 12 weeks prior to randomization (Visit 3); - If the patient is taking metformin, stable dose (at least 1500 mg daily or maximum tolerated dose) must be maintained for at least 12 weeks without dose adjustments prior to randomization (Visit 3); 4. HbA_{1c} ≥ 7.5% and ≤ 11.0% at Visit 1; 5. Fasting C-peptide: >0.5 ng/mL (>166pmol/L) at Visit 1; 6. 18.5 kg/m^2 ≤ BMI ≤ 45 kg/m^2 at Visit 1. **Exclusion criteria** 1. Diagnosis of Type 1 diabetes; 2. Patients receiving MDI insulin or insulin pump treatment; 3. eGFR <45ml/min/1.73m^2 calculated based on MDRD formula; 4. Uncontrolled hyperglycemia (glucose level >13.9 mmol/l after an overnight fast during placebo run-in); 5. Severe hypoglycemia episode (event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions) within 6 months prior to Visit 1; 6. History of diabetic ketoacidosis or hyperosmolar non-ketotic coma; 7. Myocardial infarction, Stroke or transient ischaemic attack within 3 months prior to Visit 1; 8. Bariatric surgery; 9. SGLT2 inhibitors intake within 12 weeks prior to Visit 1; 10. Treatment with anti-obesity drugs within 12 weeks prior to Visit 1; 11. Treatment with Glucagon-Like Peptide-1 (GLP-1) receptor agonists within 12 weeks prior to Visit 1; 12. Treatment with Sulphonylurea (SU) if the patient is on premixed insulin within 12 weeks prior to Visit 1; 13. Impaired hepatic function (serum alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase >3 times the upper limit of normal) at V1; 14. Contraindication to background anti-diabetes medication according to the local label; 15. Disorders causing hemolysis or unstable red blood cells; 16. Treatment with systemic steroids at the time of consent; 17. Change in dosage of thyroid hormones within 6 weeks prior to Visit 1; 18. Alcohol or drug abuse within 12 weeks prior to Visit 1; 19. History of unstable or rapidly progressing renal disease; 20. Conditions of congenital renal glucosuria; 21. Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors.
Test product(s)	Empagliflozin

dose	10 or 25 mg daily
Mode of administration	oral
Comparator product(s)	Placebo
dose	Not applicable
Mode of administration	oral
Duration of treatment	2-week placebo run in 24-week double-blind treatment 1-week follow up
Statistical methods	The primary endpoint in this trial is the change in HbA_{1c} from baseline after 24 weeks of treatment. The primary analysis is a restricted maximum likelihood (REML) based approach using a mixed model for repeated measures (MMRM) comparing the mean change in HbA_{1c} from baseline after 24 weeks of treatment. The analysis will include treatment, background therapy, and visit as fixed classification effects, baseline HbA_{1c} and baseline eGFR as the linear covariates, treatment by visit interaction, and baseline HbA_{1c} by visit interaction. The primary analysis will be performed on mITT set with patients assigned to the treatment they are randomised to and include on-treatment HbA_{1c} values only. The primary treatment comparisons will be the contrasts between active treatment (Empagliflozin 10 mg and 25 mg, respectively) and placebo at week 24.

FLOW CHART

Trial Periods	Screening	Run-in	Randomised Treatment						Follow-up
Visit	**1**	**2**	**3**	**4[N]**	**5[N]**	**6[N]**	**7[N]**	**8 (EoT[A])**	**9 FUP**
Weeks	-3	-2	0	4	8	12	18	24	25
Study Day	-21	-14	1	29	57	85	127	169	176
Time window for visits	±7 days	-7 days	0	±7 days	±7 days	±7 days	±7 days	+ 7 days	+ 7 days
Informed consent	X								
Demographics[B]	X	X							
Medical history	X								
In-/Exclusion criteria	X	X	X						
Physical examination		X						X	
Vital signs	X	X	X	X	X	X	X	X	X[M]
Height	X								
HbA_{1c}	X		X	X	X	X	X	X	
Home Blood Glucose Monitoring[C]		X	X	X	X	X	X	X	X
Dispense placebo run-in kit[D]		X							
Randomisation (via IRT)			X						
Weight	X		X	X	X	X	X	X	
Waist circumference			X					X	
Diet and exercise counselling[E]		X	X	X	X	X	X	X	
12 lead-ECG[F]			X					X	
8-point glucose profile[L]			X			X		X	
Pregnancy test[G]	X		X			X		X	
Glomerular filtration rate[H]	X		X			X		X	
Fasting C-peptide	X								
Safety lab tests[I] (urine and blood)	X[I]	X	X			X		X	X[M]
FPG		X	X	X	X	X	X	X	X[M]
2-hour PPG test[J]			X					X	
Lipid lab panel			X					X	
MTT test (including Insulin + c-peptide)[J]			X					X	
Dispense trial drugs[D]			X	X	X	X	X		
All AEs/SAEs/AESIs[K]	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X
Compliance check			X	X	X	X	X	X	
Completion of patient participation									X

A Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit as soon as possible and allow to attend all clinic visits up to the FUP Visit thereafter in order to collect all the data as other treatment completed patients.

B Only screening relevant demographics (gender, date of birth, race and ethnicity) at Visit 1. Smoking and alcohol status could be collected at Visit 2.

C Instruction and training of the patient to use the device at Visit 2. A full overnight fast (nothing to eat or drink except water for at least 10 hours) for all planned tests. Daily measurements during Run-in and Follow-up. 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 without fasting state required.

D At all visits, the respective kit number has to be allocated to the patient via IRT.

E Diligent diet and exercise counselling by a diet specialist or delegated staff member at Visit 2. Counselling is based on local diet recommendations. At all visits, patients should be reminded about the importance to follow the recommended diet and exercise plan.

F In addition to the visits indicated, ECG should be recorded in case of respective cardiac symptoms (indicating rhythm disorders or cardiac ischaemia).

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

H Calculated based on MDRD formula (see Section 5.2.3).

I Fasting blood samples (full overnight fast (nothing to eat or drink except water for at least 10 hours)). For the screening (Visit 1) safety laboratory only includes liver transaminases, alkaline phosphatase, and serum creatinine, for which patients do not have to be fasting.

J At Visit 3, AFTER blood sample of insulin, C-peptide and FPG drawing, patients will have a standardised breakfast which should be finished within 15 minutes and intake accepted pre-mixed insulin and/ or OAD (if applicable) according to the local insert label, and blood samples for insulin, C-peptide and PPG will be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast. Study medication will be taken after blood samples drawing.

At Visit 8, 30 min after blood sample of insulin, C-peptide and FPG drawing and administration of study medication (except the visit is after EOT), patients will have a standardised breakfast which should be finished within 15 min and intake accepted pre-mixed insulin and/ or OAD according to the local insert label (if applicable), and blood samples for insulin, C-peptide and PPG would be collected at time points 60 ±10 minutes and 120 ±10 min after the start of standardised breakfast. (All patients at all sites should participate)

K After the individual patient's end of the trial the investigator should report only cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the SAE form, please see protocol Section 5.2.6.1.

L The 8-point glucose profile must be started in the morning within one week prior to the Visit 3, 6 and 8.

M For those patients who have AEs persisting at Visit 8/EOT.

N For potential modifications of trial conduct in case of restrictions due to COVID-19, please refer to Sections 4.1.4, 6.1, 8.1, 8.3.2 and 10.2.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AGI	α-glucosidase inhibitor
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Products
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BMI	Body Mass Index
BUN	Blood urea nitrogen
CA	Competent Authority
CEC	Clinical Event Committee
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT	Computed Tomography
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
DB P	Diastolic blood pressure
DILI	Drug Induced Liver Injury
DKA	Diabetic ketoacidosis
DPP-4I	DPP-4 Dipeptidyl-peptidase IV inhibitior
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoT	End of Treatment
EoTrial	End of Trial
EudraCT	European Clinical Trials Database

FPG	Fasting plasma glucose
FUP	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP-1	Glucagon-Like Peptide-1
GMP	Good Manufacturing Practice
HA	Health Authority
HbA_{1c}	Haemoglobin A_{1c}
HBGM	Home Blood Glucose Monitoring
HDL	High Density Lipoprotein
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LDL	Low Density Lipoprotein
LPLT	Last Patient Last Treatment
MDI	Multiple daily injections
MDG	Mean Daily Glucose
MedDRA	Medical Dictionary for Drug Regulatory Activities
Met	Metformin
MRI	Magnetic Resonance Imaging
OAD	Oral Antidiabetic Drug
OPU	Operative Unit
p.o.	per os (oral)
PPG	Post-prandial glucose
q.d.	quaque die (once a day)
RA	Regulatory Authority
REP	Residual Effect Period
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
Scr	Serum creatinine

SGLT-2	Sodium-dependent glucose transporters 2
SOP	Standard Operating Procedure
SU	Sulphonylurea
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
UACR	Urine albumin-to-creatinine ratio
ULN	Upper Level of Normal
UTI	Urinary tract infections
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus (T2DM) is a progressive disease with high morbidity and mortality. Recent estimates suggest that the number of people worldwide with T2DM is currently 382 million and is expected to reach at least 592 million in 2035. In China, it is estimated that 113.9 million adults 18 years of age or older (11.6% of the adult population) have diabetes. In addition, 493.4 million Chinese adults (50.1%) have prediabetes, which is an important risk factor for the development of diabetes [R13-5351].

According to the Chinese Diabetes Society guideline, insulin therapy should be initiated in T2DM patients with insufficient glycemic control despite combination treatment of OADs and lifestyle intervention. In addition, patients on background therapy with insulin represent an important proportion of the T2DM patient population. A national wide survey showed more than 33% [R13-5351] of adults with type 2 diabetes receive insulin therapy, including both basal and premixed insulin, but only 26% of those have adequate glycemic control. Therefore, it is necessary to combine oral hypoglycemic drugs to control hyperglycemia for most patients. However, existing oral hypoglycemic drugs cannot fully meet this demand due to their characteristics and mechanism. There remains an unmet need for oral antidiabetes agents that can be added to insulin therapy to facilitate further improvements in glycemic control without causing hypoglycemia or weight gain.

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

In 2017, the guideline of Chinese Diabetes Society recommended SGLT-2 inhibitors as one of the second line OADs with special emphasis on its benefits on CV outcome and potential renal protection.

1.2 DRUG PROFILE

Empagliflozin (BI 10773) received its first marketing approval in April 2014 in Australia and is approved for the treatment of T2DM in more than 107 countries; the preferred trade name is Jardiance®. Based on a dedicated cardiovascular outcome trial (EMPA-REG OUTCOME®), a separate indication, reduction of the risk of cardiovascular death in patients with T2DM and established CV disease, was approved in more than 40 countries including the US, Canada and Australia. In over 50 countries including the EU, the indication was modified and/or the results included in the clinical trial section acknowledging the positive results of the CV outcome study.There have been no marketing withdrawals or suspensions, no failures to obtain marketing authorization renewal, no restrictions placed on the

distribution of the product and no clinical trial suspensions for any product containing empagliflozin.

Mode of action
Empagliflozin (BI 10773), an orally available potent selective SGLT-2 inhibitor, has been studied as part of a global development program including more than 20000 patients with type 2 diabetes treated in clinical studies of which more than 13000 were treated with empagliflozin, either alone or in combination with metformin, a sulfonylurea, a PPARγ agonist, dipeptidyl peptidase-4 (DPP-) inhibitors, or insulin. This agent lowers both the saturation threshold and the transport maximum of SGLT-2 for glucose, resulting in increased glucosuria, insulin-independent reduction of plasma glucose levels with a low risk of hypoglycemia, and negative energy balance with weight reduction.

Key pharmacokinetic characteristics
Empagliflozin showed mainly linear pharmacokinetics in humans reaching peak levels at approximately 1.5 h with a biphasic decline and a 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 faeces and urine, respectively. None of the detected metabolites were major. Empagliflozin tablets can be administered with or without food.

Drug interactions
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. At therapeutic doses, the potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 isoforms and UGT1 isoforms is remote. Drug-drug interactions involving the major CYP450 isoforms and UGT1 isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

No clinically meaningful interactions were observed when empagliflozin was coadministered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of empagliflozin is recommended when co-administered with commonly prescribed medicinal products.

Empagliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, in healthy volunteers and with or without co-administration of torasemide and hydrochlorothiazide in patients with T2DM. Increases in overall exposure (AUC) of empagliflozin were seen following co-administration with gemfibrozil (59%), rifampicin (35%), or probenecid (53%). These changes were not considered to be clinically meaningful.

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

Residual Effect Period
The Residual Effect Period (REP) of empagliflozin is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from non-clinical studies
A comprehensive package of safety pharmacology, general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology studies were conducted in mice, rats, rabbits and dogs to support the chronic administration of empagliflozin to humans. In addition, combination studies have been completed in rats with empagliflozin plus metformin or empagliflozin plus linagliptin. With the exception of the dose range finding and selected safety pharmacology studies, all studies were completed under good laboratory practice (GLP) conditions.

Data from clinical studies
Empagliflozin was well tolerated in both healthy subjects and patients with T2DM up to maximum treatment duration of 208 weeks in completed T2DM studies Treatment with empagliflozin resulted in a similar percentage of overall AEs, severe AEs, and serious AEs compared to placebo and/or active comparators.
In the global trial 1245.33 EMPA-REG BASAL™ and 1245.49 EMPA-REG MDI™, Empagliflozin was proven to significantly reduce HbA_{1c} in T2DM patients inadequately controlled with either basal insulin or MDI insulin [P15-05791, P14-09057]; Furthermore, in 1245.107, Empagliflozin was proven to be efficacious in Japanese T2DM patients inadequately controlled with insulin [c22646053]. Both Caucasian and Japanese patients were well tolerated and no new safety problems were found during the treatment period.

For a more detailed description of the Empagliflozin profile, please refer to the current Investigator's Brochure (IB) [c01678844].

1.3 RATIONALE FOR PERFORMING THE TRIAL

In China, more than 33% of adults with type 2 diabetes receive insulin therapy (basal or premixed), but only 26% of those have adequate glycemic control. Empagliflozin was approved in China in 2017 for the treatment of T2DM as an adjunct to diet and exercise and in combination with various oral anti-diabetic therapies. However, using Empagliflozin in combination with insulin has not been investigated in Chinese patients with T2DM. The aim of this study is to evaluate efficacy and safety over 24 weeks of Empagliflozin therapy in Chinese T2DM patients whose glycemia is inadequately controlled during background treatment with a stable dose of basal or premixed insulin, with or without oral antihyperglycemic drugs.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Potential general benefits for patients in this trial irrespective of the investigational medication received are: improvements in glycemic control, regular diet and exercise counselling, body weight reduction and a moderate blood pressure lowering, as well as

general medical benefit from careful and close monitoring by medical personnel, and Home Blood Glucose Monitoring (HBGM) during the trial.

1.4.2 Risks

Empagliflozin is investigational agent. Table 1.4.2: 1 displays the anticipated side effects of the study drugs, based on the mechanism of action, observed clinical data from ongoing studies, and published clinical data.

Table 1.4.2: 1 Potential risks, their rationale, and mitigation strategy

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: Empagliflozin		
Hypersensitivity and allergic reactions Unexpected adverse events	As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration.	Investigators will monitor the patients both clinically and by laboratory testing
Hyperglycemia	One third (33.3%) of patients will receive placebo and these patients thus have a higher probability of treatment failure, i.e., of increase in FPG and HbA_{1c}	Appropriate inclusion/exclusion criteria of HbA_{1c} and FPG value and criteria for rescue therapy and patient discontinuation will ensure an adequate treatment in case of any clinical concern

Table 1.4.2: 1 Potential risks, their rationale, and mitigation strategy (cont.)

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: Empagliflozin		
DKA	Rare but severe event which can be life-threatening and requires urgent hospitalization; Insulin deficiency might lead to ketoacidosis which could be life-threatening if not recognized and appropriately treated.	DKA is of particular concern for prospective safety monitoring and safety assessment within this trial. All patients in this trial will be made aware of this risk and be instructed not to reduce their insulin dose below Investigator recommendations. Investigators should also differentiate deteriorating ketosis/DKA from any mild to moderate increase of ketones expected from the mechanism of action of empagliflozin, especially in the fasted state (e.g., in the morning).
Volume depletion	Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis may lead to a modest decrease in blood pressure and dehydration.	Carefully monitor the volume status and electrolytes (e.g. blood pressure measurements, and laboratory tests including haematocrit); Patients will be requested to drink plenty of fluids as a precautionary measure.
Hypoglycemia	Because of the mechanism of action of empagliflozin, the risk of hypoglycemic episodes is considered to be low. However, with empagliflozin in combination with insulin, the risk of hypoglycemia may be increased compared to the treatment with insulin alone.	Symptoms attributed to hypoglycemia as well as glucose levels will be closely monitored in the trial.

Table 1.4.2: 1 Potential risks, their rationale, and mitigation strategy (cont.)

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: Empagliflozin		
Urinary tract infection (UTI)	Based on the mode of action of SGLT-2 inhibitors, the incidence of UTI may increase. The pooled analysis of UTI showed that, in general, empagliflozin 10 and 25 mg had similar frequencies of UTIs as placebo. Although rare, urosepsis was reported for more patients treated with empagliflozin than placebo, but there was no increase in frequencies for overall complicated urinary tract infections, including pyelonephritis. The frequency of UTIs leading discontinuations of studydrug was 0.6% with both empagliflozin groups compared to 0.3% in the placebo group.	Symptoms attributed to UTI will be closely monitored in the trial. UTI should be documented as an AE and appropriate therapy should be initiated.
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.
Trial procedures		
Commonly experienced in association with blood sampling		The amount of blood taken during the whole course of the trial is not believed to be excessive and is associated with the standard of care for the patients.

Risk evaluation in relation with COVID-19

Patients with serious underlying medical conditions such as T2D are at higher risk for severe illness from coronavirus disease 2019 (COVID-19). Therefore, in case of local high risk of

COVID-19 infection, on-site visits may not be carried out. In the event of restriction to visit the investigator site, a remote visit can be performed. This change is meant to keep the integrity of the trial and it will not affect the assessment of benefit-risk of empagliflozin.

There is no indication that empagliflozin may increase the risk of COVID-19 infection. As with any acute illness, empagliflozin use / treatment during COVID-19 infection has the potential to increase the risk of diabetic ketoacidosis. The risk of diabetic ketoacidosis in case of acute illness is adequately addressed in the IB and in the patient information and consent form.

In case of a confirmed COVID-19 infection, trial treatment will be discontinued (see Section 3.3.4.1).

1.4.3 Discussion

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 HBGM. Patients who are not adequately controlled, as evidenced by a confirmed high glucose value (refer to Section 4.2.1), will receive rescue therapy to ensure their safety or will be excluded from further study participation. The patient will continue to receive standard therapy throughout and the trial medication will be given in addition to this. Therefore they will continue to receive appropriate treatment.

Given the good safety profile in the toxicity studies of empagliflozin and the good tolerability seen in the human studies so far, the careful monitoring to be conducted during the study visits, and the blood glucose monitoring to be performed by the patients at home during the study, the sponsor considers the risks for the participating patients will be minimised and justified when compared with the potential benefits from this trial.

2. TRIAL OBJECTIVES AND ENDPOINTS

The objective of the current study is to investigate the efficacy and safety of Empagliflozin (10 mg or 25 mg, administered orally, once daily) compared to placebo given for 24 weeks in combination with stable insulin with or without up to two oral antidiabetic drugs in Chinese patients with T2DM with insufficient glycemic control.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

To determine the efficacy and safety of Empagliflozin added to stable insulin in Chinese patients with type 2 diabetes.

2.1.2 Primary endpoint(s)

The primary endpoint is the change from baseline in glycosylated haemoglobin $A1_c$ (HbA_{1c}) after 24 weeks of treatment. Throughout the study protocol, the term "baseline" refers to the last observed measurement prior to administration of any randomised study drug.

2.1.3 Secondary endpoint(s)

Secondary efficacy endpoints are:

- Percentage of patients with HbA_{1c}<7.0% after 24 weeks of treatment
- Change in body weight from Baseline to week 24
- Change in systolic blood pressure (SBP) from baseline to week 24
- Change in diastolic blood pressure (DBP) from baseline to week 24
- Change in Fasting Plasma Glucose (FPG) from baseline to week 24
- Change in 2-hour Post-prandial Glucose (PPG) from baseline to week 24

Secondary safety endpoints are:

- Occurrence of hypoglycemic events
- Occurrence of adjudicated diabetic ketoacidosis (DKA) events

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, multi-center, placebo-controlled, parallel group study compares Empagliflozin (10 mg or 25 mg) to placebo as add-on therapy to stable insulin with or without up to two oral antidiabetic drugs. The trial design is illustrated in Figure 3.1: 1.

In total, approximately 216 patients with T2DM who meet the entry criteria are planned for inclusion in this trial. The randomised treatment will be double-blind between Empagliflozin and placebo (i.e.each patient will receive one of two active treatments of Empagliflozin or placebo matching Empagliflozin).

Patients already on treatment with insulin with or without other OADs enter a 2-week open-label placebo run-in period. Patients who successfully complete the run-in period and who still meet the inclusion /exclusion criteria will be randomised to the 24-week treatment period of the study.

An independent external Clinical Event Committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see Section 5.2.6.1.4). 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.

Certain hepatic events will be adjudicated by external independent experts for severity and causal relationship with the trial medication in a blinded fashion. The events which will be reviewed are defined in a charter for hepatic events. Events may either be defined by 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 laboratory values, histological analysis, results of ultrasound, CT, 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 based on empagliflozin data combined from multiple trials (i.e. on project level).

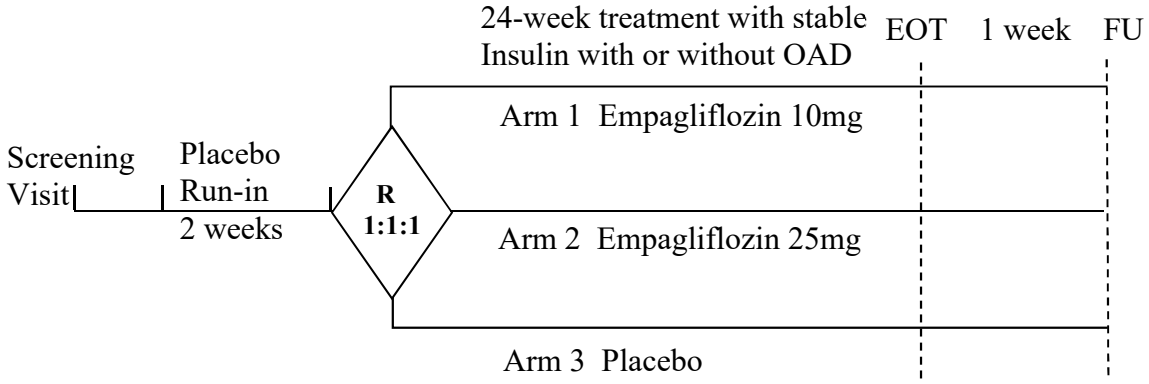

Figure 3.1: 1 Trial design

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The aim of this study is to evaluate efficacy and safety over 24 weeks of Empagliflozin therapy in Chinese T2DM patients whose glycemia is inadequately controlled during background treatment with a stable dose of basal or premixed insulin, with or without oral antihyperglycemic drugs.

As the patients entering the study will receive stable insulin as a part of standard of care and will receive rescue medication if indicated, a placebo-controlled trial is justified. Since patients will continue their baseline treatment, the risk of significant hyperglycemia is low during the 24 weeks. Additionally, rescue therapies can be applied during this time frame to assure patient safety.

The intention of the run-in period is to ensure central lab data availability for randomization, to assess the compliance of the IMP administration, to stabilize glucose related parameters other than HbA_{1c}, diet and exercise and background medication and act as a regular monitoring of blood glucose with a HBGM device for hyperglycemia assessment at baseline.

A double-blind and double-dummy design is adopted in order to minimize bias to evaluate the efficacy and safety of two doses (i.e. 10 mg and 25 mg) of empagliflozin and in comparison with placebo.The randomised treatment period is planned for 24 weeks because this corresponds to the expected relevant efficacy and safety exposure to support the submission of Empagliflozin as a drug for treatment of a chronic disease.

The one week follow-up period, after treatment, is considered to be sufficient since the pharmacodynamic effect of Empagliflozin, with respect to urinary glucose excretion, only extends to a maximum of 6-7 days after the last dose.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients will be enrolled into the trial in China. Approximately 25 trial centers will be participating to ensure that approximately 216 patients are randomised to one of three treatments (72 to Empagliflozin 10 mg, 72 to Empagliflozin 25 mg, and 72 to matched placebo for Empagliflozin).

It is expected that at least 5 patients will be enrolled at each trial center. Investigators who fail to enrol at least 1 patient in the first 6 weeks of the trial may be excluded from further participation. If enrolment is delayed, additional centers may be recruited.

Permission to randomise more than 30 patients per site must be obtained from the Clinical Trial Leader at Boehringer Ingelheim. This will only be allowed after a careful review of the enrolment status.
Enrolment of patients for this trial is competitive, i.e., enrolment for the trial will stop at all centers when it is anticipated that a sufficient number of patients will be randomised to trial treatment. Investigators will be notified when the appropriate numbers of patients have been enrolled and enrolment 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.
If the patient's background treatment type is not balanced as expected, the impact on the study conduct will be carefully considered. The sponsor will further monitor the recruitment of the trial with regard to the type of patient's background treatment. The intent is to obtain a balanced mix of patients pre-treated with insulin alone or up to two OADs. In the event of an imbalance, recruitment will remain open to all patients but investigators may be asked to preferentially recruit from a particular subgroup.
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 enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.
If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

The study will be performed in Chinese patients with T2DM who have insufficient glycemic control despite diet and exercise and receiving insulin alone or in combination with other OADs.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Age ≥18 years and ≤75 years old at Visit 1;
2. Chinese patient with diagnosis of Type 2 diabetes prior to Visit 1;
3. A stable treatment with premixed Insulin (≥ 20IU/day) or basal insulin (≥ 16 IU/day) for at least 12 weeks prior to enrolment with or without up to two OADs
    - With maximum insulin dose of ≤ 1 unit/kg/day. Acceptable basal insulins should have duration of action up to 24 h such as insulin Degludec, insulin glargin, insulin detemir or NPH (neutral protamine hagedorn) insulin; Acceptable pre-mixed insulins could be once or twice daily posology only. The total insulin dose should not be changed by more than 20% of the baseline value within the 12 weeks prior to randomisation (Visit 3). Both human insulin & insulin analogue are acceptable;
    - If the patient is taking OADs, regimen has to be unchanged for at least 12 weeks prior to randomization (Visit 3);
    - If the patient is taking metformin, stable dose (at least 1500 mg daily or maximum tolerated dose) must be maintained for at least 12 weeks without dose adjustments prior to randomization (Visit 3);
4. HbA_{1c} ≥7.5% and ≤11.0% at Visit 1;
5. Fasting C-peptide: >0.5 ng/mL (>166pmol/L) at Visit 1;
6. 18.5 kg/m^2 ≤ BMI ≤ 45 kg/m^2 at Visit 1;
7. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial;
8. Male or female patients. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

3.3.3 Exclusion criteria

1. Diagnosis of Type 1 diabetes;
2. Patients receiving MDI insulin or insulin pump treatment;
3. eGFR <45ml/min/1.73m^2 calculated based on MDRD formula;
4. Uncontrolled hyperglycemia [glucose level >13. 9 mmol/l after an overnight fast during placebo run-in];
5. Severe hypoglycemia episode (event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions) within 6 months prior to Visit 1;
6. History of diabetic ketoacidosis or hyperosmolar non-ketotic coma.
7. Myocardial infarction, stroke or transient ischaemic attack within 3 months prior to Visit 1;
8. Bariatric surgery;

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

9. SGLT-2 inhibitors intake within 12 weeks prior to Visit 1;
10. Treatment with anti-obesity drugs within 12 weeks prior to Visit 1;
11. Treatment with GLP-1 receptor agonists within 12 weeks prior to Visit 1;
12. Treatment with SU if the patient is on premixed insulin within 12 weeks prior to Visit 1;
13. Impaired hepatic function (serum alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase >3 times the upper limit of normal) at V1;
14. Contraindication to background anti-diabetes medication according to the local label;
15. Disorders causing hemolysis or unstable red blood cells;
16. Treatment with systemic steroids at the time of consent;
17. Change in dosage of thyroid hormones within 6 weeks prior to Visit 1;
18. Alcohol or drug abuse within 12 weeks prior to Visit 1;
19. History of unstable or rapidly progressing renal disease;
20. Conditions of congenital renal glucosuria;
21. Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors;
22. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned within 28 weeks after screening, e.g. hip replacement;
23. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix;
24. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g.chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant);
25. Previous enrolment in this trial;
26. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s);
27. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
28. Any other clinical condition that would jeopardize patient's safety while participating in this clinical trial (e.g. frequent hypoglycemic events on current therapy) in the opinion of the investigator.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment. You may refer to Sections 4.2.1 and 4.2.2.
- Introduction of rescue therapy due to hyperglycemia as described in section 4.2.1 does not lead to sufficient treatment efficacy (rescue criteria still met). In this case, the reason for discontinuation will be classified as “lack of efficacy”.
- Occurrence of hypoglycemia that may put the patient at risk with continued participation (e.g. repeated hypoglycemic episodes).
- 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.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy). In case of a temporary reason, trial treatment should be restarted if medically justified.
- The patient experiences an infection with SARS-CoV-2. The patient may resume trial treatment following recovery from SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

Patients who discontinue treatment prematurely will be followed up until the end of the trial as outlined in the Flow Chart and Section 6.2.2.
If a patient becomes pregnant during the trial the investigational drug will be stopped, the patient will be discontinued from the trial and the patient will be followed up until birth or otherwise termination of the pregnancy.

A patient can be discontinued from the trial after discussion between the sponsor and the investigator if the eligibility criteria are being violated.

Patients who discontinue or withdraw from the study during placebo run-in period and before being randomised at Visit 3 will be considered a run-in failure. They have to be recorded in eCRFs and no further follow-up is required (except for AEs, if needed).
Patients who are discontinued from the study after randomisation (Visit 3) and before completing 24 weeks of treatment will be considered as early discontinuations and the reason for the discontinuation must be recorded in the eCRFs. The reason will be included in the trial database and reported. If determined by the investigator as necessary for the patient’s safety, a new antidiabetic medication regimen can be started immediately after discontinuation and must be recorded in the eCRFs. In this case, end of treatment (EOT) visit must be performed before taking any new antidiabetic drug.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, and explain the scientific relevance of their data even if he/she discontinue the trial treatment as well as explain the options for continued planned visit up to follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial 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 invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The study medication will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1: Empagliflozin

Substance:	Empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg
Posology:	1 tablet once daily
Mode of administration:	p.o.

Table 4.1.1: 2 Test product 2: Empagliflozin

Substance:	Empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	25 mg
Posology:	1 tablet once daily
Mode of administration:	p.o.

Table 4.1.1: 3 Test product 3: Placebo to Empagliflozin

Substance:	Placebo to Empagliflozin 10mg and 25mg
Pharmaceutical formulation:	film-coated tablet

Table 4.1.1: 3 Test product 3: Placebo to Empagliflozin (cont.)

Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	1 tablet once daily
Mode of administration:	p.o.

4.1.2 Selection of doses in the trial and dose modifications

The doses of Empagliflozin chosen for this study are the doses approved in China for the treatment of T2DM.

4.1.3 Method of assigning patients to treatment groups

When a patient is confirmed eligible 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 interactive response technology (IRT). To facilitate the use of the IRT, the Investigator will receive an IRT manual including all necessary instructions for using the IRT. A copy of the manual will be available in the ISF.

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups of Empagliflozin film-coated tablet 10 mg, 25 mg or placebo for Empagliflozin tablet according to a randomisation plan in a 1:1:1 ratio at Visit 3 via Interactive Response Technology (IRT). The randomisation will be stratified by HbA_{1c} (< 8.5% vs. ≥ 8.5%) as determined from the blood sample taken at Visit 1 and background medication (Insulin alone or Insulin+OAD). For further details please refer to Section 7.5.

Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System). 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.

4.1.4 Drug assignment and administration of doses for each patient

Eligible patients will be randomised to Empagliflozin 10 mg, 25 mg or placebo. Medication will be dispensed in a double-blind manner. The Empagliflozin dosing is described in the Table 4.1.4:1.

Patients will be assigned a placebo run-in kit at the beginning of the placebo run-in period (Visit 2), and this kit will contain sufficient medication for the run-in period within visit window. Dispensing of kits for the double-blind treatment period will begin at Visit 3 and occur on 5 occasions over a period of 24 weeks.

During the COVID-19 pandemic, there might be situations that would not allow a patient to come to the site for Visit 4, 5, 6 or 7. If the investigator judges it as favourable and safe to continue trial medication, trial medication might be shipped from the site to the patient.

From the start of the placebo run-in period (Visit 2), patients should be instructed to take their trial medication, 2 tablets, once daily with water. To ensure a dose interval of about 24 hours, the medication is proposed to be taken at the same time every day. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken, 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 trial site. 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 for each visit. The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.
Patients will continue with their standard insulin with or without concomitant OADs therapy throughout the entire study.

Table 4.1.4: 1 Empagliflozin dose administration per dose group

Dose group	Empagliflozin 10 mg	Empagliflozin 25 mg	Total units per dose	Timing
Placebo run-in period (open-label)				
All patients	matching placebo	matching placebo	2 tablets	once daily, morning
Randomized treatment period (double-blind, double-dummy)				
10 mg	active drug	matching placebo	2 tablets	once daily, morning
25 mg	matching placebo	active drug	2 tablets	once daily, morning
Placebo	matching placebo	matching placebo	2 tablets	once daily, morning

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.
The access to the randomisation code will be kept restricted until its release for analysis.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.
The study medication will consist of packs labelled with the trial identification and medication kit number. Each pack will contain an appropriate number of Empagliflozin tablets or matching Empagliflozin placebo with some reserve (see below) for dosing until the next scheduled visit.
The placebo run-in kit, assigned to all patients successfully completing Visit 2, will contain 42 tablets (i.e. sufficient supply for 2 weeks, with 1 week in reserve). Each double-blind treatment period kit will contain 70 tablets (i.e sufficient supply for 4 weeks, with 1 week in reserve). At Visit 3, 4 and 5, the patient will receive 1 treatment kit. At Visit 6 and 7, the patient will receive 2 treatment kits. The dose administration for each group and kits please refer to Table 4.1.4: 1.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Trial Manager (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority

- Availability of the curriculum vitae of the Principal Investigator
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the Principal Investigator

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution center or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution center will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee 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.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Throughout the duration of the trial, patients should continue to take insulin alone or in combination with acceptable OADs as background therapy.
Acceptable basal insulins should have duration of action up to 24 h such as insulin degludec, insulin glargin, insulin detemir or NPH (neutral protamine hagedorn) insulin. The background medication of OADs should remain unchanged throughout the study. Acceptable pre-mixed insulins could be once or twice daily posology only.The total prescribed insulin dose should not be changed by more than 10% of the baseline value in the 24 weeks after randomisation unless rescue therapy criteria for treatment of hyperglycemia are met or in case of hypoglycemia requiring insulin dose reduction beyond the defined limits.The background medication will not be provided as part of the clinical trial supplies.

The patients can take their background medication as they are used to and should have the same habits of dosing throughout the trial, where it is suggested that basal insulin is always given in the evening. Morning dose of OADs/any permitted pre-mixed insulin and study medication should be taken after the visits blood sample taken.

Hyperglycemia
If the following FPG criteria in Table 4.2.1: 1 are met and confirmed, investigators may increase the insulin dose for the treatment of hyperglycemia according to their discretion and the change should be documented in the eCRF [R08-2669].

The first choice of rescue therapy should be the adjustment of insulin therapy. Its dosage will be left to the discretion of the investigator. However the insulin regimen and daily number of injections should remain unchanged. In very rare cases, adjustment of background therapy or addition of another oral anti-diabetic medication except SGLT-2 inhibitors would be appropriate. Such cases should be discussed with the Manager (CTM) or the Clinical Trial Leader (CTL).

Table 4.2.1: 1 FPG criteria for hyperglycemia

Week	Visit	FPG level
Week 1- 4	up to Visit 4 (included)	>270 mg/dl (>15.0 mmol/l) after overnight fast
Week 4-12	up to Visit 6 (included)	>240 mg/dl (>13.3 mmol/l) after overnight fast
Week 12-24	after Visit 6 until Visit 8	>200 mg/dl (>11.1 mmol/l) after overnight fast

To confirm the above results, there should be a minimum of two measurements, at least one of which performed after an overnight fast at the investigational site, and on a different day to the initial measurement.

A FPG, HbA_{1c} sample should be taken before initiation of rescue therapy and sent to central lab for analysis. The HbA_{1c} sample is not required if a sample has been taken and sent to the central lab for analysis within the last 4 weeks.

If, in the Investigator's clinical opinion, no further effect from the rescue medication is anticipated, and the patient's hyperglycemia cannot be controlled, the patient should be discontinued from the treatment as specified in section 3.3.4.

Hypoglycemia
If the patient is experiencing hypoglycemia (criteria see section 5.2.7), the investigator should review the HBGM log to determine the appropriate approach to reduce occurrences of hypoglycemia (e.g., encouraging the patient not to skip meals, increasing carbohydrate intake if increasing exercise, decreasing or adjusting the patient's permitted antidiabetic therapy).
In the case of hypoglycemia that may put patient on risk (e.g. repeated symptomatic hypoglycemia or severe hypoglycemia), appropriate adjustment of anti-diabetic therapy such as a dose reduction / discontinuation of ongoing rescue medication or existing background therapy should be initiated. Reduction or discontinuation of ongoing rescue medication should be considered before a reduction in the dose of existing background therapy.
Reduction of insulin dose should be the first choice among the existing background therapy while the insulin regimen and daily number of injections should remain unchanged.

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.
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.

In this trial, the background therapy (i.e. insulin alone or in the combination with OADs) are considered as non Auxiliary Medicinal Product (AMP).

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following restrictions are applicable during the screening, run-in and treatment period:

- Treatment with anti-obesity drugs, herbal medications with antidiabetic effects or systemic steroids due to their influence on glucose metabolism. However, one off or short-term use (i.e. ≤ 1 week's duration) of systemic steroids will be permitted as well as therapy with non-systemic steroids such as inhaled or local steroids.
- 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.
- SGLT-2 inhibitors are not allowed even as a rescue therapy.

Please also refer to section 3.3.3 regarding the permitted use of antidiabetic agents pre-trial.

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 delegated staff member. The counselling will be based on local diet recommendations. The patients will be reminded to follow the agreed diet and exercise plan at every visit. To avoid DKA, extreme diets (e.g., ketogenic diets) should be avoided. SGLT-2 inhibitor has a diuretic action and therefore dehydration may occur. Therefore, the investigator should instruct the patients to drink appropriate volume of water every day. Patients also should not take part in another clinical trial involving an investigational medicinal product within 30 days prior to informed consent.

4.2.2.3 Contraception requirements

Women of childbearing potential must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablet actually taken} \times 100}{\text{Number of tablet which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

HbA_{1c}
Blood samples for the determination of HbA_{1c} at the central laboratory will be taken at all the visits except Visit 2, the blood sample can be taken at any time during the visit. For the determination of HbA_{1c}, 3 mL of blood will be collected. The samples will be analysed at a central laboratory having a National Glycohaemoglobin Standardization Program (NGSP) Level I certificate. Further details about sample handling, shipment, and assay procedures can be found in the ISF (Lab manual).

Fasting plasma glucose (FPG)
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).

Meal Tolerance Test (MTT)
Meal Tolerance Test (MTT) will be performed using a standardised breakfast. MTT at Visit 3 would be performed before randomisation, i.e. without intake of trial medication during the MTT.
At Visit 3, after blood sample of insulin, C-peptide and FPG drawing, patients would have a standardised breakfast and intake OADs and/ or accepted pre-mixed insulin (if applicable), finished within 15 min, and blood samples for insulin, C-peptide and PPG would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast. Study medication will only be taken after last blood samples drawing, i.e. following randomisation.
At Visit 8, 30 min after blood sample of insulin, C-peptide and FPG drawing and administration of study medication (except the visit is after EOT), patients would have a standardised breakfast and intake OADs and/ or accepted pre-mixed insulin (if applicable), finished within 15 min, and blood samples for insulin, C-peptide and PPG would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast.

8-Point glucose profile
Eight-point blood glucose profiles are to be collected over a single 24-hour time period (approximately) within one week prior to scheduled visits as indicated in the Flow Chart.
Weighted mean daily glucose (MDG) will be evaluated only on Visits 3, 6 and 8/EOT.
Mean daily glucose (MDG) will be defined as the area under the curve (calculated using the trapezoidal method) divided by the measurement time.
Site should contact patients in advance to remind the conduction of the test. The timing of the 8-point blood glucose measurement is proposed as follows:

- Fasting before study drug administration, directly (defined as 0-5 minutes) before breakfast and fasting for at least 10 hours except for water
- 120 minutes after study medication administration and end of breakfast
- Directly (0-5 min) before lunch
- 120 minutes after end of lunch

- Directly (0-5 min) before dinner
- 120 minutes after end of dinner
- Directly (0-5 min) before bedtime
- Fasting before study drug administration, directly (0-5 min) before breakfast, and fasting

The 8-point blood glucose measurements will be performed by patients using HBGM equipment. The 8-point glucose data will be recorded manually on paper HBGM log. At the trial centers the 8-point glucose data will be transferred to the eCRF manually at Visits 3, 6 and 8/EOT visit for MDG evaluation. If a measurement is not done exactly at the planned time point, the data from the assessments done closest to the planned time point will be used. If any additional measurements are done that are not scheduled, the results will not be transferred to the eCRF.

Systolic and diastolic blood pressure:
SBP and DBP as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position. The blood pressure measurement should be performed three times at each time point and each value of these measurements will be entered in the eCRF. Further details on the procedure for blood pressure measurements are given in Appendix 10.1.

Weight and Waist circumference
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)

Waist circumference measurements should be made around a patient's bare midriff, after the patient exhales while standing without shoes and with both feet touching and arms hanging freely. The measuring tape should be made of a material that is not easily stretched, such as fibreglass. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface.
Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height will be performed at the time points specified in the Flow Chart.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.
This includes systolic and diastolic blood pressure (see Appendix 10.1) and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.
The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1, Table 5.2.3: 2 and Table 5.2.3: 3. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Safety laboratory samples (C-peptide at Visit 1 and all other visits) will be collected after a full overnight fast (nothing to eat or drink except water for at least 10 hours) and before background antidiabetic therapies and investigational drug as described in the Flow Chart and Section 6. The blood sample at Visit 1 (screening visit) except C-peptide can be taken with the patient in a fasted or nonfasted state.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.
The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF and EDC system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

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 and fasting C-peptide.
- Lipid fractions will only be determined at baseline (Visit 3) and end of treatment/ Visit 8

The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3: 1 Safety laboratory tests – Haematology

- Haematocrit
- Haemoglobin
- 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: 2 Safety laboratory parameters – Clinical Chemistry

• Amylase • Lipase • AST (aspartate transaminase,SGOT) • ALT (alanine transaminase,SGPT) • γ-GT (gamma-glutamyltransferase) • Alkaline phosphatase • Lactic dehydrogenase (LDH) • Total bilirubin • Direct bilirubin, if total bilirubinis elevated • Total Protein • Albumin • C-peptide (at Visit 1 only) • Creatine kinase (CK)Troponin, if CK is elevated	• Potassium • Sodium • Bicarbonate • Creatinine • BUN • Calcium • Inorganic phosphorous • Uric acid • Cholesterol (total)* • HDL cholesterol* • LDL cholesterol* • Triglycerides* • Glucose *Visits 3, 8, EOT only

Table 5.2.3: 3 Safety laboratory parameters – urine

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

The urine albumine-to-creatinine ratio (UACR) will be calculated at the central lab. Urine sediment will only be done if there is a positive finding on the urinalysis.

Glomerular filtration rate

The glomerular filtration rate (GFR) will be derived from serum creatinine* values based on the standard MDRD formula:
eGFR(ml/min/1.73 m^2) = 175 x [Screatinine (umol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is of African origin]
*: creatinine methods calibrated to an IDMS reference method

Pregnancy testing (urine) will be performed at site locally in female patients of child bearing potential only according to the timepoints indicated in the Flow Chart.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.
Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Home Blood Glucose Monitoring
All patients will be provided with HBGM equipment and supplies for use at home during the study period. Instruction on the proper use of the HBGM equipment 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 glucose value measured by HBGM will be recorded in the eCRF.
During placebo run-in and follow-up period, HBGM testing should be performed once daily in the fasted state and at any time the patient is symptomatic related to hypoglicemia or hyperglicemia through the entire period. If during placebo run-in period, results of a HBGM test reveal blood glucose of >240 mg/dL (13.3 mmol/L) after an overnight fast, the patient should contact the site. 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 is recommended to be done 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.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on 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. 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.

5.2.6.1.3 AEs considered “Always Serious”

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

The latest list of "Always Serious AEs" can be found in the EDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described above.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.
The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥5 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF and EDC system.
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.

Diabetic ketoacidosis (DKA)
The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty in breathing, confusion, unusual fatigue or sleepiness.
In case of a suspected DKA, the investigator should ensure that appropriate tests are performed at the earliest opportunity according to 2017 China T2DM guidelines, such as blood tests (glucose, BUN/creatinine, ketone) and blood gas test (pH, bicarbonate, anion gap). The results will be collected on the relevant page of the eCRF.
Investigators should also differentiate deteriorating ketosis/DKA from any mild to moderate increase of ketones which may be seen due to the mechanism of action of empagliflozin, especially in the fasted state (e.g. in the morning).
Due to its mechanism of action, empagliflozin may potentially modify the clinical

presentation of KA which may occur at lower plasma glucose levels in patients with DM. The diagnosis of KA in these patients can be based on arterial pH ≤ 7.30, serum bicarbonate levels < 15 and measurement of serum betahydroxybutrate levels. Other diagnostic criteria which can support the diagnosis of KA are urine ketones and anion gap > 10.
Investigators should note that not all criteria mentioned above need to apply for the diagnosis of KA, and clinical judgment should also be taken into consideration.

Decreased renal function
Decreased renal function is defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN.
For the AESI "decreased renal function" the patient needs to be followed-up appropriately based on local clinical guidance.

Events leading to lower limb amputation
Any event leading to a lower limb procedure of amputation, auto-amputation or disarticulation as defined below is considered as an AESI.
Amputation is a resection of a limb through a bone. Disarticulation is a resection of a limb through a joint. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb.
Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation). (International Working Group of Diabetic Foot, 2015).
Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.
The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report cancers of new histology and exacerbations of existing cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (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. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.3 Pregnancy

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

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

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

5.2.7 Criteria for hypoglycemic 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. Such hypoglycemic events should be documented in the eCRF 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
- Severe hypoglycemic episode: Event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

Note for severe hypoglycemia: If another person hands the carbohydrate or glucagon to the patient without having to actively administer the substance because the patient is able to take the substance on his or her own, the hypoglycemic episode does not qualify as severe.

Any hypoglycemia with glucose values < 54 mg/dl (< 3.0 mmol/l) and all symptomatic or severe hypoglycemia events should be documented as an adverse event of hypoglycemia.

Further details on documentation of hypoglycemia are provided on the respective eCRF pages.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in sections 5.1 and 5.2.

5.4.1 Biochemical and cellular biomarkers

Biomarker assays will be measured in a central laboratory.
1) C-peptide
2) Insulin

C-peptide will be tested with the sample collected on Visit 3 and Visit 8 at both fasting and postprandial status to assess the beta cell function, which will contribute to a better understanding of the influence of Empagliflozin in combination with insulin on the course of disease in the patients with T2DM.

Based on the analysis of fasting plasma insulin (FPI) and FPG, the Homeostasis Model Assessment (HOMA) indices will be derived in the following way [R07-1029]:
HOMA-Index (to assess insulin resistance (IR))
HOMA-IR = [FPG (mmol/L) × FPI (mU/mL)/22.5]
HOMA-Index (to assess insulin secretion)
HOMA-β = (20 × FPI (mU/mL)) / (FPG (mmol/L)-3.5)

5.4.2 Pharmacogenomics biomarkers

Not applicable.

5.4.3 Methods of sample collection

Additional biomarkers such as C-peptide and insulin will be determined according to the Flow Chart. Further details about sample handling and shipment can be found in the ISF (Lab manual).

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects in an appropriate way.
The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values, biomarkers specific to efficacy of treatment of T2DM, and ECG.
The primary and secondary endpoints are standard and accepted for evaluation of safety and tolerability of an oral antidiabetic drug, and they are widely used in respective pivotal phase III studies.
Measurements of insulin and c-peptide will be conducted in order to characterise endogenous insulin production and will contribute to a better understanding of the influence of empagliflozin combination with insulin with or without OADs on the pathogenesis and possible recovery of diabetes in the patients.
Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits should take place in the morning. If a patient mistakenly takes trial medication in the morning of a visit before attending the clinic (excluding visits starting before randomisation) or comes in fed condition where a fasting condition is required (all visits), the visit should be rescheduled for another day (except screening) as soon as possible reminding the patient of the expected conditions. The rescheduled visit must take place in a short enough time-frame so that the patient has sufficient trial medication available.
All patients are to adhere to the visit schedule as specified in the Flow Chart. 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. The run-in period must be 14-21 days long prior to randomization.
In the event of force majeure or other disruptive circumstances (e.g. pandemic) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments, and direct-to-patient shipments of trial treatment.
If it is not recommended to conduct Visit 4, 5, 6 or 7 at the trial site, it may be performed remotely (via telephone and/or internet- based means of communication). In the event of a remote Visit 4, 5, 6 or 7 trial medication may be shipped by courier from site to patient, if legally acceptable according to local regulations and considered safe for patient to continue treatment. It is important that any remote Visit 4, 5, 6 and 7 is discussed with and approved by the sponsor/CRO to ensure delivery of trial medication fulfil the trial specific and country-specific requirements. All efforts should be made to at least perform two of the four visits with the patient visiting the site. The maximum time interval without a face to face contact with the patient should not exceed 16 weeks (e.g. the 12 week site visit could only be done remote if a face to face contact was performed at the 4 week or 8 week visit). The patient must be made aware of any conduct modifications and agreement needs to be obtained prior to them being implemented. See Appendix 10.2 on the details of potential modification of trial conduct in case of restrictions due to COVID-19.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Trial procedures to be performed at each visit are listed in the Flow Chart and the respective protocol sections. Explanations of procedures are provided in section 5. Additional details regarding visit procedures are provided below. Please also reference the RDC instructions provided in the ISF for clarification on eCRF issues.
Sample collection for C-peptide at screening (Visit 1) and all other visits must be performed in fasted state (at least 10 hours with nothing to eat or drink except water).

At the end of every visit from Visit 2 to 8 the patient must be reminded to bring HBGM log, and the dispensed medication kit (from Visit 3) at the next scheduled visit. Preferably, a phone call to remind the patient must take place one or two days before the patient's next visit.

6.2.1 Screening and run-in period(s)

Screening Period
No trial procedures should be done unless the patient has consented to taking part in the trial. Once they have consented, the patient is considered to be enrolled in the trial and should then be recorded in the enrolment log, and screening will be started. The patient should be registered in the IRT and recorded in the eCRF as a screened patient at Visit 1.
Sample collection for C-peptide should be in fasted state, other prodedures at the visit can be in fed condition. If the patient comes for screening visit in fed state, all the procedures can be performed that day and those for fasting is conducted as soon as possible within the screen window. Hence all the procedures for Visit 1 may be performed at different days.
All patients on Visit 1 do not proceed to the next visit until laboratory results are reviewed by investigator.
Details of any patient who is screened for the study but is found to be ineligible must be entered in an enrolment log, registered as a screen failure in the IRT (refer to IRT user manual) and documented in the eCRF.

Run-in Period
From this visit on, patients should be fasting (no food or drinks, water only for at least 10 hours) prior to each visit.
Patients who fail the run-in period following Visit 2 procedures should be registered as a screen failure in the IRT (refer to IRT user manual).
For background treatment details please see section 4.2.1

Monitor adverse events, document in the patients' file (source data) and eCRF.
Instruct patients on the correct use of HBGM for glucose testing during the 2 week Run-In Period

- Patients should use the HBGM equipment/supplies to test glucose levels in a fasting state. During the Run-in period patients should test once a day before breakfast (i.e. after an overnight fast). Additionally, patients should test their glucose levels if they experience signs/symptoms of hypo- or hyperglycemia. Test results should be documented on the HBGM testing log. More frequent HBGM testing is permitted at the Investigator's and/or patient's discretion.
- If the HBGM test reveals an overnight fasted blood glucose of >240 mg/dl (>13.3 mmol/l), the patient should contact the study site for a visit at the next day. The investigator will then draw a new blood sample (overnight fasted samples for FPG determination) to confirm the hyperglycemia, document the AE if appropriate and decide about the possible exclusion from randomisation (screening failure).

The subject will be instructed to perform an 8-point HBGM over a single 24-hour time period (approximately) within one week prior to Visit 3. The plasma glucose levels should be measured and recorded in the log (including date, time and value) at the defined time points, details please see section 5.1.

Baseline Conditions
Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding T2DM) will be reported on the Baseline Condition eCRF page.

Medical History:
Medical history will be collected and reported in the Medical History eCRF page.
Information on clinically significant previous and concomitant illnesses, other than T2DM, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening on the Baseline Condition page in the eCRF.

6.2.2 Treatment period(s)

Patients must satisfy all inclusion and exclusion criteria prior to randomisation (see Section 3.3). In addition, if during the placebo run-in period, there is any indication that a patient's conditions of T2DM are not stable enough for the patient to complete the study or that the patient will not be compliant with the study medication or restrictions, the patient should not be randomised to the treatment.
The date of visit should be determined based on the date of Visit 3 and visits should occur within the allowed time frame shown in the Flow Chart.
The treatment period is from Visit 3 to Visit 8/EOT. Patients will be dispensed medication at each of these visits (except for Visit 8/EOT). Medication number of each occasion will be allocated by IRT (refer to IRT user manual).
Patients should not take study medication at home on the morning of trial visits during the treatment period.

Randomisation visit (Visit 3)
Visits should be performed fasting and as indicated in the Flow Chart and the respective protocol sections.
- Collection of urine and blood for laboratory testing must be performed prior to administration of study medication
- ECG is performed and evaluated
- Blood pressure should always be measured before taking any blood sample, details see Appendix 10.1
- Collect returned run-in medication
- Collect the HBGM test log
- Contact IRT to randomize patient and obtain medication kit numbers and dispense the medication to the patient
- After the patient has finished breakfast and last blood sample collected as MTT, administer first dose of study medication, which should be the last activity at this visit
- Patients should be reminded about the importance to follow the agreed diet and exercise plan
- Instruct patient NOT to take study medication and background medications on the morning of trial visits as described in Section 4.1.4

Visits 4-8/EOT
Visits should be performed as mentioned in the Flow Chart and the respective protocol sections.
- Collection of urine and blood for laboratory testing must be performed prior to

administration of study medication according to the Flow Chart
- All the patients including the treatment discontinued should perform the MTT and follow the process described in Section 5.1
- Blood pressure should always be measured before taking any blood sample, details see Appendix 10.1
- Collect returned medication prior to dispensing new medication
- Collect the HBGM test log
- New medication kit must be dispensed according to the Flow Chart, and IRT must be contacted at those visits to obtain medication kit numbers to be dispensed
- Patients should be reminded about the importance to follow the agreed diet and exercise plan.
- Instruct patient NOT to take study medication as well as background medications on the morning of trial visits as described in section 4.1.4
- Instruct patients to perform 8-point glucose profile within one week prior to visits as indicated in the Flow Chart
- Visit 8/EOT is the last visit of the treatment period. Study medication will not be dispensed at Visit 8/EOT

If a patient prematurely discontinues from the 24-week treatment period, the patient must return to the trial site for EOT (within 7 days of stopping study treatment) including MTT. The reason for premature trial drug discontinuation must be documented in the eCRF. In addition patients will be encouraged to attend all subsequent planned onsite visits despite not being under treatment anymore and perform all study procedures. If the EOT visit occurs within the time window of a planned visit, the EOT visit will replace the planned visit.

The need for coming to future visits in case of premature discontinuation of trial medication will be explained to patients prior to their participation in the trial.

The investigator may initiate any additional antidiabetic therapy for the patient, based on his or her discretion, no sooner than one day after discontinuing study medication or after Visit 8. Patients who prematurely discontinue the study should be registered as discontinued, and patients who complete the full 24-week double-blind treatment period should be registered as completed in the IRT.

6.2.3 Follow-up period and trial completion

For all patients completing the study according to protocol or prematurely discontinued without persisting AE at Visit 8, a follow-up contact (Visit 9) with the patient (preferably by phone) should be done by the investigator at the end of the followup period of 7 days. The following should be confirmed and recorded at Visit 9:

- Concomitant therapies
- Any AEs
- HBGM result

For patients completing the study according to the protocol or prematurely discontinued from the 24 week treatment period however, agree to return, with persisting AE at Visit 8, the following examinations should be performed at Visit 9 additionally:

- Vital signs
- Collection of blood and urine samples for safety laboratory evaluation
- FPG

Trial completion

The trial completion eCRF page has to be filled-in when the patient has terminated the trial. The end of the trial is:

- At the end of the follow-up visit for patients who have completed the trial on treatment as planned;
- After the early end of treatment (EOT) and follow-up visits, if a patient did not agree to come to the remaining planned study visits;
- At the end of Visit 9 for patients who discontinued drug early but agreed to come to the remaining planned study visits.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The superiority of Empagliflozin (10 mg q.d. and 25 mg q.d.) over placebo will be tested using the hierarchical hypothesis testing procedure. The following two sets of hypotheses will be tested sequentially each at the level of $\alpha = 0.05$ (two-sided). The second null hypothesis ($H_{0,2}$) for Empagliflozin 10 mg vs. placebo will be tested confirmatively only if the first null hypothesis ($H_{0,1}$) for Empagliflozin 25 mg vs. placebo is rejected. If the first null hypothesis ($H_{0,1}$) is not rejected, the second null hypothesis ($H_{0,2}$) will be tested in an exploratory fashion.

Step 1: The superiority of empagliflozin 25 mg against placebo will be tested for change from baseline in HbA_{1c} after 24 weeks of treatment at the level of α=0.05 (two-sided).

> $H_{0,1}$: Mean change from baseline in HbA_{1c} after 24 weeks of treatment with Empagliflozin (25 mg q.d.) = Mean change from baseline in HbA_{1c} after 24 weeks of treatment with placebo
>
> $H_{1,1}$: Mean change from baseline in HbA_{1c} after 24 weeks of treatment with Empagliflozin (25 mg q.d.) ≠ Mean change from baseline in HbA_{1c} after 24 weeks of treatment with placebo

Step 2: The superiority of empagliflozin 10 mg against placebo will be tested for change from baseline in HbA_{1c} after 24 weeks of treatment at the level of α=0.05 (two-sided).

> $H_{0,2}$: Mean change from baseline in HbA_{1c} after 24 weeks of treatment with Empagliflozin (10 mg q.d.) = Mean change from baseline in HbA_{1c} after 24 weeks of treatment with placebo
>
> $H_{1,2}$: Mean change from baseline in HbA_{1c} after 24 weeks of treatment with Empagliflozin (10 mg q.d.) ≠ Mean change from baseline in HbA_{1c} after 24 weeks of treatment with placebo

7.2 PLANNED ANALYSES

7.2.1 General considerations

The statisitical analyses will be performed on the following population.

Treated set (TS)

The TS will consist of all patients who are randomized and treated with at least one dose of the study drug. The assignment of patients to treatment groups will be based on the actual first study drug intake in the double-blind treatment period.

Modified Intention-to-Treat (mITT) set

The mITT set will consist of all randomized patients who are treated with at least one dose of the study drug and have a baseline HbA_{1c} assessment. The assignment of patients to treatment groups will be based on the planned randomised study drug at the time of randomisation.

Per Protocol set (PPS)

The PPS will consist of all patients in mITT set who do not have important protocol deviation (iPD) that may have a distorting influence on the assessment of the primary endpoint. The definitions of iPDs and the details of the handling of iPDs will be provided in the trial statistical analysis plan (TSAP).

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

7.2.2 Primary endpoint analyses

The primary endpoint in this trial is the change in HbA_{1c} (in unit of %) from baseline after 24 weeks of treatment. The baseline HbA_{1c} refers to the last HbA_{1c} assessment prior to the administration of any randomized study drug and not to the HbA_{1c} assessment used for the stratification in the randomisation.

7.2.2.1 Primary analysis of the primary endpoint

The primary analysis is a restricted maximum likelihood (REML) based approach using a mixed model for repeated measures (MMRM) comparing the mean change in HbA_{1c} from baseline after 24 weeks of treatment. The analysis will include treatment (Empagliflozin 10 mg, Empagliflozin 25 mg, placebo), background therapy (insulin only, insulin with OAD), and visit as fixed classification effects, baseline HbA_{1c} and baseline eGFR as the linear covariates, treatment by visit interaction, and baseline HbA_{1c} by visit interaction.

The statistical model will be as follows.

HbA_{1c} change from baseline at each on-treatment visit = overall mean
+ treatment + background therapy
+ baseline HbA_{1c} + baseline eGFR
+ visit + treatment-by-visit interaction
+ baseline HbA_{1c}-by-visit interaction
+ random error

Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurement.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α=0.05 (two-sided 95% confidence intervals). The residuals are assumed to

have a multivariate normal distribution with zero means and covariance matrix as specified above. The primary treatment comparisons will be the contrasts between active treatment (Empagliflozin 10 mg and 25 mg, respectively) and placebo at week 24.

The primary analysis will be performed on mITT set with patients assigned to the treatment they are randomised to and include on-treatment HbA_{1c} values only. If a patient misses a visit, the missing data will not be imputed. And all HbA_{1c} values measured after premature discontinuation of study drug or after rescue therapy is initiated will be set to missing. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

7.2.2.2 Secondary analyses of the primary endpoint

Sensitivity analysis

In order to check the sensitivity of the primary analysis results to missing data handling or to premature treatment discontinuation, sensitivity analyses will be performed as follows.

Multiple imputation of HbA_{1c} change from baseline after 24 weeks is planned for on- and off-treatment values for the three treatment groups individually. These analyses will be performed based on all randomised patients who have a baseline HbA_{1c} measurement.

Missing on-treatment values will be imputed using Markov Chain Monte Carlo (MCMC) simulation and standard techniques. Missing off-treatment data will be imputed based on the observed off-treatment data by treatment group, providing at least 6 patients provide off-treatment data at Week 24 in each treatment group. If fewer than 6 patients per treatment group provide off-treatment data at Week 24, on-treatment information from the placebo group will be used as a basis for the imputation. The imputation model will include baseline HbA_{1c} and the last on-treatment value. The analysis model will be an analysis of covariance (ANCOVA) model including treatment, background therapy, and continuous baseline HbA_{1c} and baseline eGFR; a common treatment estimate will be derived based on Rubin's method.

The number of imputations will be set to 100 in order to ensure adequate efficiency and stability of estimation of missing data.

Analysis on further patient set

The analysis of the primary endpoint will be repeated on the PPS using the same MMRM model as for the primary analysis to assess the impact of important protocol deviations.

Analysis of effectiveness

The analysis of the primary endpoint will be repeated on the mITT set but include all on- and off-treatment (i.e. measured after premature discontinuation of study drug or after rescue therapy is initiated) HbA_{1c} values using the same MMRM model as for the primary analysis to assess the effectiveness of the study drug.

[redacted]

7.2.2.4 Supplementary analysis

To explore the efficacy of pooled Empagliflozin doses (10 mg q.d. and 25 mg q.d.) over placebo, additional analysis on the primary endpoint will be repeated on the mITT set using the same MMRM model as for the primary analysis. More details will be specified in TSAP.

7.2.3 Secondary endpoint analyses

The percentage of patients with HbA_{1c} <7.0% after 24 weeks of treatment will be summarised in a frequency table by treatment groups and analysed using logistic regression. Odds ratios and their respective 95% confidence intervals and p-values will be obtained.

For continuous secondary endpoints of change from baseline in body weight, SBP, DBP and FPG at week 24, the similar MMRM approach based on on-treatment values for the primary analysis of the primary endpoint will be used. The model will include "baseline value for the corresponding endpoint" and its interaction with visit as additional covariates.

For continuous secondary endpoint of change from baseline in 2-hour PPG at week 24, an ANCOVA model will be applied since PPG is only measured at baseline and week 24. The ANCOVA model will include treatment and background therapy as classification effects, baseline PPG and baseline eGFR as the linear covariates.

Number of patients with hypoglycemic events and DKA events will be tabulated in frequency tables by treatment groups. Logistic regression will be performed to compare the occurrence of hypoglycemic events and DKA events between empagliflorin groups (10 mg and 25 mg, respectively) and placebo. Odds ratios and their respective 95% confidence intervals and p-values will be obtained.

More details of the analysis of secondary endpoints will be specified in TSAP.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 7 days after the last dose of trial medication, will be assigned to the on-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, i.e. all adverse events occurring between start of treatment and end of the REP. 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 MedDRA at database lock.

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 summarised. 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.

Further details of the safety analysis will be specified in TSAP.

7.2.6 Interim Analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

For the analysis of the primary endpoint, the handling of missing data is described in section 7.2.2.

For percentage of patients with HbA_{1c} <7.0% after 24 weeks of treatment, the missing data will not be imputed. Patients who prematurely discontinue the treatment or initiate rescue therapy will be treated as non-responder (i.e., HbA_{1c} ≥7.0% after 24 weeks of treatment).

No imputation for missing data will be performed for secondary efficacy endpoints of change from baseline in body weight, SBP, DBP and FPG. The missing data will be handled by MMRM model based on a likelihood method under the "missing at random" assumption.

Baseline Observation Carried Forward (BOCF) approach will be used for 2-hour PPG in ANCOVA analysis.

[redacted]

Missing or incomplete AE date will be imputed according to BI standards. Other missing safety data will not be imputed.

7.4 RANDOMISATION

The trial will be performed as a double-blind design with respect to placebo and the two active dose groups of Empagliflozin (10 mg q.d. and 25 mg q.d.). The randomization will be stratified by the following factors:

- HbA_{1c} value at screening visit (Visit 1) (<8.5%, ≥8.5%)
- Background antidiabetic therapy (insulin alone, insulin + OAD)

Block randomization will be used to randomize patients in a ratio of 1:1:1 to placebo or Empagliflozin 10 mg or Empagliflozin 25 mg.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

In the primary MMRM analysis (with excluded off-treatment and post-rescue values), the superiority of empagliflozin 25 mg and the superiority of empagliflozin 10 mg compared to placebo will be tested separately in a hirachical order at the two-sided alpha level of 0.05.

The effective sample size is calculated from the assumed treatment effect and the assumed covariate-adjusted standard deviation based on a two-sided t-test at alpha-level of 0.05. The effective sample size corresponds to the sample size in the absence of treatment drop-out or censoring, i.e. when all patients complete the 24 week treatment period without prematurely

discontinuing treatment and without initiating rescue therapy. Censored patients still contribute some information to the analysis and are accounted for in the actual sample size. Censored patients are assumed to contribute to sample size according to the amount of information provided as a fraction of a completer. This fraction is referred to as the information content. The sample size (SS) is derived from the effective sample size (SS_{eff}), the assumed censoring rate (CR) and the assumed information content (IC) using the following formula:

$$SS = \frac{SS_{eff}}{1 - CR(1 - IC)}$$

Based on the experience in previous studies with Empagliflozin add-on to insulin (e.g. U12-3817-01, U13-2122-01, P19-10212), it is estimated that the difference between Empagliflozin (10 mg q.d., 25 mg q.d.) and placebo in the change in HbA_{1c} from baseline at week 24 is about 0.62% with standard deviation of 1.1%. Given those assumptions, an effective sample size of 68 patients per treatment arm will provide 90% power to detect the standardized effect size of 0.564 (0.62/1.1) based on two-sample t-test at two-sided alpha level of 0.05 for each dose group. Assuming an 8% censoring rate (including premature treatment discontinuation and rescue therapy use) and an information content of 0.4 (based on results from previous studies), 72 patients per treatment arm are needed, leading to a total of 216 patients for three treatment arms.

The sensitivity of the sample size to the different scenarios of the assumptions is shown in Table 7.5: 1. Calculations were performed using nQuery Advisor® 7.0 statistical package by Statistical Solutions Ltd.

Table 7.5: 1 Power estimates for different scenarios for the MMRM analysis at two-sided $\alpha = 0.05$

Treatment effect (%)	Covariate adjusted standard deviation (%)	Censoring rate	Information content	Effective sample size per treatment arm	Sample size per treatment arm	Power
0.62	1.0	0.08	0.4	68	72	94.8
0.62	1.0	0.15	0.4	66	72	94.2
0.62	**1.1**	**0.08**	**0.4**	**68**	**72**	**90.3**
0.62	1.1	0.15	0.4	66	72	89.5
0.62	1.2	0.08	0.4	68	72	84.8
0.62	1.2	0.15	0.4	66	72	83.7

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".

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

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

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

The certificate of insurance cover is made available to the investigator and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to 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 patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

If study conduct may need to be adjusted (see Sections 6.1 and 10.2) during the COVID-19 pandemic, the patient must be made aware of any modifications and agreement needs to be obtained prior to them being implemented.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. 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

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be attributable, legible, contemporaneous, **o**riginal and accurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.
Copies of source documents necessary for adjudication will be provided to CRO responsible for adjudication . Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

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

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.
In the event of force majeure or other disrupting circumstances (e.g. pandemic, see Section 6.1), site access may be restricted thus limiting the ability to perform standard site monitoring activities such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised 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 at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

Not applicable.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in China will be performed by the local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

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10. APPENDICES

10.1 BLOOD PRESSURE MEASUREMENT PROCEDURE

The preferred method for blood pressure measurement is electronic sphygmomanometer. If, for some reason, the electronic sphygmomanometer cannot be used for the measurement of blood pressure, a standard mercury sphygmomanometer may be used as an alternate method. Initially, blood pressure should be taken 3 times in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), the arm with the higher pressure (systolic or – if needed to decide- diastolic) 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 must be used throughout the trial, for a given patient, i.e., if a patient receives the first blood pressure measurement for example with an electronic device, the same method and the same model of device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patients variability is acceptable, i.e., a study site is allowed to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient.
After patients have rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken approximately two minutes apart. The seated pulse rate of the second measurement will be used as the study data when an electronic device is used for the blood pressure measurement. In case of the measurement by using standard mercury sphygmomanometer, the seated pulse rate will be taken during the two-minute interval between the second and third blood pressure reading.

10.2 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19

As mentioned in section 6.1, in case of any restrictions during the COVID-19 pandemic, study conduct may need to be adjusted. The following contingency measures have been introduced to ensure patient safety and appropriate trial continuation based on a thorough benefit risk assessment (see Protocol Section 1.4.2).

In exceptional cases, when it is impossible to conduct the visits at the trial site, visits may be performed remotely (via telephone and/or internet based means of communication). Based on a thorough benefit-risk assessment (see Protocol Section 1.4.2), the visit procedures may be adjusted for the purpose of particular visits, whereby critical safety measures will remain in place. All remote visits need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements of the participating country need to be respected for all modifications.

Under these circumstances, the below modifications can be considered. Patients need to be informed about the modifications and agree to them before implementation:

Remote visit

If a patient is not able to come to the site for an outpatient visit, a remote visit (by phone) should be performed instead and all assessments that can be done by phone performed.

Assessments that should be performed during a remote visit are:
Adverse Events, concomitant therapy, Diet and exercise counselling,

Safety lab, other laboratory tests

If taking blood samples for central lab is not possible, blood analysis for safety lab can be done in a local lab for remote visit 6. The results of the lab tests are to be reported and transferred to the investigator, who has to ensure medical review and proper documentation. Minimum required safety lab parameters are eGFR, liver enzymes and urine pregnancy test in women of child bearing potential which will be captured in the eCRF. A urine analysis should not be performed locally. On top of this the home blood glucose monitoring by the patient needs to be reported to the investigator at each remote visit 4, 5, 6 and 7 anyway.

COVID-19 PCR testing at remote visits is not part of trial procedures and may only be performed based on investigator judgement about the needs.

Dispensation of Trial medication (IMP)

If a patient is not able to come to visit 4, 5, 6 or 7 as planned but the investigator considers it favourable and safe for patient to continue with IMP, IMP can be shipped from site directly to the patient (if legally acceptable according to the local regulations). Temperature monitoring will be considered, and the documentation should be filed in ISF

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		20Apr2021
BI Trial number		1245-0191
BI Investigational Medicinal Product(s)		Jardiance®, Empagliflozin BI 10773
Title of protocol		A phase III, randomised, double-blind, placebo-controlled, parallel group study of Empagliflozin (10 mg and 25 mg) administered orally once daily in combination with insulin with or without up to two oral anti-diabetic agents for 24 weeks in Chinese type 2 diabetic patients with insufficient glycemic control.
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Title page
Description of change		CTL information changed
Rationale for change		Team member hand over
Section to be changed		Synopsis
Description of change		Trial design, number of patients, inclusion criteria and statistical methods
Rationale for change		To be consistent with the sections 3.1, in the protocol.
Section to be changed		section 3.1
Description of change		Added Empagliflozin pooled doses in design and updated the total patient number
Rationale for change		To reflect the update in 7.2 planned analysis and 7.5 sample size calculation.
Section to be changed		section 3.3
Description of change		updated the total patient number and each treatment number
Rationale for change		To reflect the update in section 7.5 sample size calculation.
Section to be changed		section 3.3.2, section 4.2.1
Description of change		Inclusion criteria #3 is updaed “Acceptable basal insulins should have duration of action up to 24 h such as Insulin Degludec, insulin glargin, insulin detemir or NPH (neutral protamine hagedorn) insulin;”

		Inclusion criteria #5, the SI unit for Fasting C-peptide is added
Rationale for change		To clarify better the acceptable basal insulins definition To be consistant with the unit in the lab report;
Section to be changed		section 3.3.4.1
Description of change		Added one more criteria of treatment discontinuation: The patient experiences an infection with SARS-CoV-2. The patient may resume trial treatment following recovery from SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor. Removed "as run-in falure" from "They have to be recorded in eCRFs and no further follow-up is required (except for AEs, if needed)."
Rationale for change		COVID-19 pandemic; To consistent with eCRF form.
Section to be changed		section 4.1.4
Description of change		To ensure a dose interval of about 24 hours, the medication **is proposed to** be taken at the same time every day.
Rationale for change		To clarify the medication taken time requirement which is not at the exact same time every day for actual practise.
Section to be changed		section 4.2.1
Description of change		added the adverbial clause in "The total prescribed insulin dose should not be changed by more than 10% of the baseline value in the 24 weeks after randomisation **unless rescue therapy criteria for treatment hyperglycemia are met or in case of hypoglycemia requiring insulin dose reduction beyond the defined limits.**"
Rationale for change		To clarify the insulin dose is allowed to change under the specific condition as described in the same section.
Section to be changed		section 5.1
Description of change		Site should contact patients in advance to remind the conduction of the test. The timing of the 8-point blood glucose measurement is **proposed** as follows

Rationale for change		To clarify better the requirement for the 8-point glucose measurement.
Section to be changed		section 6.2.1
Description of change		If the HBGM test reveals an overnight fasted blood glucose of >240 mg/dl (>13.3 **m**mol/l), the patient should contact the study site for a visit at the next day.
Rationale for change		To correct typo in the unit
Section to be changed		Section 7.2.2.1
Description of change		In MMRM, the response variable HbA1c change from baseline at week 24 were changed HbA1c change from baseline to at each on-treatment visit.
Rationale for change		To correct the typo in the response variable.
Section to be changed		Section 7.2.2.4
Description of change		Added supplementary analysis to explore the efficacy of empagliflozin pooled doses (10 mg + 25 mg) against placebo.
Rationale for change		To better address the scientific question whether Empagliflozin is efficacious as add-on to insulin in Chinese patients with T2DM.
Section to be changed		Section 7.5
Description of change		The estimated difference between Empagliflozin (10 mg q.d., 25 mg q.d.) and placebo in the change in HbA_{1c} from baseline at week 24 is updated to 0.62% and 72 (instead of 91) patients per treatment arm and a total of 216 patients are needed.
Rationale for change		A study of Empagliflozin as add-on to insulin in Japanese patients with T2DM has shown a more pronounced effect.
Section to be changed		section 8.3.2
Description of change		Added the **extra** access to source data and documents**:** In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see section 6.1), site access may be restricted thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be

		performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.
Rationale for change		COVID-19 pandemic
Section to be changed		Section 9.1
Description of change		Published reference P19-10212 is added.
Rationale for change		As reference for the updated estimated treatmnent difference.
Section to be changed		Section 1.4.2
Description of change		Risk evaluation in relation with COVID-19 added: Patients with serious underlying medical conditions such as T2D are at higher risk for severe illness from coronavirus disease 2019 (COVID-19). Therefore, in case of local high risk of COVID-19 infection, on-site visits may not be carried out. In the event of restriction to visit the investigator site, a remote visit can be performed. This change is meant to keep the integrity of the trial and it will not affect the assessment of benefit-risk of empagliflozin. There is no indication that empagliflozin may increase the risk of COVID-19 infection. As with any acute illness, empagliflozin during COVID-19 infection has the potential to increase the risk of diabetic ketoacidosis. The risk of diabetic ketoacidosis in case of acute illness is adequately addressed in the IB and in the patient information and consent form. In case of a confirmed COVID-19 infection, trial treatment will be discontinued.
Rationale for change		COVID-19 pandemic
Section to be changed		Flow Chart, Section 4.1.4, 6.1, 8.1 and 10.2;
Description of change		Contingency measures have been introduced to ensure patient safety and appropriate trial continuation based on a thorough benefit risk assessment (see Section 1.4.2) and above. Introduce flexibility for trial visits: to allow in exceptional cases visits to be done as remote visits; to allow for IMP shipment from site to

		patient in this case. Patients need to agree to changes prior to them being implemented. Comment added below the Flow Chart to refer to the contingency measures if they are needed.
Rationale for change		COVID-19 pandemic

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	[redacted]	06 May 2021 13:33 CEST
Author-Trial Statistician		07 May 2021 03:48 CEST
Approval-Clinical Trial Leader		07 May 2021 05:58 CEST
Approval		07 May 2021 07:57 CEST
Verification-Paper Signature Completion		07 May 2021 10:14 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed