CLINICAL TRIAL PROTOCOL

	Document Number:	**c03122592-02**
BI Trial No.:	1245.107	
BI Investigational Product:	Jardiance®, Empagliflozin	
Title:	A 52-week randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of empagliflozin once daily, as add-on to insulin in Japanese patients with Type 2 Diabetes Mellitus with insufficient glycaemic control	
Brief Title:	Empa add-on to Insulin (Japan)	
Clinical Phase:	IV	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone/Fax:	
Status:	Final Protocol	
Version and Date:	**Version:**	**Date:**
	2.0	13 September 2016

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Jardiance®	
Name of active ingredient:		Empagliflozin	
Protocol date: 1 SEP 2015	**Trial number:** 1245.107		**Revision date:** 13 SEP 2016

Title of trial:	A 52-week randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of empagliflozin once daily, as add-on to insulin in Japanese patients with Type 2 Diabetes Mellitus with insufficient glycaemic control
Coordinating Investigator:	
Trial site:	Multi-centre trial in Japan
Clinical phase:	IV
Objective:	The objective of the study is to investigate the efficacy and safety of empagliflozin (10 mg and 25 mg, once daily) compared to placebo given for 16 weeks as add-on therapy to stable insulin treatment and the long-term safety and efficacy of empagliflozin (10 mg and 25 mg, once daily) compared to placebo given for an additional 36 weeks as add-on therapy to adjustable-dose insulin treatment in Japanese patients with type 2 diabetes mellitus (T2DM) with insufficient glycaemic control
Methodology:	Randomised, double-blind, placebo-controlled, parallel group
No. of patients:	
total entered:	267 patients (399 patients enrolled)
each treatment:	3 treatment groups, 1:1:1 ratio of randomisation Empagliflozin 10 mg : 89 patients Empagliflozin 25 mg : 89 patients Placebo : 89 patients
Diagnosis :	Type 2 Diabetes Mellitus

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Main criteria for inclusion:	1. Diagnosis of type 2 diabetes mellitus prior to informed consent. This diagnosis should be confirmed by clinical judgment and negative results of Anti-GAD antibody and Anti-IA-2 antibody at Visit 1 (screening). 2. Male and female patients on diet and exercise regimen who are pre-treated with any insulin therapy[a)] alone [c)] or in combination with 1 oral antidiabetic drug (OAD) [b), c)] for at least 12 weeks prior to Visit 1 (screening). a) Any kind of insulin therapy (Basal-Bolus therapy, Bolus insulin therapy, Premix insulin therapy and Basal insulin therapy) approved in Japan is allowed. The choices of insulin product, dosage and usage have to follow respective insulin product label in Japan at Visit 1 (screening). b) Sulfonylurea is permitted as a pre-treatment drug only if the dose is not more than a half of daily maximum approved dose. Any other OADs except thiazolidinedione and SGLT-2 inhibitors are allowed at any dose within approved dose. c) If patients are pre-treated by insulin with 1 OAD at Visit 1, the OAD should be stopped and washed-out for 10 weeks prior to Visit 4 (placebo run-in). For patients receiving insulin alone at Visit 1, no wash-out (of any drug) is necessary. Insulin product and its usage must be unchanged at least from 12 weeks prior to Visit 1 (screening). Total prescribed insulin dose must be ≥10 U/day, and it has to be within a defined area at least 12 weeks prior to Visit 5 (randomization) in patients who are pre-treated by insulin alone and from Visit 1 in patients who are pre-treated by insulin in combination with 1 OAD. The defined area is as follows, In case of the insulin dose at 12 weeks prior to Visit 5 in patients who are pre-treated with insulin therapy alone (at Visit 1 in patients who are pre-treated with insulin in combination with 1

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	OAD) is • ≥20 U/day: Within +/- 10% change from the dose at Visit 5 is allowed. • ≥10 U/day and <20 U/day: Within +/- 2 U change from the dose at Visit 5 is allowed. (insulin dose <10U is not allowed prior to and at Visit 5) 3. Fasting C-peptide: >0.5 ng/mL at Visit 4 in patients who are pre-treated with insulin alone (at Visit 2 in patients who are pre-treated with insulin in combination with 1 OAD) 4. Patients who are treated with insulin alone: HbA_{1c} at Visit 1: ≥7.5% and ≤10.0% 5. Patients who are treated with insulin with 1 OAD: HbA_{1c} at Visit 1: ≥7.0% and ≤9.5% HbA_{1c} at Visit 4: ≥7.5% and ≤10.0% 6. Age at informed consent: ≥ 20 years and <75 7. BMI (body mass index) at Visit 1 : >22 and ≤40 kg/m^2 8. Signed and dated written informed consent by date of Visit 1 in accordance with GCP and Japanese legislation
Test product:	Empagliflozin
dose:	10 mg and 25 mg
mode of administration:	Oral administration
Comparator products:	Placebo matching for empagliflozin
dose:	Not applicable
mode of administration:	Oral administration

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Duration of treatment:	Screening period: 1 week Wash-out period (only for patients who are pre-treated by insulin with 1 OAD): 10 weeks Placebo run-in period (open label): 2 weeks Double-blind treatment period: 52 weeks Follow-up period: 1 week
Endpoints	Primary endpoint is the change from baseline in HbA_{1c} after 16 weeks of treatment. The secondary endpoint is proportion of patients with drug-related adverse events during 52 weeks of treatment.
Safety criteria:	Adverse events, serious adverse events, adverse events of special interest, adverse events leading to discontinuation, hypoglycaemic adverse events, clinical laboratory assessments, vital signs
Statistical methods:	The primary analysis is an analysis of covariance (ANCOVA) comparing the change from baseline in HbA_{1c} after 16 weeks of treatment. The statistical model includes treatment, renal function and type of insulin therapies as fixed effects, and baseline HbA_{1c} as a covariate. The hierarchical testing procedure will be used to evaluate superiority of empagliflozin 10 mg against placebo followed by superiority of empagliflozin 25mg against placebo, while maintaining the overall probability of type I error at 0.05 (two-sided). Descriptive statistics will be used to analyse the safety endpoints.

FLOW CHART

Trial period	**Screening**	**Wash-out**[1]		**Placebo run-in**	**Double-blind treatment period 1 (fixed dose of insulin)**							**Double-blind treatment period 2 (adjustment of insulin dose permitted) Double-blind**									**Follow up**
Visit	**1**	**2**[1]	**3**	**4**[1]	**5**	**5.1**[2]	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ EOT**[12]	**20/ F-up**[14]
Study week	**-3/-13**	**-12**	**-8**	**-2**		**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**EOT+1w**
Study day	**-21/-91**	**-84**	**-56**	**-14**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**EOT+7**
Visit window (in days)	+/-7	**-7**	+/-7	**-7**	na	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+7
Informed Consent	X																				
Medical history / concomitant diagnoses	X																				
Demographics	X																				
In-/Exclusion criteria	X			X	X[3]																
Physical Examination					X						X									X	(X)[14]
Vital Signs[4]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)[14]
Height	X																				
Diet and exercise counselling[18]	X	X	X	X	X		X	X	X	X	X	X		X			X			X	
Review Food log, completed for 3 days[18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead-ECG[4,5]	X				X				X		X			X			X			X	
Pregnancy testing[6]	X				X				X		X			X			X			X	
Safety Labs[4, 7]	X[10,11]			X	X		X[16]	X[16]	X	X[16]	X	X[16]	X[16]	X	X[16]	X[16]	X	X[16]	X[16]	X	(X)[14]
FFA and Ketone bodies				X	X			X	X		X		X		X		X		X	X	
Bone markers					X						X									X	

Trial period	**Screening**	**Wash-out**[1]		**Placebo run-in**	**Double-blind treatment period 1 (fixed dose of insulin)**							**Double-blind treatment period 2 (adjustment of insulin dose permitted) Double-blind**									**Follow up**
Visit	**1**	**2**[1]	**3**	**4**[1]	**5**	**5.1**[2]	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ EOT**[12]	**20/ F-up**[14]
Study week	**-3/-13**	**-12**	**-8**	**-2**		**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**EOT+1w**
Study day	**-21/-91**	**-84**	**-56**	**-14**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**EOT+7**
Visit window (in days)	+/-7	**-7**	+/-7	**-7**	na	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+7
Antibodies (Anti-GAD, Anti-IA-2)	X[11]																				
Fasting C-peptide[17]		X[17]		X[17]																	
HbA_{1c}	X[11]			X[13]	X				X		X			X			X			X	
SMBG measurement and log[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT transaction	X[3]			X[3]	X[3]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense placebo run-in medication[9]				X																	
Medication compliance check					X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomisation (via IRT)					X[3]																
Dispense double-blind medication[9]					X			X	X	X	X	X	X	X	X	X	X	X	X		

1. Only patients who are pretreated by insulin with 1 OAD proceed to the wash-out period and are requested to refrain from taking their OAD during the wash-out period. Patients who are pretreated by insulin therapy alone skip the washout period and proceed to the placebo run-in period. In either case, the next visit (i.e., Visit 2 or Visit 4) should be made after receiving the result of the laboratory tests performed at Visit 1.
2. The investigator or designated site staff makes a call to patients to confirm patient's safety through checking patient's food log, SMBG results, adverse events and concomitant therapies.
3. Inclusion and exclusion criteria should be checked before making the IRT call/notification.
4. Vital signs and ECG must be measured prior to blood sampling.
5. In addition to the visits indicated, ECG should be recorded in case of respective cardiac symptoms (indicating rhythm disorders or cardiac ischaemia)
6. For female patients (local urine pregnancy test in women of child bearing potential)
7. Fasting blood samples for central lab testing except for urine dipstick, which is to be done locally; upon positive result at site for leukocyte esterase (for WBC) or nitrites a midstream urine sample for urine culture (central lab analysis) should be taken.
8. Self-Monitoring Blood Glucose (SMBG) device to be provided at Visit 2 to patients who need wash-out of an OAD or at Visit 4 to patients who do not need washout. Patients should be instructed to monitor fasting blood glucose at least once daily before breakfast (if possible, it is recommended to monitor fasting blood glucose in preprandial state and before bedtime) and at any time the patient is symptomatic related to hypoglicaemia or hyperglicaemia through the entire study period (i.e., after providing the SMBG device until the end of follow-up). In addition, in 3 consecutive days in the week before each scheduled visit, patients will be requested to monitor fasting blood glucose at preprandial state (i.e., before breakfast, lunch and dinner), before bedtime and at any time when the patient is symptomatic. Patients are requested to maintain a diary with daily recordings of glucose values measured by SMBG and of insulin dose through the entire study period.
9. At all the visits which are marked on the flow chart, the respective kit number has to be allocated to the patient via IRT.
10. Only includes liver transaminases (i.e. AST and ALT), ALP, serum creatinine, TSH and urinalysis.
11. No need to be collected in fasted state.
12. In case of early discontinuation from treatment, the end of treatment (EOT) visit has to be performed within 7 days of the last dose of the study drugs. And the follow up (F-up) visit has to be performed after 7 days of the EOT (with +7 days allowance).
13. Patients who are pretreated with insulin alone skip the HbA_{1c} measurement at Visit 4.
14. For patients who completed the trial without any persisting adverse event at EOT, a follow-up visit can be performed as a phone visit (only information on SMBG log, adverse events, and concomitant therapies are to be obtained). For patients who completed the trial with persisting adverse event(s) at EOT and patients who early discontinued the 52 weeks treatment period, an EOT and a follow-up visit (at the follow up-visit, physical examination, vital signs, and safety lab and should be performed additionally) should be performed at clinic visits.
15.
16. Only blood sampling for haematology and urinalysis will be performed.
17. C-peptide will be measured at Visit 2 in patients who need wash-out of an OAD or Visit 4 in patients who do not need wash-out.
18. Diligent diet and exercise counselling by a diet specialist or trained staff member. Counselling is based on the diet and exercise recommendations of the Japanese Diabetes Society and should include a food log (recording of food intake for 3 consecutive days in the week before the actual visit).

TABLE OF CONTENTS

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BI	Boehringer Ingelheim
BMI	body mass index
CEC	clinical event committee
CK	creatinine kinase
CML	local clinical monitor
CRA	clinical research associate
CRO	contract research organization
CTP	clinical trial protocol
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGRF	estimated glomerula filtration rate
EOT	end of treatment
EudraCT	European Clinical Trials Database
FAS	full analysis set
FFA	free fatty acid
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GTI	genital tract infection
Hb	haemoglobin
HbA_{1c}	glycosylated haemoglobin A_{1c}
IB	investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
ISF	investigator site file
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	mixed model repeated measures
NBI	Nippon Boehringer Ingelheim
OAD	oral antidiabetic drug

OC	observed case
PPS	per protocol set
PT	preferred term
RBC	red blood cell
RDC	remote data capture
REP	residual effect period
SAE	serious adverse event
SGLT-2	sodium-glucose co-transporter 2
SMBG	self-monitoring blood glucose
SOC	system organ class
SOP	standard operation procedure
SUSAR	suspected serious unexpected adverse reaction
TCM	trial clinical monitor
TS	treated set
TSAP	trial statistical analysis plan
TSH	thyroid stimulation hormone
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell

1. INTRODUCTION

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

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 387 million affected people worldwide. Its prevalence is expected to increase to approximately 592 million people during the next 20 years. Complications induced by hyperglycaemia are a common and serious global health problem, which have evolved from adult-onset loss of vision, renal failure, and amputation in the industrialised world. Diabetes is also associated with macrovascular complications with a 2- to 4-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of life expectancy.

Commonly available oral antidiabetic drugs are efficacious for a time, but still fail to achieve an optimal blood glucose control in many patients. In Japan, approximately 9.5 million people are strongly suspected to be affected by T2DM and approximately 11.0 million people are undeniable to be affected by T2DM; total 20.5 million people are suffering from either T2DM or pre-diabetic, which is approximately 1 out of 6 of Japanese population (Ministry of Health, Labour and Welfare, National Health and Nutrition Examination Survey, 2012)

The Treatment Guide for Diabetes 2014-2015 in Japan recommends to achieve the glycaemic goal of glycosylated haemoglobin A_{1c} (HbA_{1c}) to <7.0% in preventing the onset of microangiopathy and inhibiting its progress, while it states that suitable current treatment aims should be established according to age and complications on a case-by-case basis [R14-4302]. If good control cannot be achieved with one type of oral antidiabetic agent, combination therapy with another drug having a different mode of action should be recommended.

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 glycosuria typically seen in patients with diabetes mellitus. The capacity to reabsorb glucose can be decreased by inhibition of SGLT-2. In humans, empagliflozin very highly selectively blockades glucose transport via SGLT-2 (IC_{50} 1.3 nmol/l), with a 5000-fold selectivity over SGLT-1 (IC_{50} 6278 nM).

In 2014, the Japan Diabetes Society released a recommendation for a proper use of SGLT2 inhibitors. In the recommendation, it is told that when using SGLT2 inhibitors in combination with insulin or sulfonylureas, occurrence of hypoglycaemia should be carefully watched and the administration of SGLT2 inhibitor should be done carefully for elderly patients; and also

it is mentioned that the occurrence of dehydration should be paid attention. For further details see the recommendation [R15-2908].

1.2 DRUG PROFILE

Empagliflozin received its first worldwide marketing approval in Australia on 17 April 2014. As of May 2015, marketing approval has been received in many countries including European countries and US. In Japan, empagliflozin was approved for marketing on 26 Dec 2014.

The efficacy of empagliflozin is expected to be similar to the current oral antidiabetic drugs (OADs) and empagliflozin can be administrated in combination with other OADs and may show additional efficacy in terms of glucose control when used in combination with insulin or glucagon-like peptide-1 (GLP-1) receptor agonist in diabetic patients.

Non-clinical assessment of safety
A comprehensive package of safety pharmacology, genetic toxicology, reproductive toxicology and general toxicology studies were conducted in mice, rats, rabbits and dogs to support the chronic administration of the two doses of empagliflozin (10 mg/day and 25 mg/day) to humans. The compound is well tolerated in animals at clinically relevant plasma exposures, while adverse effects were observed at higher exposures.

For further preclinical details see the current version of the empagliflozin Investigator's Brochure (IB) [c01838761].

Clinical pharmacokinetics
Empagliflozin predominantly showed linear pharmacokinetics following single oral doses and at steady-state after multiple oral doses in Caucasian and Japanese subjects. Empagliflozin was rapidly absorbed reaching peak levels at approximately 1.5 hours in Caucasian and 1 to 2.5 hours in Japanese, and showed a biphasic decline with the terminal elimination half-life ranging from 10 to 19 hours in Caucasian and from 8 to 12 hours in Japanese.

In Caucasian subjects, following oral administration of [^{14}C]-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.

Empagliflozin exposure increased with hepatic and/or renal impairment; however, no dose adjustment is recommended for patients with renal and hepatic impairment as the observed changes in empagliflozin exposure in those patients were not clinically meaningful.

No clinically relevant pharmacokinetic interactions were observed
with metformin, glimepiride, pioglitazone, sitagliptin, warfarin, linagliptin, verapamil, ramipril, simvastatin, digoxin, hydrochlorothiazide, torasemide, gemfibrozil, rifampicin,

probenecid and oral contraceptives.

Clinical efficacy and safety

The empagliflozin clinical program is expected to include a total of approximately 21,000 patients by the end of 2015.

Empagliflozin demonstrated good efficacy with approximately 70 to 90 g/day of urinary glucose excretion (UGE), without inducing any increased risk in overall frequency of hypoglycaemia. The 12-week global Phase II studies demonstrated an HbA_{1c} reduction of up to 0.72 % (placebo subtracted), a fasting plasma glucose (FPG) reduction of up to 33 mg/dL and a weight loss of approximately 1.5 kg, in both the monotherapy setting and as an add-on to metformin (≥ 1500 mg/day).

In clinical studies, empagliflozin was well tolerated in both healthy subjects and patients with T2DM up to maximal treatment duration of 104 weeks in completed studies. Treatment with empagliflozin resulted in similar percentage of adverse events (AEs) to that of placebo and active comparators. Treatment with empagliflozin showed a higher frequency of genital tract infections and symptoms of increased micturition frequency and/or volume, yet was not associated with a higher incidence of urinary tract infections or hypoglycaemia.

In Japan, phase II/III trials were conducted and approximately 2000 patients were participated in those trials. Treatment with once daily empagliflozin 10 mg and 25 mg showed continuous blood glucose control as shown in improvement/reduction in both HbA_{1c} and FPG. In addition, reductions in body weight and blood pressure strongly suggest that empagliflozin can offer additional benefits.

Based on the Japanese guideline of "Clinical Evaluation Guidelines for Oral Antihyperglycemic Drugs [R10-4692]" which was released in July 2010, an add-on therapy to an oral antidiabetic drug (sulfonylurea, biguanide, thiazolidinedione, alpha glucosidase inhibitor, DPP-IV inhibitor, or glinide) was carried out in Japanese patients (study:1245.52 [U13-1730-01]) and the result showed that empagliflozin 10 mg and 25 mg were well tolerated, safe, and efficacious when used in combination with one other oral antidiabetic drug.

Although no Japanese were participated in, to evaluate the use of empagliflozin as add-on to insulin regimen two clinical studies, Study 1245.33 [U12-3817-01] and Study 1245.49 [U13-2122-01] were carried out. In the results of these studies, empagliflozin 10 mg and 25 mg were well tolerated, with overall AE rates being comparable with placebo.

In summary, given the safety profile in the preclinical studies, and the safety, tolerability, and efficacy seen in the adequately designed clinical studies to date, the available clinical and non-clinical data support safe and efficacious use of empagliflozin in humans and its further development in adults and adolescents with type 1 and type 2 diabetes mellitus.

More information about the known and expected benefits, risks, and anticipated AEs can be found in the current version of IB [c01838761].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Empagliflozin was approved as an antihyperglycemic drug for indication of Type 2 diabetes on 26 Dec 2014 in Japan. There is no limitation regarding combination with empagliflozin and any existing antihyperglycemic drug. However, no clinical data has been obtained in Japanese patients that demonstrate safety and efficacy results of empagliflozin as add-on to insulin therapy.

To evaluate the use of empagliflozin once daily as add-on to insulin regimen two clinical studies, Study 1245.33 [U12-3817-01] and Study 1245.49 [U13-2122-01] were carried out but no Japanese patients were enrolled in the studies. The use experience of empagliflozin concomitantly with insulin regimen is not enough in Japanese patients with T2DM.

We carry out this randomised, double-blind, placebo-controlled, and parallel-group study to investigate efficacy and safety study of empagliflozin as add-on to insulin, to further establish the adverse event profile of empagliflozin, and to assess the long term safety and efficacy when used with insulin in Japanese patients with T2DM with insufficient glycaemic control.

This trial will be implemented on the risk management plan of empagliflozin submitted to the Japanese authorities.

2.2 TRIAL OBJECTIVES

The objective of the study is to investigate the efficacy and safety of empagliflozin (10 mg and 25 mg once daily) compared to placebo given for 16 weeks as add-on therapy to stable insulin treatment and the long-term safety and efficacy of empagliflozin (10 mg and 25 mg once daily) compared to placebo given for an additional 36 weeks as add-on therapy to adjustable-dose insulin treatment in Japanese patients with T2DM with insufficient glycaemic control.

2.3 BENEFIT - RISK ASSESSMENT

The currently-known safety profile of empagliflozin is outlined in the latest IB [c01838761].

According to the drug assignment planned in this trial, 2/3 (66.6%) of the patients with T2DM participating in this trial may derive a direct benefit from being treated with and additional active compound and not a placebo. The patients will receive an investigational medication empagliflozin that has already demonstrated favorable HbA_{1c} and glucose changes at the tested doses. 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}. However, 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.

Because of the mechanism of action of empagliflozin, the risk of hypoglycaemic 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 will be closely monitored in the trial.

In addition, although, diabetic ketoacidosis (DKA) has not been observed in clinical trials of empagliflozin in Type 2 DM patients so far in Japan, special attention will be paid to prevent DKA according to the recommendation from "Committee on the proper use of SGLT2 inhibitors" of the Japanese Diabetes Society that requests physicians to pay attention to DKA when using an SGLT2 inhibitor [R15-2908].

Rare cases of DKA have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).

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

Insulin deficiency might lead to ketoacidosis which could be life-threatening if not recognized and appropriately treated. All patients in this trial will be made aware of this risk and be instructed not to reduce their insulin dose below Investigator recommendations.

Furthermore, patients will be reminded of insulin dose adjustment during "sick days" and of the importance of keeping themselves hydrated. 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).

The overall frequency of volume depletion defined in the IB was similar between empagliflozin and placebo. However, the frequency of volume depletion events was increased in patients at the age of 75 years or over treated with empagliflozin compared to placebo. Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis may lead to a modest decrease in blood pressure and dehydration. Therefore, careful monitoring of volume status and electrolytes (e.g. physical examination, blood pressure measurements, and laboratory tests including haematocrit) is recommended. Also, patients will be requested to drink plenty of fluids as a precautionary measure. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

Patients will be carefully selected for the trial in line with the eligibility criteria, to ensure, in investigator's judgement, that patients have a good understanding of their disease and how to

manage it. They should also be selected in terms of their ability to be compliant with the demands of the trial.

Beneficial effects like body weight reduction and a moderate blood pressure lowering are expected based on Phase III studies of empagliflozin and publications of other SGLT-2 inhibitors.

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

In the embryo-foetal and fertility studies in rats and rabbits, no effects on early embryonic development, mating, male and female fertility, and bearing live young were observed up to a dose of 300 mg/kg. Therefore, women who are of child-bearing potential may participate in this study provided that they are using adequate contraceptive methods.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety. See Section 5.3.6.1 for details.

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 Self-Monitoring Blood Glucose (SMBG). 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. Special measurements are performed like follow-up on genito-urinary tract infections (urine culture) in order to evaluate if possible side effects observed for other SGLT-2 inhibitors are also present for empagliflozin.

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.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomised, double-blind, placebo-controlled, parallel-group study designed to compare 2 doses of empagliflozin (10 mg and 25 mg once daily) with placebo as add-on therapy to insulin in Japanese patients with T2DM.

In total, approximately 400 patients with T2DM are planned to be screened to ensure that 267 patients are randomised in this trial (89 in each treatment group). The randomised treatment will be administered in a double-blinded fashion.

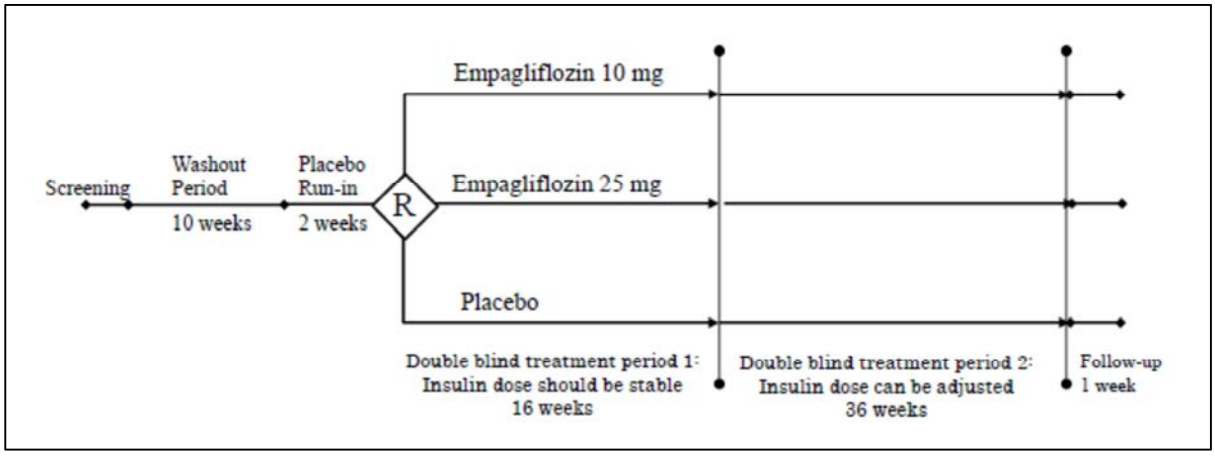
Patients are included in the study once they have signed the informed consent. After screening, patients who are pre-treated with insulin in combination with 1 OAD undergo a 10-week wash-out period. Then patients proceed to a 2-week open-label placebo run-in period. Patients who are pre-treated with insulin alone skip the wash-out period and proceed to an open-label placebo run-in period. Patients who successfully complete the periods and who still meet the inclusion but not meet the exclusion criteria will be randomised to the 52-week double-blind treatment period of the study in which they will receive either 1 of the 2 doses of empagliflozin and/or placebo in addition to insulin.

The double-blind treatment period is divided into 2 periods:

- Double-blind treatment period 1 (from Visit 5 to Visit10) - insulin dose should not be adjusted for reasons other than patient's safety reasons or unless the patient met the criteria for rescue therapy.

  Total daily insulin dose should remain within +/-10% of the prescribed insulin dose at Visit 5 in patients whose prescribed dose is ≥20 U/day at Visit 5. Patients whose prescribed dose is ≥10 U/day and <20 U/day at Visit 5, total daily insulin dose should remain within +/- 2 U/day from the dose at Visit 5. (For rescue therapy, see Section 4.2.1.)

- Double-blind treatment period 2 (after Visit 10 to end of treatment [EOT]) - insulin dose can be adjusted at the investigators' discretion.



R=randomisation

Figure 3.1: 1 Trial design

The first part of the double-blind treatment period (Double-blind treatment period 1) is intended to show a superiority of empagliflozin over placebo when added on to insulin therapy. The change from baseline in HbA_{1c} after 16 weeks of treatment will be analysed as the primary endpoint. It is also intended to investigate the safety of empagliflozin in this period.

The second part of the double-blind treatment period (Double-blind treatment period 2) is intended to investigate the long-term safety and efficacy of empagliflozin when added on to insulin therapy.

The patient participation is completed when they have undergone last planned visit.
The time period, for which adverse events will still be considered on-treatment, is 7 days following the last intake of trial medication.

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

The overall trial design is displayed in Figure 3.1: 1

3.1.1 Administrative structure of the trial

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

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

Data management and statistical evaluation will be done by Boehringer Ingelheim (BI) according to the BI standard operation procedure (SOP)s.

A list of responsible persons and relevant information as protocol reference can be found in the Investigator Site File (ISF).

A coordinating investigator will be nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (principal) investigators and other important participants, including their curricula vitae, will be filed in the ISF.

3.1.1.1 Data Monitoring Committee

A data monitoring committee (DMC), independent from the sponsor, will be established to assess the progress of the trial, including unblinded safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop one or more of the trials covered by the DMC. Measures will be in place to ensure blinding of the sponsor and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

3.1.1.2 Clinical Event Committee for Diabetic ketoacidosis (DKA)

An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see Section 5.3.3). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication.

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

3.1.1.3 Hepatic external adjudication

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).

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

The aim of this study is to evaluate the efficacy and safety of empagliflozin 10 mg and 25 mg in Japanese patients with T2DM whose glycaemic control is insufficient despite diet/exercise and treatment with insulin.

The design of this study is decided according to the draft version of the revised Japanese guideline 'Clinical Evaluation Guidelines for Antihyperglycemic Drugs' [R15-2907] in which 1-year long-term study is required for any antihyperglycemic investigational product when used as added-on therapy to existing antihyperglycemic drugs which are expected to be co-administered in clinical practice.

Patients who are pre-treated with insulin in combination with 1 OAD will undergo a 10-week wash-out period before a 2-week open-label placebo run-in period. Patients who are pre-treated with insulin alone will skip the wash-out period and proceed to the placebo run-in period.

The 10-week wash-out period will minimise the effect of pre-treated OAD on glycaemic control in patients treated with insulin in combination with the OAD prior to randomisation.

The 2-week open-label placebo run-in period is set to confirm whether the patients fulfil the entry criteria for the double-blind treatment period and to check medical compliance by mimicking the dosing in the double-blind treatment period.

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, and the 52 weeks of treatment duration is planned in order to investigate the long term efficacy and safety of empagliflozin.

The 1-week follow-up period is considered to be sufficient, as previous studies with empagliflozin have shown that the pharmacodynamic effect of empagliflozin only extends to about 3 days after the last dose and half-life of empagliflozin in Japanese T2DM after 4 weeks of treatment was 12 to18 hours.

3.3 SELECTION OF TRIAL POPULATION

It is planned that about 399 patients will be screened for the trial. Approximately 50 trial centres will participate in the trial to ensure that 267 patients are randomised to trial treatment.

Centres which fail to enrol at least one patient in the first 10 weeks of the trial may be excluded from further participation. If enrolment of the study is delayed, additional centres may be recruited.

Permission to enter more than 25 patients per site must be obtained from the Trial Clinical Monitor (TCM) at Nippon Boehringer Ingelheim (NBI). 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 centres 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 signed written informed consent before this notification may not participate in the double-blind period after 267 patients are randomised, and patients who are in the wash-out or run-in period should be discontinued quickly when the sponsor notify to stop the randomisation.

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 ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

Re-testing
Re-testing for eligibility criteria is to be performed only for the laboratory result which is obviously received beyond stability at the central laboratory or thought to be a spurious result based on the previously available laboratory results only for the corresponding laboratory test. The re-test should be carried out as soon as possible so that the laboratory test results will be received within the next planned visit windows in order to avoid visit violations.

3.3.1 Main diagnosis for trial entry

The study will be performed in Japanese patients with T2DM whose glycaemic control is insufficient despite diet/exercise and treatment with insulin alone or in combination with 1 OAD.

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

3.3.2 Inclusion criteria

1. Diagnosis of type 2 diabetes mellitus prior to informed consent. This diagnosis should be confirmed by clinical judgment and negative results of Anti-GAD antibody and Anti-IA-2 antibody at Visit 1 (screening).

2. Male and female patients on diet and exercise regimen who are pre-treated with any insulin therapy[a)] alone [c)] or in combination with 1 oral antidiabetic drug (OAD) [b), c)] for at least 12 weeks prior to Visit 1 (screening).

    a) Any kind of insulin therapy (Basal-Bolus therapy, Bolus insulin therapy, Premix insulin therapy and Basal insulin therapy) approved in Japan is allowed. The choices of insulin product, dosage and usage have to follow respective insulin product label in Japan at Visit 1 (screening).
    b) Sulfonylurea is permitted as a pre-treatment drug only if the dose is not more than a half of daily maximum approved dose. Any other OADs except thiazolidinedione and SGLT-2 inhibitors are allowed at any dose within approved dose.
    c) If patients are pre-treated by insulin with 1 OAD at Visit 1, the OAD should be stopped and washed-out for 10 weeks prior to Visit 4 (placebo run-in). For patients receiving insulin alone at Visit 1, no wash-out (of any drug) is necessary.

    Insulin product and its usage must be unchanged at least from 12 weeks prior to Visit 1 (screening). Total prescribed dose must be ≥10 U/day, and it has to be within a defined area at least 12 weeks prior to Visit 5 (randomization) in patients who are pre-treated by insulin alone and from Visit 1 in patients who are pre-treated by insulin in combination with 1 OAD.

    The defined area is as follows,
    In case of the insulin dose at 12 weeks prior to Visit 5 in patients who are pre-treated with insulin therapy alone (at Visit 1 in patients who are pre-treated with insulin in combination with 1 OAD) is
    - ≥20 U/day: Within +/- 10% change from the dose at Visit 5 is allowed.
    - ≥10 U/day and <20 U/day: Within +/- 2 U change from the dose at Visit 5 is allowed. (insulin dose <10 U is not allowed prior to and at Visit 5)

3. Fasting C-peptide: >0.5 ng/mL at Visit 4 in patients who are pre-treated with insulin alone (at Visit 2 in patients who are pre-treated with insulin in combination with 1 OAD)

4. Patients who are treated with insulin alone:
    - HbA_{1c} at Visit 1: ≥7.5% and ≤ 10.0% (HbA_{1c} at Visit 4 is to be skipped)

5. Patients who are treated with insulin with 1 OAD:
    - HbA_{1c} at Visit 1: ≥7.0% and ≤9.5%
    - HbA_{1c} at Visit 4: ≥7.5% and ≤10.0%

6. Age at informed consent: ≥ 20 years and <75

7. BMI (body mass index) at Visit 1: >22 and ≤40 kg/m^2

8. Signed and dated written informed consent by date of Visit 1 in accordance with Good Clinical Practice (GCP) and Japanese legislation

3.3.3 Exclusion criteria

1. Uncontrolled hyperglycaemia with a glucose level >270 mg/dl (>15.0 mmol/L) after an overnight fast during wash-out, and placebo run-in period and confirmed by a second measurement (not on the same day and one of the measurement should be performed at the investigational site after overnight fast).

2. Patients who are treated with sulfonylurea whose dose is more than a half of daily maximum approval dose, glucagon-like peptide 1(GLP-1) analogue, thiazolidinedione and SGLT-2 inhibitor within 12 weeks prior to informed consent

3. Acute coronary syndrome (ST elevation myocardial infarction [STEMI], non-STEMI, and unstable angina pectoris), stroke or transient ischemic attack (TIA) within 12 weeks prior to informed consent

4. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase (ALP) above 3 x upper limit of normal (ULN) as determined during screening and/or run-in period

5. Impaired renal function, defined as eGFR<45 mL/min/1.73m^2 (Japanese equation) as determined during screening and/or run-in phase

6. Bariatric surgery within the past 2 years and other gastrointestinal surgeries that induce chronic malabsorption

7. Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years

8. Blood dyscrasias or any disorders causing hemolysis or unstable red blood cell (e.g., malaria, babesiosis, haemolytic anemia)

9. Contraindications to the background therapy, insulin and empagliflozin according to the Japanese label

10. Known allergy or hypersensitivity to insulin or empagliflozin

11. Treatment with anti-obesity drugs (e.g. mazindol) 12 weeks prior to informed consent or any other treatment at the time of screening (i.e., surgery, aggressive diet regimen, etc.) leading to unstable body weight

12. Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM

13. Pre-menopausal women (last menstruation ≤1 year prior to informed consent) who:
    - are nursing or pregnant or plan to become pregnant while in the trial
    - are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial. Acceptable methods of birth control include intra uterine devices/systems (IUDs/IUSs), oral contraceptives, barrier method* and vasectomised partner

    * Barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

14. Alcohol or drug abuse within 12 weeks prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake

15. Participation in another trial with an investigational drug within 30 days prior to informed consent

16. Any other clinical condition that would jeopardize patients safety while participating in this trial by investigator's judgement

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient needs to take concomitant drugs, including herbal/nutritional supplements/medication that interfere with the investigational product or other trial medication (see Section 4.2.2.1).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- If a patient becomes pregnant during the trial, the investigational drug will be stopped, and the patient will be discontinued from the trial and followed up until birth or otherwise termination of the pregnancy.
- Occurrence of hypoglycaemia that may put the patient at risk with continued participation (e.g., repeated hypoglycaemic episodes) and are not manageable by insulin dose adjustments.
- 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.

- Occurrence of hyperglycaemia that meets the following criteria. In this case, the reason for study drug discontinuation will be classified as "lack of efficacy".

  During Double-blind treatment period 1 (i.e., from Visit 5 to Visit 10):
  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).

  After Double-blind treatment period 1 (i.e., from 1 day after Visit 10 to Follow-up visit):
  The patient has glucose level >240 mg/dL (>13.3 mmol/l) after an overnight fast despite the insulin dose adjustment by investigator

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

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

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow-up as outlined in the flow chart and Section 6.2.3.

For all patients the reason for withdrawal (e.g., adverse events) must be recorded in the electronic case report forms (eCRFs). These data will be included in the trial database and reported.

Patients who drop out before placebo run-in period will be considered a screening failure. They have to be recorded as a screening failure in the eCRFs and no further follow-up is required (except for AEs, if needed).

Patients who discontinue or withdraw from the study during placebo run-in period and before being randomised at Visit 5 will be considered a run-in failure. They have to be recorded as run-in failure in eCRFs and no further follow-up is required (except for AEs, if needed).

Patients who are discontinued from the study after randomisation (Visit 5) and before completing EOT 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.

Patients who are discontinued from the trial after randomisation will not be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for 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. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The study medication will be provided by Nippon Boehringer Ingelheim.

4.1.1 Identity of BI investigational products and comparator products

The characteristics of test product 1 are below.

Substance: Empagliflozin
Pharmaceutical form: Film-coated tablet
Source: Boehringer Ingelheim
Unit Strength: 10 mg
Route of administration: Per oral (po), once daily

The characteristics of test product 2 are below.

Substance: Empagliflozin
Pharmaceutical form: Film-coated tablet
Source: Boehringer Ingelheim
Unit Strength: 25 mg
Route of administration: po, once daily

The characteristics of the reference product placebo 1 are below.

Substance: Placebo matching empagliflozin 10 mg
Pharmaceutical form: Film-coated tablet
Source: Boehringer Ingelheim
Unit Strength: -
Route of administration: po, once daily

The characteristics of the reference product placebo 2 are below.

Substance: Placebo matching empagliflozin 25 mg
Pharmaceutical form: Film-coated tablet
Source: Boehringer Ingelheim
Unit Strength: -
Route of administration: po, once daily

4.1.2 Method of assigning patients to treatment groups

After the patient's eligibility has been confirmed, the patient will be assigned to placebo at Visit 4 and randomly assigned to empagliflozin 10 mg, 25 mg or placebo in a 1:1:1 ratio at Visit 5 via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

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

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

4.1.3 Selection of doses in the trial

The selected doses of empagliflozin are based on the approved and marketed doses for T2DM in Japan. Approximately 33% of the patients will receive empagliflozin 25 mg without starting lower dose of empagliflozin 10 mg although the Japanese label defines the starting dose of empagliflozin 10 mg. Empagliflozin 25 mg as well as 10 mg were used in the phase III clinical trials as for the expected therapeutic doses and both empagliflozin doses were well tolerated as initial dosage.

4.1.4 Drug assignment and administration of doses for each patient

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. Patients who are qualified will be randomised to one of the treatment arm schedules described below. Medication will be dispensed in a double-blind and double-dummy fashion.

All patients will be assigned to a placebo run-in kit at the beginning of the placebo run-in period (Visit 4), and dispensing will be done just once. Dispensing of kits for the double-blind treatment period will begin at Visit 5. Dispensing will be done on 13 occasions over a period of 52 weeks (i.e., every 4 weeks in Visit 5 to Visit 18). Patients will receive empagliflozin or placebo as trial medication. However, background medication (i.e., insulin) will not be dispensed as trial medication. Therefore, background medication will be prescribed at each clinical site. For details regarding packaging (e.g., number of tablets per container) please see Section 4.1.6.

Table 4.1.4: 1 Treatments 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
Double-blind treatment period				
Empagliflozin 10 mg arm	Active drug	Matching placebo	2 tablets	Once daily, Morning
Empagliflozin 25 mg arm	Matching placebo	Active drug	2 tablets	Once daily, Morning
Placebo arm	Matching placebo	Matching placebo	2 tablets	Once daily, Morning

Placebo run-in period (open label):
From the start of the placebo run-in period, patients should be instructed to take their trial medication once daily with water. The medication can be taken with or without food but it should be taken at the same time point every day. If a dose is missed by more than 12 hours, this dose should be skipped and the next dose should be taken as scheduled.

Double-blind treatment period:
During the treatment period, patients should be instructed to take their trial medication once daily with water. To ensure a dose interval of about 24 hours, the medication should be taken at the same time every day. If a dose is missed but the patient realizes that within 12 hours from planned intake, the dose should be taken immediately, and if a dose is missed by more than 12 hours, this dose should be skipped and the next dose should be taken as scheduled. On days before the next visit, patient should be instructed to take their trial medication approximately 22-26 hours before the planned dose at the visit. No double doses should be taken at onece. The trial medication can be taken with or without food.

Through the double-blind period (Double-blind treatment period 1and 2), the usage of insulin should be unchanged if at all possible. The dosage of insulin should remain unchanged until the end of double-blind treatment period 1. After completing the double-blind treatment period 1 (i.e. from Visit 10), daily insulin dose can be adjusted at the investigators' discretion. For further details, see Section 4.2.1.

Patients should be instructed not to take their trial medication in the morning of study visits as they will be dosed whilst in the study site. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day. Patients are asked to bring their

trial medication to the sites. Visits should be routinely scheduled in the morning, at approximately the same time of day for each visit.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Trial medication during run-in period will be open-labelled.

After randomisation at Visit 5, 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. To achieve all dose combinations and to ensure blinding, empagliflozin and placebo tablets are combined in double-dummy fashion as shown in Table 4.1.4: 1 and patients will have to take two tablets for each dose.

However, due to the requirements to report suspected serious unexpected adverse reactions (SUSARs), it may be necessary for a representative from BI's pharmacovigilance department to access the randomisation code for individual patients during study conduct. In such cases, access to the code will be permitted only by authorised pharmacovigilance representatives. Access to the code will be done via the IRT.

The randomisation code will be kept secret by Clinical Trial Support until completion of database lock. Please see Section 4.1.5.2 for the rules regarding breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

In this blinded trial, an emergency code break will be available to the investigator via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the investigator cannot be reached, the code can be opened by calling emergency code manager (see Emergency Code Break Manual in the ISF).

4.1.6 Packaging, labelling, and re-supply

Study medications will be provided by Nippon Boehringer Ingelheim.

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

The placebo run-in kit will contain 42 tablets in a wallet (i.e., sufficient supply for 2 week administration, with 1 week in reserve).

The double-blind treatment kit, dispensed from Visits 5 to 18 with 4 week interval. It will contain 84 tablets in a wallet (i.e., sufficient supply for 4 week administration, with 2 week in reserve). The total number of tablets dispensed to a patient during the double-blind treatment period will therefore be 1092 at a maximum.

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

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

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 local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB),
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- 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

The investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigational drug storage manager will maintain records that document adequately that the

patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor or appointed contract research organization (CRO), the investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Details of all concomitant therapies during the clinical trial will be recorded on the appropriate pages of the eCRFs.

4.2.1 Rescue medication, emergency procedures, and additional treatments

Throughout the duration of the trial, patients should continue to use insulin as a background therapy. Insulin will not be provided as part of the clinical trial supplies.

During the Week 1 to 16 of the double-blind treatment period (Double-blind treatment period 1), the dose and usage of insulin must not be changed. (The dose adjustment within +/-10% [for patients whose prescribed dose is ≥20 U/day at Visit 5] or +/- 2 U [for patients whose prescribed dose is ≥10 U/day and <20 U/day] of the prescribed insulin dose at Visit 5 is allowed. The usage of insulin should be unchanged if at all possible.)

Only for the safety reason mentioned below or when the patient met the criteria for initiating rescue therapy, insulin dose can be changed over the above mentioned range, and the dose change is treated as rescue therapy. Only dose and usage adjustment of insulin which is used as background treatment are allowed as a rescue therapy in this study. All other antidiabetic agents are prohibited even as a rescue therapy. The dose of insulin will be left to the discretion of the investigator, however, it should follow each Japanese label.

Safety reason for initiating a rescue therapy:

- The patient had hypoglycaemia that may put him/her on risk (i.e., repeated symptomatic hypoglycaemia or severe hypoglycaemia)

Criteria for initiating a rescue therapy:

- Weeks 1 – 12 (i.e., from Visit 5 to Visit 9)
  The patient has glucose level >270 mg/dL (>15.0 mmol/L) after an overnight fast
- Weeks 12 – 16 (i.e., from the day after Visit 9 up to Visit 10):
  The patient has glucose level >240 mg/dL (>13.3 mmol/L) after an overnight fast

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

If the above criteria are met, the initiation of rescue therapy is at the investigator's discretion, based on the patients' current clinical condition (e.g., ongoing illness etc.). A fasting glucose sample and an HbA_{1c} sample should be taken before initiation of a rescue therapy and sent to

the 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.

Patients will continue taking study medication and continue participation in the trial even if rescue medication is required, and rescue medication can be used from when it is initiated until the end of the trial.

Short term adjustments of insulin dose for up to 7 days due to disease or hospitalisation, and other occasional short term adjustments for up to 7 days as a part of the standard insulin therapy, are allowed; this is not considered as a rescue therapy.

After Week 16 (after Visit 10), daily insulin dose can be adjusted at the investigators' discretion. The usage of insulin should be unchanged if at all possible.

If, in the investigator's clinical opinion, the patient's hyper- or hypoglycaemia cannot be controlled, the patient should be discontinued from the trial as specified in Section 3.3.4.1.

Special attention must be paid to the prevention of DKA. Patients receiving empagliflozin are at risk to underestimate their need for insulin in case of blood sugar levels within their individual target range. Insulin deficiency might lead to ketoacidosis which could be life-threatening if not recognized, and appropriately treated. All patients must be made aware of this risk and need to be instructed to contact the Investigator or other healthcare professional in case of symptoms of DKA. In addition patients must be instructed not to reduce their insulin intake below Investigator recommendations. For further details see Section 2.3.

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

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving IMPs. Temporary interruption of treatment with IMPs should be considered until the fluid loss is corrected.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Through the study period, the use of other antidiabetic agents such as GLP-1 analogues, any oral antidiabetic drugs, or any insulin product other than background therapy will be prohibited. (Background therapy except insulin must be washed out at Visit 2.) In addition,

during the Double-blind treatment period 1, the dose and usage of insulin must not be changed unless meeting the criteria mentioned in Section 4.2.1.

However, short-term use of other insulin therapy than background therapy will be permitted (only in the event of an emergency situation and/or hospitalisation) based on clinical judgement of the investigator or treating physician. Whether to prolongation of such insulin treatment over more than 2 weeks or to discontinue treatment should be discussed on a case-by-case basis between the investigator and the TCM.

Additionally, treatment with anti-obesity drugs or systemic steroids will be prohibited due to their influence on glucose metabolism. However, one off or short-term use (i.e., ≤2 weeks) of systemic steroids will be permitted as well as therapy with non-systemic steroids such as inhaled or local steroids. Furthermore, for patients taking thyroid hormones, any change in the dose should be avoided. If a change in dose of thyroid hormones changes do occur, this should be recorded in the source documents and in the eCRF.

The risk of volume depletion may be increased in a patient treated with diuretic in addition to SGLT-2 inhibitor. Therefore, the co-administration of diuretics had to be avoided if there are not sufficient reasons to use these drugs according to the investigators' clinical judgment.

4.2.2.2 Restrictions on diet and life style

At the beginning of the placebo run-in period, patients who are pre-treated with insulin alone will receive diet and exercise counselling by a diet specialist or a trained staff member, and patients who are pre-treated with insulin with 1 OAD will receive the counselling at the beginning of the wash-out period. The counselling should be based on the diet and exercise recommendation of the Japanese Diabetes Society. To avoid DKA, extreme diets (e.g., ketogenic diets) should be avoided.

In principle, the contents of diet and exercise should not be changed through the study period. Patients will keep record (a food intake diary) of the actual food intake over a time of 3 consecutive days in the week before the clinic visit indicated in the flow chart (these 3 consecutive days should be the same days that blood glucoses at preprandial state and before bedtime are monitored by SMBG) and bring the diary at each visit. The patients will be reminded to follow the agreed diet and exercise plan at every visit. The investigator will check compliance with the diet and exercise therapy based on the records of the food intake diary and also by interview with patients.

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 or drink every day.

Patients also should not participate in other trials within the last 30 days before the date of informed consent and throughout the study.

There are no other restrictions on diet and lifestyle.

4.2.2.3 Restrictions regarding women of childbearing potential

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

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medications including empty package materials when attending visits.

Based on tablet counts, treatment compliance will be calculated as the number of tablet taken, divided by the number of tablet which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the Sponsor.

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is the change from baseline in HbA_{1c} after 16 weeks of treatment. Throughout the study protocol, the term "baseline" refers to the last observation prior to the administration of any randomised study drug.

5.1.2 Secondary Endpoint

The secondary endpoint is proportion of patients with drug-related adverse events during 52 weeks of treatment.

5.2 ASSESSMENT OF EFFICACY

HbA_{1c}:
Blood samples for the determination of HbA_{1c} at the central laboratory will be taken.

At the screening visit 1, the blood sample can be taken in non-fasted state. At all other visits, the blood samples should be taken before breakfast and before trial drug administration. 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).

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A complete physical examination (including cardiac, neurological, dermatological, pulmonary) will be performed by the investigator as described in the flow chart. Documentation of, and findings from the physical examination, must be part of the source documents available at the site.

5.3.2 Vital Signs

The seated pulse rate (electronically or by palpation, count for 1 minute) will be measured as described in the flow chart. Further details on the procedure for seated pulse rate measurements are given in Appendix 10.1.

5.3.3 Safety laboratory parameters

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

All parameters that will be determined during the trial conduct are listed in Tables 5.3.3: 1 and 5.3.3: 2. The analysis will be performed by a central laboratory. The respective reference range and details about sample handling and shipment will be provided in the ISF (Lab Manual).

Reduced lab panels are planned for the following visits (For details, see the flow chart):

- For the screening Visit 1, laboratory only includes liver transaminases (i.e., AST and ALT), alkaline phosphatase, serum creatinine, thyroid stimulation hormone (TSH) , anti-GAD antibody, Ant-IA-2 antibody, FPG, HbA_{1c} and urinalysis.
- C-peptide will be measured at Visit 2 in patients who need washout an OAD or Visit 4 in patients who do not need washout period.
- Free fatty acid (FFA) and Blood ketone bodies will be measured at selected visits. For the details, see the flow chart.
- Bone markers; iPTH (intact parathyroid hormone), 25OH Vitamin D, NTx in urine: planned at Visits 5, 10 and EOT.
- Hematology and urinalysis will also be measured at Visit 6, 7, 9 11, 12, 14, 15, 17 and 18.

Table 5.3.3: 1 Safety laboratory parameters – whole blood, serum or plasma

Haematology

- Haematocrit
- Haemoglobin
  - Reticulocyte count (reflex test if Hb outside normal range)
- Red blood cells (RBC)/Erythrocytes
- White blood cell (WBC)/Leukocytes
- Platelet count/Thrombocytes
- Differential automatic (relative and absolute count):
  Neutrophils, eosinophils, basophils, monocytes, lymphocytes

Clinical chemistry

- Albumin
- ALP
- γ-GT (gamma-glutamyl transferase)
- ALT (alanine aminotransaminase, SGPT)
- AST (aspartate aminotransaminase, SGOT)
- Bicarbonate
- Bilirubin total, fractionated if increased
- C-peptide
- Calcium
- Chloride
- Creatinine
- Creatinine kinase (CK)
- hs troponin T (reflex tests if CK is elevated)
- Lactate dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- TSH (only at Visit 1)
- Urea (BUN)
- Uric acid
- Cholesterol (total)
- HDL cholesterol
- Calculated LDL cholesterol
- Triglycerides (reflex test for direct measurement of LDL cholesterol triggered if triglycerides are >400 mg/dL or 4.52 mmol/L)

Table 5.3.3: 1 Safety laboratory parameters – whole blood, serum or plasma (continued)

Bone Marker (only at selected visits) • iPTH • 25OH Vitamin D • NTx in Urine
FFA and Ketone bodies (only at selected visits) • Total ketone body • Acetoacetic acid • 3-hydroxybutyric acid • Free fatty acid (FFA)
Other • Anti-GAD antibody • Anti-IA-2 antibody

Table 5.3.3: 2 Safety laboratory parameters – urine

Urinalysis **Semi quantitative (dipstick)** • Nitrite* • Protein • Ketone • Urine pH • Leukocyte esterase (for WBC)* **Quantitative** • Albumin • Creatinine	**Microscopic analysis** Will be performed as reflex test if any of the semi quantitative tests/dipsticks are abnormal: • Urine RBC/Erythrocyte • Urine WBC/Leukocytes • Urine sediment microscopic examination • Urine culture (including antibiogram test): - reflex test triggered by positive leukocyte esterase (for WBC) and/or nitrite in the semi-quantitative test/dipstick

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

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

Glomerular filtration rate:

The eGFR will be derived from serum creatinine values for Japanese equation:
eGFR (mL/min/1.73m^2) = 194 x [Screatinine (mg/dL)]$^{-1.094}$ x [age]$^{-0.287}$ x [0.739 if patient is female]

Renal function impairment will be classified in the following way:

- No renal function impairment: eGFR ≥90 mL/min/1.73m^2;
- Mild renal function impairment: eGFR 60 to <90 mL/min/1.73m^2;
- Moderate renal function impairment: eGFR 30 to <60 mL/min/1.73m^2;
- Severe renal function impairment: eGFR <30 mL/min/1.73m^2.

These classes of renal impairment will be the basis for stratification of subgroup analysis.

Pregnancy testing:

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

Criteria for hypoglycaemic events:

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

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

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

Follow-up on suspicion for urinary tract infections:

Patients having a history of chronic/recurrent urinary tract infections (UTIs) or genital tract infections (GTIs) or an acute episode of UTI or GTI at screening will be identified and this condition has to be documented as medical history or baseline condition in the eCRF, respectively.

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

- In any case of suspected UTI (symptomatic or asymptomatic) a urine culture sample (including antibiogram) has to be taken and sent to the central lab for confirmation of the diagnosis.
- To be able to identify asymptomatic UTIs immediately, a dipstick-test (leukocyte esterase [for WBC] and Nitrite) will be performed at the site at each safety visit with urinalysis. In case of a positive result at site, a urine culture (including antibiogram) sample has to be taken and sent to the central lab for confirmation of the diagnosis.

5.3.4 Electrocardiogram

Printed paper traces from 12 lead electrocardiogram (ECG)s (I, II, III,aVR,aVL,aVF,V1-V6) will be collected at Visit 1, 5, 8, 10, 13, 16 and EOT for all patients. In the event of any cardiac symptoms (i.e., suspicion of heart rhythm disorders or cardiac ischemia), an additional ECG will be recorded. All ECGs will be evaluated, (signed, dated and commented upon) by the investigator and stored locally. Any clinically relevant changes in the ECG will be reported as AEs and followed up and/or treated locally until normal or stable condition.

Any ECG abnormalities will be carefully monitored and if necessary the patient will be removed from the trial and medically treated.

Investigators will use the ECG machine available at the site. NBI will not provide ECG machine centrally.

5.3.5 Other safety parameters

Self-Monitoring blood Glucose (SMBG)

All patients will be provided with Self-Monitoring Blood Glucose (SMBG) equipment and supplies for use at home during the study period. Instruction on the proper use of the SMBG equipment will be provided by the study staff. The patient will be asked to record the results of the SMBG test on a SMBG Testing Log that will be included in the patients source document file. Only in the case of linked adverse events or of hypoglycaemia, the glucose value measured by SMBG will be recorded in the eCRF.

During wash-out, placebo run-in, double-blind treatment and follow-up period, SMBG testing is recommended to be performed at least once daily before breakfast (if possible, it is recommended to monitor fasting blood glucose in preprandial state and before bedtime) and at any time the patient is symptomatic related to hypoglicaemia or hyperglicaemia through the entire study period. In addition, in 3 consecutive days in the week before each scheduled visit, patients will be requested to monitor fasting blood glucose at preprandial state (i.e.,

before breakfast, lunch and dinner), before bedtime and at any time when the patient is symptomatic. Patients are requested to maintain a diary with daily recordings of glucose values measured by SMBG and of insulin dose through the entire study period.

If during wash-out and placebo run-in period, results of a SMBG test reveal blood glucose of >270 mg/dL (15.0 mmol/L) after an overnight fast, the patient should contact the site.

The investigator should ask the patient to visit the site for FPG determination as soon as possible, preferably on the next day. The investigator will take two blood samples, one for local determination of FPG for acute patient management, and one for central laboratory determination for trial analysis. If two consecutive measurements at either the local or central laboratory, or SMBG on different days (at least one measurement has to be done at the local or central lab) reveal overnight fasted blood glucose of >270 mg/dL (15.0 mmol/L), then the patient should be withdrawn from the trial (see Section 3.3.3).

Until Visit 9 after randomization, results of a SMBG test reveal blood glucose of >270 mg/dL (15.0 mmol/L), or until the completion of trial from one day after Visit 9, results of a SMBG test reveal blood glucose of >240 mg/dL (13.3 mmol/L) after an overnight fast the patient should contact the site, and the investigator should follow procedure described in the Sections 4.2.1 and 3.3.4.1.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical 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.

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

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may

require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

The following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE.

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 given above.

The latest list of "Always Serious AEs" can be found in the remote data capture (RDC) system.

These events should always be reported as SAEs as described in Section 5.3.7.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation at Visit 5:

- An elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- Marked peak 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 via the RDC-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.

Decreased renal function
A decreased renal function is defined by the following alterations of renal laboratory parameters:

- Creatinine value shows a ≥2 fold increase from baseline and is above the upper limit of normal (ULN)

The patient with any of the events is mentioned above need to be followed up appropriately. The investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per investigator discretion.

For any of these AESI, the investigator should report the event to the pharmacovigilance centre immediately (within 24 hours of being informed, and without waiting for confirmation of the result via a second measurement) on the SAE form, even if they do not meet any of the seriousness criteria.

The investigator should collect the relevant unscheduled laboratory samples as soon as possible (i.e., lipase, creatinine, or hepatic enzymes). Further follow-up laboratory tests should be done according to medical judgment depending on the clinical course.

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

Diabetic ketoacidosis (DKA) is defined as a state in which a severe shortage of insulin and an increase in counter regulatory hormones combine to induce hyperglycemia (≥250 mg/dL), hyperketonemia (increased β-hydroxybutyric acid), and acidosis (pH<7.30; bicarbonate concentration<18 mEq/L), and as defined by the Japanese guideline, Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 [R13-3738].

Investigators should note that not all criteria in the described above need to apply for the diagnosis of DKA, and clinical judgment should also be taken into consideration.

Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated above.

Medical history of DKA prior to the informed consent will be reported in the eCRF.

Events involving lower limb amputation
This definition includes amputation (i.e. resection of a limb through a bone), disarticulation (i.e. resection of a limb through a joint) and auto-amputations (i.e. 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).

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.

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

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

Causal relationship of AEs
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the eCRFs. The reason for the decision on causal relationship other than the related listed AEs in the IB [c01838761] and respective Japanese package insert needs to be provided in the eCRF.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

5.3.7 Adverse event collection and reporting

AE Collection

The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards through the residual effect period (REP), until 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 AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.

The REP is defined as a period of 7 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on

treatment (see Section 7.3.4). Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (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.

All SAEs and AESIs must be reported immediately to the head of the trial site.
With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drugs. The investigator should determine the causal relationship to the trial medication.

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

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

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.
All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In the rare case that a female subject or a female partner to a male subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the pharmacovigilance centre. The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not Applicable

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER

Not Applicable

5.6 OTHER ASSESSMENTS

No other assessment such as pharmacogenomics samples will be performed in this study.

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 type 2 diabetes mellitus, and ECG. The primary and secondary endpoints are standard and accepted for evaluation of safety and tolerability of an OAD, and they are widely used in this kind of study.

Therefore, all measurements applied in this trial are appropriate.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits (except Visit 1, 5.1 and phone contact for Follow up visit) should take place in the morning. If a patient mistakenly takes trial medication on the morning of a visit before attending the clinic (excluding visits starting before randomisation) or comes in fed condition where a fasting condition is required (all visits except screening), the visit should be rescheduled for another day as soon as possible reminding the patient 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.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in periods

Screening Period
The screening visit is the only visit in this study that does not need to be done in fasting.

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 as a screened patient at Visit 1.

ECG and BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see Appendix 10.1.

At the end of the screening visit, patients will be given a food intake log/booklet which is requested to be completed for three consecutive days in the week prior to the next visit. Details of any patient who is screened for the study but is found to be ineligible must be entered in an enrolment log and documented in the eCRF.

Patients who are treated with insulin alone and qualify at Visit 1 will undergo a 2-week placebo run-in period. And patients who are treated with insulin in combination with one OAD and qualify at Visit 1 will undergo a 10-week wash-out period.

Wash-out Period
Only the patients who are treated with insulin in combination with one OAD as the previous treatments will undergo this period. These patients will be requested to wash-out the OAD at Visit 2. Patients who are treated with insulin alone will skip this period.

From Visit 2, the patients should be fasting (no food or drinks, water only for at least 10 hours) prior to each visit. And at Visit 2, patients will be requested not to take OAD on the morning of a visit before attending the clinic.

The patients will be provided Self-Monitoring Blood Glucose (SMBG) equipment and supplies at Visit 2. Instruction on the proper use of the SMBG equipment will be provided by site staff. Please refer to Section 5.3.5 (Self-Monitoring blood Glucose) for the details of measurement frequency and the record.

If the SMBG test reveals an overnight fasted blood glucose of >270 mg/dL (15.0 mmol/L), the patient should contact the study site for a visit as soon as possible, on ideally the next day
See Section 5.3.5.

At the end of the each visit in this period, patients will be given a food intake log/booklet which is requested to be completed for three consecutive days in the week prior to the next visit. These 3 consecutive days should be the same days that blood glucoses at preprandial state and before bedtime are monitored by SMBG.

Investigators will ask the patients to visit the site 4 weeks after Visit 2 to check the patient's safety after wash-out of the OAD. After completing the wash-out period, the patients will proceed to a 2-week placebo run-in period.

Placebo Run-in Period
From Visit 4, patients who are pre-treated with insulin alone should be fasting (no food or drinks, water only for at least 10 hours) prior to each visit.

And these patients will be provided SMBG equipment and supplies at Visit 4. Instruction on the proper use of the SMBG equipment will be provided by site staff. Please refer to Section 5.3.5 (Self-Monitoring blood Glucose) for the details of measurement frequency and the record.

If the SMBG test reveals an overnight fasted blood glucose of >270 mg/dL (15.0 mmol/L), the patient should contact the study site for a visit as soon as possible, ideally on the next day
See Section 5.3.5.

At the end of Visit 4, patients will be given a food intake log/booklet which is requested to be completed for 3 consecutive days in the week prior to the next visit (Visit 5). These 3 consecutive days should be the same days that blood glucoses at preprandial state and before bedtime are monitored by SMBG.

6.2.2 Treatment period

The double-blind treatment period is from Visit 5 to EOT. Patients will be dispensed medication at each of these visits (except Visit 5.1, 6 and EOT) and will receive a new kit number through the IRT on each occasion.

Patients must satisfy all inclusion but not meet the 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 safely 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 each visit after Visit 5 should be determined based on the date of Visit 5 and visits should occur within the allowed time frame shown in the flow chart.

Throughout the double treatment period, the usage of insulin should be unchanged if at all possible. And during the Double-blind treatment period 1, the insulin dose must not be changed unless patient meets the rescue criteria, but the insulin dose can be adjusted within +/- 10% from the dose at Visit 5 in patients whose insulin dose is ≥20 U/day at Visit 5, and within +/- 2 U/day from the dose at Visit 5 in patients whose insulin dose is <20 U/day at Visit 5.

After completing the double-blind treatment period 1 (i.e., from Visit 10), daily insulin dose can be adjusted at the investigators' discretion. For further details, see Section 4.2.1.

Throughout the double-blind treatment period, ECG and BP should always be measured before any blood samples are taken.

Visit 5.1 will be done via phone by investigator or designated site staff to confirm patient's safety through checking SMBG results, adverse events and concomitant therapies. The investigator should ask the patient to visit the clinic, if determined by the investigator as concerning the patient's safety.

Randomisation/treatment allocation and dispensing of study medication should be the last activity at each visit. And trial medication for the day of the visit will be administered at the investigational site after all necessary procedures are completed. The time patients visit the investigational site should be arranged to allow patients to take the trial medication at the same time as usual.

Until Visit 9 after randomization, results of a SMBG test reveal blood glucose of >270 mg/dL (15.0 mmol/L), or until the end of the double blind period from one day after Visit 9, results of a SMBG test reveal blood glucose of >240 mg/dL (13.3 mmol/L) after an overnight fast the patient should contact the site, and the investigator should follow procedure described in the Sections 4.2.1 and 3.3.4.1.

At the end of each visit, patients will be given a food intake log/booklet which is requested to be completed for 3 consecutive days in the week prior to the next visit. These 3 consecutive days should be the same days that blood glucoses at preprandial state and before bedtime are monitored by SMBG.

EOT visit will need to be performed for any patients who are administered study medication, i.e. both for patients who complete the full 52-week double-blind treatment period and for patients who discontinue study medication early. Patients who discontinue study medication early should be registered as discontinued, and patients who complete the full 52-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 the protocol without persisting AE at EOT, a follow-up visit can be performed as a phone visit by the investigator at the end of the follow-up period of 7 days. Follow-up visit should occur 7 days after EOT (+7 days visit allowance).

During the follow-up period, results of a SMBG test reveal blood glucose of >240 mg/dL (13.3 mmol/L) after an overnight fast the patient should contact the site, and the investigator should follow procedure described in the Sections 4.2.1 and 3.3.4.1.

The following should be confirmed and recorded at follow-up visit via telephone:

- concomitant therapies
- any AEs
- SMBG log

Patients completing the study according to the protocol with persisting AE at EOT or in case of early discontinuation from the 52-week double-blind treatment period, however, EOT should be performed and the patient should return to follow-up visit (7 days after EOT). The following examinations should be performed at follow-up visit in addition to the above mentioned items:

- Physical examination
- Vital signs
- Collection of blood (include FPG sample) and urine samples for safety laboratory evaluation

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, double-blind, placebo-controlled, parallel-group study designed to compare 2 doses of empagliflozin (10 mg and 25 mg once daily) to placebo as add-on therapy to insulin in Japanese patients with T2DM.

The primary analysis is an analysis of covariance (ANCOVA) comparing the change from baseline in HbA_{1c} after 16 weeks of treatment. The statistical model includes treatment, renal function and type of insulin therapies as fixed effects, and baseline HbA_{1c} as a covariate.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following hierarchical testing procedure will be used to evaluate superiority of empagliflozin 10 mg against placebo followed by superiority of empagliflozin 25mg against placebo, while maintaining the overall probability of type I error at 0.05 (two-sided).

Step 1: The superiority of empagliflozin 10 mg against placebo will be tested for change from baseline in HbA_{1c} after 16 weeks of treatment at the level of α=0.05 (two-sided).

- $H_{0,1}$: Mean change from baseline in HbA_{1c} after 16 weeks of treatment with empagliflozin 10 mg = Mean change from baseline in HbA_{1c} after 16 weeks of treatment with placebo
- $H_{1,1}$: Mean change from baseline in HbA_{1c} after 16 weeks of treatment with empagliflozin 10 mg ≠ Mean change from baseline in HbA_{1c} after 16 weeks of treatment with placebo

If the null hypothesis for the superiority of empagliflozin 10 mg against placebo is rejected at the 5% level, then the following Step 2 will be performed. If the null hypothesis for the superiority of empagliflozin 10 mg against placebo cannot be rejected, then the testing of the superiority of the empagliflozin 25mg against placebo will be done in an exploratory manner only.

Step 2: The superiority of empagliflozin 25 mg against placebo will be tested for change from baseline in HbA_{1c} after 16 weeks of treatment at the level of α=0.05 (two-sided).

- $H_{0,1}$: Mean change from baseline in HbA_{1c} after 16 weeks of treatment with empagliflozin 25 mg = Mean change from baseline in HbA_{1c} after 16 weeks of treatment with placebo
- $H_{1,1}$: Mean change from baseline in HbA_{1c} after 16 weeks of treatment with empagliflozin 25 mg ≠ Mean change from baseline in HbA_{1c} after 16 weeks of treatment with placebo

7.3 PLANNED ANALYSES

The assignment of patients to treatment groups will be based on the first study drug taken in the study for safety evaluation, and as randomised for efficacy evaluation. The statistical analysis will be based on the following populations.

[Treated set]
The treated set (TS) will consist of all randomised patients who were treated with at least one dose of the study drug.

[Full analysis set]
The full analysis set (FAS) will consist of all patients in TS who had a baseline measurement of the primary endpoint.

[Per protocol set]
The per protocol set (PPS) will consist of all patients in FAS who have no important protocol violations which may affect the efficacy evaluation. The important protocol violations will be specified in the trial statistical analysis plan (TSAP).

Baseline for any parameter is defined as the last measurement prior to the administration of any randomised study drug.

7.3.1 Primary endpoint analyses

The primary analysis will be performed on the FAS with missing data imputed using a last observation carried forward (LOCF) approach as described in Section 7.4.

The primary endpoint will be analysed using an ANCOVA. The model includes 'treatment', 'baseline renal function' and 'type of insulin therapies' as a fixed effect, and baseline HbA_{1c} as a covariate as follows:

Change from baseline in HbA_{1c} after 16 weeks = overall mean + baseline HbA_{1c} + treatment + baseline renal function + type of insulin therapies + random error

The random error is assumed to be normally distributed with mean 0 and variance σ^2.

[Sensitivity analysis]
Sensitivity analyses of the primary endpoint will be performed as follows:

- The primary analysis as specified in Section 7.3.1 will be repeated on the PPS (LOCF).
- The primary endpoint will be analysed on the FAS (observed case, OC) using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM). The model includes 'treatment', 'baseline renal function', 'type of insulin therapies', 'visit', 'treatment by visit interaction' and 'baseline HbA_{1c} by visit interaction' as a fixed effect, and baseline HbA_{1c} as a covariate as follows:

Change from baseline in HbA_{1c} at each on-treatment visit = overall mean + baseline HbA_{1c} + treatment + baseline renal function + type of insulin therapies + visit + treatment by visit interaction + baseline HbA_{1c} by visit interaction + random error

For each patient, the error terms from the on-treatment visits represent the within-patient variability, and are assumed to follow a multivariate normal distribution with an unstructured covariance matrix.

If this unstructured covariance structure fails to converge, the following structures will be tested: compound symmetry, variance components and Toeplitz. The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Additional sensitivity analyses on the primary endpoint may be performed. Such sensitivity analyses will be specified in the TSAP.

7.3.2 Secondary endpoint analyses

Refer to Section 7.3.4 for the analysis of secondary endpoint.

7.3.4 Safety analyses

Standard safety analyses will be performed on the TS.

Safety analyses will be descriptive in nature and will be based on BI standards. No formal inferential analysis is planned.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs occurring one day before the first intake of the double-blind treatment will be assigned to the 'screening period'. AEs occurring between the first intake of the double-blind treatment and seven days after the last intake of double-blind treatment will be assigned to 'double-blind treatment period' for evaluation. AEs occurring thereafter will be assigned to 'post-treatment period'.

Frequency of patients with AEs will be summarised by system organ class (SOC) and preferred term (PT). In addition, AEs by intensity, drug-related AEs, serious AEs, AESIs and hypoglycaemic events will also be summarised.

Descriptive statistics of laboratory values for the change from baseline will be provided. Frequency tables of changes with respect to the reference range between baseline and last value on treatment will also be presented.

Change from baseline will be summarised for vital signs.

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

7.3.5 Pharmacokinetic analyses

Not specified in this protocol.

7.4 INTERIM ANALYSES

No interim analysis is planned in this trial.

7.5 HANDLING OF MISSING DATA

Censoring rules for the efficacy data will be defined in the TSAP. Censored efficacy data will be set as missing, and different methods for handling missing data will be used as below.

Missing data for the primary analysis will be imputed using the last observation carried forward (LOCF) approach. The baseline value will be carried forward if no post-baseline value is available.

The impact of all methods of handling missing data on the primary endpoint will also be investigated using sensitivity analyses.

MMRM will be applied in order to handle missing data in the sensitivity analysis. Only the available data will be included in the analysis (observed case, OC). Missing data are handled implicitly by MMRM model, rather than using any imputation.

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

Further details will be provided in the TSAP.

7.6 RANDOMISATION

The trial will be performed as a double-blind design with respect to placebo and 2 active treatment groups of empagliflozin (10 mg and 25 mg). Patients who meet the inclusion criteria but not meet the exclusion criteria will be randomised in 1:1:1 ratio to each treatment group at Visit 5.

The randomisation will be stratified by the following factors:

- Baseline HbA_{1c} (at Visit 1 for insulin alone, Visit 4 for insulin with one OAD) (<8.5% or <69.4 mmol/mol, ≥8.5% or ≥69.4 mmol/mol)
- Baseline Renal function (at Visit 4) (eGFR <60 mL/min/1.73 m^2, eGFR ≥60 mL/min/1.73 m^2)
- Type of insulin therapies (basal insulin therapy, other insulin therapy)

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

7.7 DETERMINATION OF SAMPLE SIZE

Based upon previous experience with empagliflozin [U12-3817-01], it is estimated that the difference of change from baseline in HbA_{1c} after 16 weeks of treatment between empagliflozin (10 mg or 25 mg) and placebo add-on to insulin is 0.5% and that the standard deviation of this difference is 1.0%. The Type I error for each hierarchical testing procedure to evaluate superiority of empagliflozin 10 mg against placebo followed by superiority of empagliflozin 25 mg against placebo, is assumed to be 5% (two-sided), while maintaining the overall probability of type I error at 0.05.

The number of analysed patients should be 86 per treatment arm to have 90% power to test the primary endpoint of each empagliflozin 10 mg and 25 mg, leading to 81% overall power. Assuming that approximately 3% of patients will not be eligible for inclusion into the FAS, 3 additional patients should be randomised per arm. As such sample size will be 89 per arm. Calculations were performed using nQuery Advisor® 7.0.

Meanwhile, the draft version of the revised Japanese guideline “Clinical Evaluation Guidelines for Antihyperglycemic Drugs” [R15-2907] requires at least 100 patients who are treated for 1 year with oral antihyperglycemic drug. Therefore, assuming a 20 % loss of

randomised patients during the 52 weeks of treatment, at least 63 patients should be randomised per arm (126 patients from both empagliflozin 10 mg and 25 mg arms).

On the basis of the above, a total of 267 patients (89 per arm) need to be randomised.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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 Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs) and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and the Japanese GPSP regulations (Ministry of Health, Labour and Welfare Ordinance No. 171, December 20, 2004).

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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 subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The rights of the investigator / trial site and of the sponsor with regard to publication of the results of this trial are described in the trial site's contract. As a general 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 the patients, and is stored in the ISF (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) 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 Investigator must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator 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 must sign and date the informed consent form.

If a trial collaborator has given a supplementary explanation, the trial collaborator also signs 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.

8.2 DATA QUALITY ASSURANCE

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

eCRF for individual patients will be provided by the Sponsor via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.
For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data

and process. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to subject safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e., is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For empagliflozin this is the current version of IB [c01838761]. In addition to that the Japanese package insert of empagliflozin is used to assess local expectedness in Japan.

The current versions of these reference documents are provided in the ISF. No AE are classified as listed for matching placebo, trial design.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 STATEMENT OF CONFIDENTIALITY

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

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial

need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB and the regulatory authorities.

8.6 END OF TRIAL

The end of the trial is defined as the last patient out.

When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

The investigator should document any deviation from the protocol regardless of their reasons.

Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R05-0939 Wright EM, Turk E. The sodium/glucose cotransport family SLC5. Pfluegers Archiv - European Journal of Physiology 2004; 447 (5), 510 - 518.

R10-4692 MHLW Guideline - Clinical Evaluation Guidelines for Oral Antihyperglycaemic Drugs

R13-3738 Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013

R14-4302 The Japan Diabetes Society. Treatment Guide for Diabetes 2014-2015. Tokyo, Bunkodo; 2014.

R15-2907 MHLW draft revised guideline (draft) - Clinical Evaluation Guidelines for Antihyperglycemic Drugs

R15-2908 The Japan Diabetes Society. Recommendation from “Committee on the proper use of SGLT2 inhibitors”

9.2 UNPUBLISHED REFERENCES

c01838761 Investigator’s Brochure: empagliflozin and empagliflozin/linagliptin FDC, Indication: type 2 diabetes mellitus, Project No. 1275.P1, 1245.P1, Current Version

U12-3817-01 . A phase IIb, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 10773 (10 mg and 25 mg) administered orally, once daily over 78 weeks in type 2 diabetic patients receiving treatment with basal insulin (glargine, detemir, or NPH insulin only) with or without concomitant metformin and/or sulfonylurea therapy and insufficient glycaemic control. BI Trial No. 1245.33. 11 Jan 2013.

U13-1730-01 A 52-week, randomised, multi-centre, parallel group study to investigate the safety and efficacy of BI 10773 (10 mg or 25 mg administered orally once daily) as add-on therapy to an oral antidiabetic drug (sulfonylurea, biguanide, thiazolidinedione, alpha glucosidase inhibitor, DPP-IV inhibitor, or glinide) in patients with type 2 diabetes mellitus with insufficient glycaemic control. BI Trial No. 1245.52. 26 September 2013.

U13-2122-01 , , A phase III, randomised, double-blind, placebo-controlled, parallel group safety and efficacy study of BI 10773 (10 mg and 25 mg administered orally once daily) during 52 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control on MDI insulin regimen alone or with metformin. BI Trial No.1245.49. 20 Sep 2013.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		13 September 2016
EudraCT number		
BI Trial number		1245.107
BI Investigational Product		Jardiance®, Empagliflozin
Title of protocol		A 52-week randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of empagliflozin once daily, as add-on to insulin in Japanese patients with Type 2 Diabetes Mellitus with insufficient glycaemic control
To be implemented only after approval of the IRB		
To be implemented immediately in order to eliminate hazard – IRB to be notified of change with request for approval		
Can be implemented without IRB approval as changes involve logistical or administrative aspects only		
Section to be changed		3.3.2 and synopsis (Change 1)
Description of change		*Text in inclusion criteria 2 is reformulated to:* Insulin product and its usage must be unchanged at least from 12 weeks prior to Visit 1 (screening). Total prescribed dose must be ≥10 U/day ~~and ≥0.2U/kg/day~~, and it has to be within a defined area at least 12 weeks prior to Visit 5 (randomization) in patients who are pre-treated by insulin alone and from Visit 1 in patients who are pre-treated by insulin in combination with 1 OAD.
Rationale for change		To carry out the study in common clinical setting in Japan, the criterion of the dose of insulin is updated. (It is estimated that there are many T2DM patients who are treated with insulin which doses are more than or equal to 10U/day but below 0.2U/kg/day in common clinical setting in Japan)
Section to be changed		3.3.2 and synopsis (Chang 2)
Description of change		*Inclusion criteria 3 is reformulated to:* Fasting C-peptide: ~~≥0.6~~ **>0.5** ng/mL at Visit 4 in patients who are pre-treated with insulin alone (at

		Visit 2 in patients who are pre-treated with insulin in combination with 1 OAD)
Rationale for change		The criterion was set up to remove the patients who are in insulin-dependent state. The treatment Guide for Diabetes 2014-2015 says that C-peptide ≤0.5 is insulin-depedent state. To match with the treatment guide, this is updated.
Section to be changed		5.3.6.1 (Chang 3)
Description of change		The following description for "events involving lower limb amputation" is added, **<u>Events involving lower limb amputation</u>** **This definition includes amputation (i.e. resection of a limb through a bone), disarticulation (i.e. resection of a limb through a joint) and auto-amputations (i.e. 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).** **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.**
Rationale for change		To align with the updated AESI definition of empagliflozin project.
Section to be changed		6.1 (Chang 4)
Description of change		*Text reformulated to:* All trial visits (except Visit 1, **5.1 and phone contact for Follow up visit**) should take place ~~between 7:00 AM and 11:00 Am~~ **in the morning**.
Rationale for change		Clarification (phone visit can be done not in the morning) / It is difficult to complete visits' procedures by 11:00 AM

Section to be changed		10.1 (Chang 5)
Description of change		*Text reformulated to:*
Rationale for change		Clarification

APPROVAL / SIGNATURE PAGE

Document Number: c03122592 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: A 52-week randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of empagliflozin once daily, as add-on to insulin in Japanese patients with Type 2 Diabetes Mellitus with insufficient glycaemic control

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		13 Sep 2016 12:12 CEST
Author-Trial Clinical Monitor		13 Sep 2016 12:31 CEST
Author-Trial Statistician		15 Sep 2016 09:47 CEST
Approval-Clinical VP		19 Sep 2016 20:17 CEST
Verification-Paper Signature Completion		28 Sep 2016 03:51 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed