Clinical Trial Protocol

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EudraCT No.:	2014-005256-26	
BI Trial No.:	1245.72	
BI Investigational Product:	Empagliflozin	
Title:	A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of **E**mpagliflozin as **A**djunctive to in**S**ulin th**E**rapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3)	
Brief Title:	**E**mpagliflozin as **A**djunctive to In**S**ulin th**E**rapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3)	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted], Fax: [redacted]	
Status:	Final Protocol (Revised Protocol based on Global Amendment 1)	
Version and Date:	**Version: 2.0**	**Date: 21 Oct 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:			
Name of active ingredient:		Empagliflozin	
Protocol date: 14 Jul 2015	**Trial number:** 1245.72		**Revision date:** 21 Oct 2016

Title of trial:	A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of **E**mpagliflozin as **A**djunctive to in**S**ulin th**E**rapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3)
Coordinating Investigator:	[redacted] Phone: [redacted]
Trial sites:	Multi-centre trial planned to be conducted in multiple countries
Clinical phase:	III
Objectives:	The objective of this study is to assess the efficacy, safety, tolerability and pharmacokinetics (PK) of once daily oral doses of empagliflozin 2.5 mg, 10 mg and 25 mg compared to placebo in patients with Type 1 diabetes mellitus (T1DM) as adjunctive to insulin therapy
Methodology:	Randomised, double-blind, placebo-controlled parallel group comparison of 3 oral once daily doses (2.5 mg, 10 mg and 25 mg) of empagliflozin to placebo. Randomisation will be stratified by: • pre-existing insulin therapy (multiple daily injections [MDI] vs continuous subcutaneous insulin infusion [CSII]) • Visit 5 estimated Glomerular filtration rate (eGFR) as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (< 60 mL/min/1.73 m^2 vs ≥ 60 mL/min/1.73 m^2) • Visit 5 glycated haemoglobin (HbA_{1c}, < 8.5% vs ≥ 8.5%) • participation in the CGM substudy (CGM participation versus non-CGM participation)
No. of patients: total entered (randomised):	960
each treatment:	240 patients per dose group Empagliflozin 2.5 mg: 240 patients Empagliflozin 10 mg: 240 patients Empagliflozin 25 mg: 240 patients Placebo: 240 patients
Diagnosis :	T1DM
Main criteria for inclusion:	Male or female patients ≥ 18 years, with an HbA_{1c} of ≥ 7.5% and ≤ 10.0% at Visit 5 (beginning of the run-in period), and a C-peptide value of < 0.7 ng/mL (< 0.23 nmol/L) at Visit 2 (beginning of T1DM therapy optimisation period). Patients should have been receiving insulin for the treatment of T1DM for at least 1 year prior to Visit 1, and be willing to continue this throughout the trial.

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	Insulin should be either MDI or CSII with a total daily dose ≥ 0.3 U/kg and ≤ 1.5 U/kg at Visit 1
Test products:	Empagliflozin film-coated tablets
dose:	2.5 mg, 10 mg, or 25 mg once daily
mode of administration:	Oral
Comparator products:	Placebo to match empagliflozin film-coated tablets
dose:	Not applicable
mode of administration:	Oral
Duration of treatment:	1 week screening period 6 week T1DM therapy optimisation period 2 week placebo run-in period 26 week randomised double-blind treatment period 3 week follow-up period after study medication termination
Endpoints	Primary endpoint is the change from baseline in HbA_{1c} after 26 weeks Key secondary endpoints are: • incidence rate of symptomatic hypoglycaemic adverse events (AEs) with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 5 to Week 26 ○ severe hypoglycaemic AEs are defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration • incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 1 to Week 26 • change from baseline in body weight (kg) after 26 weeks • change from baseline in total daily insulin dose (TDID), U/kg, after 26 weeks • change from baseline in systolic blood pressure (SBP) after 26 weeks • change from baseline in diastolic blood pressure (DBP) after 26 weeks
Safety criteria:	Incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 1 to Week 4 Frequency of patients with adverse events of special interest (AESIs): • diabetic ketoacidosis (DKA) • hepatic injury • decreased renal function • severe hypoglycaemic episodes Frequency of patients with hypoglycaemia Hypoglycaemia rate

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	Frequency of patients with adjudicated events: • cardiovascular events • severe hypoglycaemia • DKA
Statistical methods:	For the primary endpoint, change from baseline in HbA_{1c} after 26 weeks, restricted maximum likelihood estimation based on mixed-effect model for repeated measures (MMRM) analysis will be used to obtain adjusted means for the treatment effects. This model will include treatment, week and pre-existing insulin therapy as discrete fixed effects, baseline eGFR (CKD-EPI) and baseline HbA_{1c} as continuous fixed effects, as well as the interaction between week and treatment and the interaction between week and baseline HbA_{1c}. The initial primary treatment comparisons will be the Bonferroni adjusted contrast between the doses of empagliflozin 10 mg or 25 mg and placebo at Week 26. The doses of empagliflozin 10 mg or 25 mg will therefore be tested at the level of α=0.025 (two-sided). The primary analysis will be an efficacy analysis, including on-treatment data only. Following the efficacy analysis, an effectiveness analysis (on-and off-treatment data) will be performed in a hierarchical manner. If the null hypothesis is rejected for both the efficacy and effectiveness analysis then the primary endpoint (between empagliflozin 2.5 mg and placebo, on-treatment data only) and the key secondary endpoints will be tested in a confirmatory way using a gatekeeping approach, with unequal splitting of the alpha, and sequential testing. The key secondary endpoints of change from baseline in body weight after 26 weeks and change from baseline in TDID will be analysed using a similar model to the analysis of the primary endpoint, with the addition of baseline and interaction between baseline and week for the respective endpoint. The key secondary endpoint of incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs from Week 5 to Week 26 will be analysed using a negative binomial model. The model will include treatment and pre-existing insulin therapy as discrete fixed effects, baseline rate, baseline HbA_{1c} and baseline eGFR as continuous fixed effects and logarithm of days of exposure as an offset. The primary treatment comparisons will be the rate ratios comparing the incidence rates per-patient year from Week 5 to Week 26 on each dose of empagliflozin to placebo. The same analysis strategy will be applied for the key secondary endpoint of incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic events from Week 1 to Week 26. The key secondary endpoints of change from baseline in SBP and DBP after 26 weeks will be analysed using a similar model to the analysis of the primary

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	endpoint, with the addition of terms for baseline and interaction between baseline and week for the respective endpoint.		

FLOW CHART

Trial Period	**Screen-ing**	**T1DM Therapy Optimisation[B,C]**			**Placebo Run-In**		**Randomised Treatment[F]**								**Follow -Up**
Visit	**1**	**2**	**3/3T[D]**	**4T[D]**	**5**		**6[C]**	**7**	**8**	**9**	**10**	**11 CGM[W]**	**11 EOT[I]**	**eEOT Early Discn. Only[G,I]**	**12[G]**
Study week	**-9**	**-8**	**-6**	**-4**	**-2**			**1**	**4**	**12**	**18**	**24**	**26**		**29**
Study day	**-63**	**-56**	**-42**	**-28**	**-14**	**-2[E]**	**1**	**8**	**29**	**85**	**127**	**169**	**183**		**204**
Visit window (days)[A]	**-7/+4**	**+/-2**	**+/-2**	**+/-2**	**+/-3**	**+/-1**	**n/a**	**+/-2**	**+/-7**	**+/-7**	**+/-7**	**+/-3**	**+/-3**		**+/-7**
Fasting status[H]	**NF**	**F**	**NF**	**-**	**NF**	**-**	**F**	**NF**	**NF**	**F**	**NF**	**NF**	**F**	**F**	**F**
Informed consent	x														
Demographics	x														
Medical history, baseline conditions	x														
Check of in-/exclusion criteria	x	x	x	x	x		x								
Height	x														
Weight	x				x		x	x	x	x			x	x	x
[redacted]	[redacted]						[redacted]			[redacted]			[redacted]	[redacted]	
Vital signs	x	x	(x)		x		x	x	x	x	x		x	x	x
Physical examination	x						x						x	x	
12-lead ECG							x						x	x	
Safety laboratory, urinalysis[J]	x[R]	x[U]			x		x[S]		x	x			x[S]	x[S]	x[S]
Blood ketone measurement at the site with home monitoring device, urine ketone measurement[Y]		x	(x)		x		x	x	x	x	x		x	x	x
Pregnancy test[K]	x						x			x			x	x	
[redacted]							[redacted]								
[redacted]									[redacted]	[redacted]			[redacted]	[redacted]	

Trial Period	**Screen-ing**	**T1DM Therapy Optimisation[B,C]**			**Placebo Run-In**		**Randomised Treatment[F]**								**Follow -Up**
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Fasting status[H]	**NF**	**F**	**NF**	**-**	**NF**	**-**	**F**	**NF**	**NF**	**F**	**NF**	**NF**	**F**	**F**	**F**
HbA_{1c}	x				x		x		x	x	x		x	x	
FPG (central lab)							x			x			x	x	x
[redacted]						[redacted]		[redacted]	[redacted]				[redacted]	[redacted]	
Dispense run-in medication (Interactive Response Technology, IRT)					x										
Randomisation (IRT)							x								
Dispense double-blind medication (IRT)							x		x	x	x				
Compliance/drug accountability check							x	x	x	x	x		x	x	
Management of diet & physical activity, training on home monitoring device[O]		Continuous													
Home monitoring[P]		Continuous													
[redacted]					x							x			
[redacted]									[redacted]				[redacted]		
Training/dispensing of patient e-diary		x	Refresher training as required												
Check of patient e-diary			x	x	x		x	x	x	x	x		x	x	x

Trial Period	**Screen-ing**	**T1DM Therapy Optimisation[B,C]**			**Placebo Run-In**		**Randomised Treatment[F]**								**Follow -Up**
Visit	**1**	**2**	**3/3T[D]**	**4T[D]**	**5**		**6[C]**	**7**	**8**	**9**	**10**	**11 CGM[W]**	**11 EOT[I]**	**eEOT Early Discn. Only[G,I]**	**12[G]**
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Fasting status[H]	**NF**	**F**	**NF**	**-**	**NF**	**-**	**F**	**NF**	**NF**	**F**	**NF**	**NF**	**F**	**F**	**F**
[redacted]															
[redacted]															
[redacted]															
[redacted]															
Adverse events		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
Termination of trial medication													x	x	
Vital status collection													x		

A Permitted visit windows should be strictly adhered to, to ensure laboratory results from a preceding visit are available by the time of the next visit, and to ensure a sufficient supply of medication until the next visit. For patients participating in the CGM substudy, the time span between Visit 5 (Day -14) and Visit 6 (Day 1) should ideally be exactly 14 days; the time span between Visit 6 (Day 1) and Visit 8 (Day 29) should ideally be exactly 28 days; the time span between Visit 11 CGM and Visit 11EOT should ideally be exactly 14 days. For further details see Section 6.1

B The patient's therapy for T1DM (e.g. ability to review blood glucose values, skills for carbohydrate estimation and insulin adjustment) should be optimised from Visit 2 for a period of 6 weeks (i.e. until the patient reaches Visit 5 and the placebo run-in period) to achieve the best standard of care in accordance with local guidelines. This optimal therapy should then be continued from Visit 5 for eligible patients. For further details see Section 4.2.1

C During the T1DM therapy optimisation period, and daily for 5 days following clinic Visit 6, data from the electronic (e)-diary should be reviewed remotely by designated site personnel, paying particular attention to adjustments in the insulin regimen, glucose values and, if available, ketone measurements. In addition, the patient should be contacted by telephone (e.g. weekly during the T1DM therapy optimisation period) if e-diary data, including glucose data, is not available and/or if the data suggests closer monitoring of the patient is required. Additional clinic visits can also be arranged if necessary. For further details see Sections 5.2.3 and 6.2.1

D Visit 4T is a telephone visit. Visit 3 can be a telephone visit (3T), if deemed sufficient based on Investigator judgement, or a clinic visit; if performed as a telephone visit, assessments in brackets in the Flow Chart do not have to be performed

E Visit 5 includes a 9-point plasma glucose profile on Day -2. No clinic visit is required on this day, as the 9-point plasma glucose profile will be performed by the patient at home. For further details see Footnote N and Section 5.2.6

F Following randomisation and prior to the initiation of study medication, Investigators are advised to reduce the patient's total insulin dose based on need/ by 10% to avoid hypoglycaemia; thereafter further insulin adjustments may be implemented as necessary. For further details see Section 4.2.1

G An early End of Treatment (eEOT) Visit, as well as a Follow-up Visit 12, should be performed for any patient who discontinues study medication prematurely; the eEOT Visit should be completed as soon as possible after study medication is stopped. [redacted] the 9-point plasma glucose profile should only be performed if it is feasible for it to be done over a 24 hour period before the eEOT visit when study medication is still being taken; otherwise it can be omitted. Visit 12 should be performed 3 weeks after the eEOT visit, and where possible, patients should then be followed up according to the visit schedule. For further details see Section 6.2.3

H NF: non-fasting; F: fasting

I Following the termination of trial medication, and if deemed necessary based on Investigator's judgement, additional support (e.g. telephone interaction) can be given to the patient during the adjustment of T1DM therapy in the Follow-up period

J Safety laboratory includes calculation of the eGFR. Following a positive urine dipstick result (at the site) for leukocyte esterase (for WBC) or nitrite, a midstream urine sample for urine culture is triggered. For further details see Section 5.3.3

K For female patients of child-bearing potential (local urine pregnancy test)

[redacted]

O Home monitoring device: meter for monitoring of blood (plasma) glucose and ketone levels at home

P Self-Blood Glucose Monitoring (SBGM) should be performed daily from the beginning of the T1DM therapy optimisation period to the end of the Follow-up period. Measurements should be taken 4 times a day as a minimum e.g. at least before breakfast, lunch, dinner and bedtime. Additional measurements will also be warranted (e.g. after clinic Visit 6). For further details see Section 5.3.2.1. Ketone measurements should be performed by the patient in case of any symptoms of DKA. Other conditions may also trigger the need for ketone measurement. For further details see Section 5.3.2.2

Q [redacted]

R For the screening visit (Visit 1) an abbreviated, safety laboratory and urinalysis will be performed as follows: liver transaminases, alkaline phosphatase, serum creatinine, TSH, and urinalysis. For further details see Section 5.3.3

S At Visits 6, 11 EOT, eEOT (if applicable) and 12 only, the safety laboratory testing will include lipids. Samples should be obtained from the patient in a fasting state. For further details see Section 5.3.3

[redacted]

U For Visit 2, an abbreviated safety laboratory (fasting) will be performed as follows: C-peptide, beta-hydroxy-butyrate, bicarbonate and electrolytes only. For further details see Section 5.3.3

[redacted]

Y At visits with safety laboratory, ketone measurements should be done directly before or after the collection of laboratory samples. At visits which require fasting, ketone measurements should be done in a fasted state. Regular (e.g. 2-3 times a week) measurements at home before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements are recommended during the run-in period and during the first 4 weeks of the treatment period.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AUC	Area-Under-the-Curve
BP	Blood Pressure
BI	Boehringer Ingelheim
CEC	Clinical Event Committee
CGM	Continuous Glucose Monitoring
CKD-EPI	Chronic Kidney Disease Epidemiology
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CSII	Continuous Subcutaneous Insulin Infusion
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
DCCT	Diabetes Control and Complications Trial
DEDP	Drug Exposure During Pregnancy
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DTSQs/c	Diabetes Treatment Satisfaction Questionnaire status/change version
EASE	Empagliflozin as Adjunctive to InSulin thErapy in patients with Type 1 Diabetes Mellitus
eCRF	Electronic Case Report Form
EDTA	Ethylendiaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
e-PRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQoL-5Dimension-5Level
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like-peptide 1
HbA_{1c}	Glycosylated Haemoglobin
HCRU	Health Care Resource Utilisation
HFS-II	Hypoglycaemia Fear Survey II
HFS-W	Hypoglycaemia Fear Survey – Worry sub-scale
HPLC-MS	High performance liquid chromatography – tandem mass spectrometry
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICU	Intensive Care Unit
IDF	International Diabetes Federation

IEC	Independent Ethics Committee
IFCC	International Federation of Clinical Chemistry
IPV	Important Protocol Violation
IQR	Inter Quartile Range
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
MAGE	Mean Amplitude of Glycaemic Excursions
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Drug Regulatory Activities
MDG	Mean Daily Glucose
MDI	Multiple Daily Injections
MDRD	Modification of Diet in Renal Disease
mITT	Modified Intention-to-Treat
MMRM	Mixed Model for Repeated Measures
MODY	Maturity Onset Diabetes of the Young
NGSP	National Glycohemoglobin Standardisation Program
PD	Pharmacodynamic
PGx	Pharmacogenomic
PK	Pharmacokinetics
PPS	Per Protocol Set
RDC	Remote Data Capture
REP	Residual Effect Period
RS	Randomised Set
SAE	Serious Adverse Event
SBGM	Self-Blood Glucose Monitoring
SGLT	Sodium-Glucose Co-Transporter
SLC	Sodium-Glucose Co-transport
SOP	Standard Operating Procedure
STEMI	ST Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TCM	Trial Clinical Monitor
TDID	Total Daily Insulin Dose
TDM	Trial Data Manager
TIA	Transient Ischaemic Attack
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
UACR	Urine Albumin Creatinine Ratio
UGE	Urinary Glucose Excretion
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
WHO	World Health Organisation

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Type 1 diabetes mellitus (T1DM) accounts for 5 to 10% of all cases of diabetes mellitus. This disease is a complex disorder that requires constant attention to diet, exercise, glucose monitoring, and insulin therapy to achieve good glycaemic control. T1DM occurs as a consequence of the organ-specific immune destruction of the pancreas' insulin-producing β-cells in the islets of Langerhans [R10-6370, R10-6371].

Controlling blood glucose in T1DM leads to improved patient outcomes [R04-2186, R12-1489]. For this reason, several medical associations have given treatment recommendations for T1DM [P13-05979, R12-4773] including glycaemic goals. Most bodies recommend that adult patients with T1DM should obtain glycated haemoglobin (HbA_{1c}) ≤ 7.0%. However, despite advances in insulin formulation and delivery, such as the development of continuous subcutaneous insulin infusion (CSII) systems, refinement of pharmacokinetic (PK) properties of rapid- and long-acting insulin analogues, and the use of continuous glucose monitoring (CGM) systems, current therapy for patients with diabetes requiring insulin often does not lead to satisfactory glycaemic control. In fact, only a minor portion of patients achieve normalisation of HbA_{1c} and restoration of euglycaemia. Most patients generally achieve HbA_{1c} levels no lower than 8.0%. Hence, with the currently available treatment options, patients with T1DM often fail to maintain adequate blood glucose control. This may not only lead to acute conditions such as hyperglycaemia and ketoacidosis, but may also lead to debilitating secondary complications including heart disease, blindness and kidney failure [R10-6369]. In addition, inadvertent excessive administration of insulin may also contribute to acute conditions such as severe hypoglycaemia.

Empagliflozin is a reversible, highly potent (IC_{50} 1.3 nM) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT-2), a member of a larger group of sodium substrate co-transporters, the sodium-glucose co-transport 5 (SLC5) gene family [R05-0939]. Under normoglycaemia, glucose is 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 glucosuria. This threshold concentration can be decreased by SGLT-2 inhibition [c01678844]; an approximately 5000-fold selectivity over human SGLT-1 (IC_{50} 6278 nM), responsible for glucose absorption in the gut, was calculated for empagliflozin [U06-1742].

It was demonstrated, nearly four decades ago, that in patients with poorly controlled T1DM, the maximum tubular reabsorption capacity for glucose was significantly increased, whereas one would in fact have suspected that during hyperglycaemia, with increased interstitial and intracellular glucose concentrations, the reduced glucose concentration gradient across the basolateral membrane of the proximal renal epithelial cell would attenuate glucose efflux [R10-6572]. This paradoxically increased glucose reabsorption in T1DM could be explained by an up-regulation of glucose transporters, including SGLT-2 which was shown in tubular cells cultured from patients with Type 2 diabetes mellitus (T2DM) [R10-0703]. The phenomenon of an increased reabsorption of glucose when glucose concentration is elevated

could therefore be considered a maladapted response to glucosuria in diabetes, since it would rather be desirable for the kidney to excrete the excess filtered glucose load in order to restore normoglycaemia [P11-10364].

Based on these pathophysiological considerations, it follows that empagliflozin has the potential to provide a novel approach to the treatment of T1DM, as adjunctive therapy to insulin. Empagliflozin lowers both the saturation threshold and the transport maximum of SGLT-2 for glucose, resulting in increased glucosuria, insulin-independent reduction of plasma glucose levels with potentially low risk of hypoglycaemia, and negative energy balance with potential weight reduction in T1DM.

1.2 DRUG PROFILE

Empagliflozin is a novel, orally available, potent, and selective inhibitor of the renal SGLT-2. Its selective inhibition reduces renal reabsorption of glucose and promotes increased urinary glucose excretion (UGE) resulting in reduction of blood glucose levels.

Empagliflozin has been developed for the treatment of T2DM, and has received marketing approval in various regions including the European Union and the USA where it is marketed under the brand name Jardiance®.

1.2.1 Non-clinical assessment of safety

For further information regarding pre-clinical evaluation, please refer to the current version of the Investigator's Brochure (IB) for empagliflozin [c01678844].

1.2.2 Clinical pharmacokinetics

1.2.2.1 Clinical pharmacokinetics – Type 2 diabetes mellitus

In humans, empagliflozin predominantly showed linear PK. Empagliflozin reaches peak levels at approximately 1.5 hours and showed a biphasic decline with the terminal elimination half-life of 12.4 hours ranging from 10 to 19 hours.

Empagliflozin exposure increases with renal or hepatic impairment; however, no dose adjustment is recommended as the observed changes in exposure were not clinically meaningful. The observations from a Phase I study in patients with renal impairment indicate a rather low glycaemic efficacy of empagliflozin in patients with severe renal impairment and end-stage renal disease, while efficacy is assumed to be unchanged with hepatic impairment. No clinically relevant PK interactions were observed with other oral antidiabetics, warfarin, verapamil, ramipril, simvastatin, digoxin, hydrochlorothiazide, torasemide, gemfibrozil, rifampicin, probenecid and oral contraceptives (Microgynon®).

For further details refer to the current version of the IB for empagliflozin [c01678844].

[redacted]

[redacted]

1.2.3 Clinical efficacy and safety

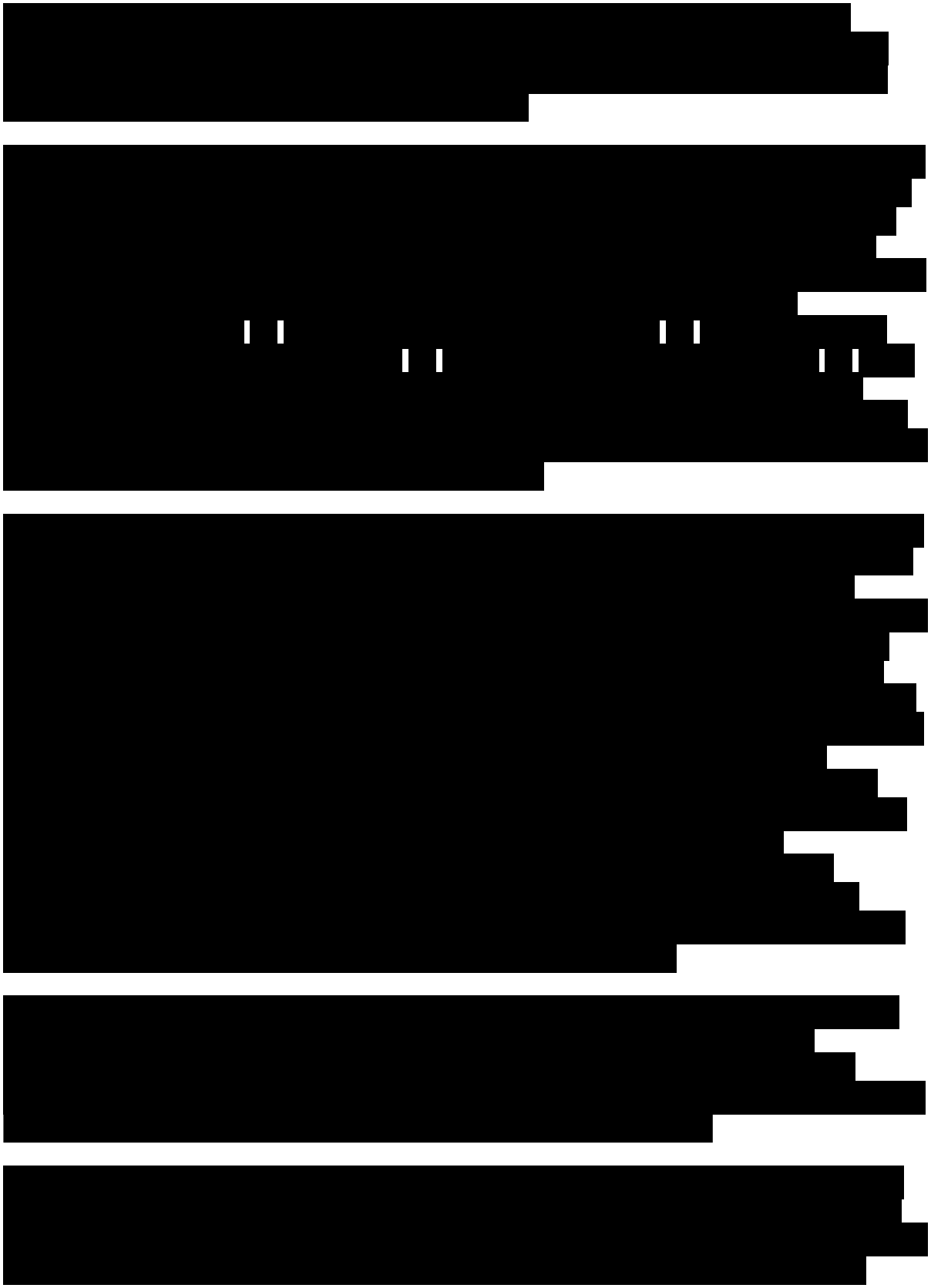
1.2.3.1 Clinical efficacy and safety – Type 2 diabetes mellitus

Empagliflozin has been studied as part of a global development program with 15582 patients with T2DM treated in clinical studies of which 10004 were treated with empagliflozin, either alone or in combination with metformin, a sulfonylurea, a PPARγ agonist, dipeptidyl peptidase-4 inhibitors, or insulin.

The Phase III studies in T2DM showed that treatment with empagliflozin 10 mg or 25 mg once daily for up to 24 weeks results in a reduction of HbA_{1c} up to 0.85%, body weight up to 2.2 kg and systolic blood pressure (SBP) up to 4.8 mmHg compared with placebo. This was consistently observed with empagliflozin as monotherapy, add on to metformin, to metformin and sulphonylurea, to pioglitazone with or without metformin, and to basal insulin with metformin and/or sulphonylurea. Phase III studies up to 104 weeks in T2DM support the sustained effect of empagliflozin.

In clinical studies, empagliflozin was well tolerated in both normal healthy volunteers and patients with T2DM up to maximal treatment duration of 104 weeks in completed studies. The frequency of overall Adverse Events (AEs), AEs leading to discontinuation and Serious AE (SAEs) were comparable to placebo. There was no significant increase in frequency of hypoglycaemia with empagliflozin compared to placebo except when used in combination with a sulphonylurea or basal insulin. In general there was a small increase in frequency of urinary tract infection (UTI) compared to placebo. There was an increase in frequency of genital infections with the use of empagliflozin. There was a small increase in total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol and no significant changes in triglycerides. No changes in electrolytes were observed with empagliflozin. There was a reduction in eGFR which gradually returned toward baseline values over the treatment period in the trials. Furthermore, eGFR returned to baseline when empagliflozin was discontinued. In a dedicated study in patients with moderate renal impairment (eGFR between 30-60 mL/min/1.73 m2) treatment with empagliflozin was well tolerated and led to statistically significant reduction of HbA_{1c} and clinically meaningful improvement in FPG (fasting plasma glucose), body weight and BP compared to placebo at Week 24. Similar results were sustained for up to 52 weeks [c01678844].

[redacted]



[redacted]

In summary, given the safety profile in the preclinical studies of empagliflozin, and the safety, tolerability and efficacy seen in the clinical study programs to date, the available clinical and non-clinical data support safe and efficacious use in humans and further development of empagliflozin in T1DM and T2DM.

For a more detailed description of the drug profile refer to the current IB which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

In an extensive Phase III program, empagliflozin (10 mg and 25 mg) was shown to be safe and efficacious in the treatment of patients with T2DM and has received marketing approval in more than 30 countries including the EU and US. Due to its insulin-independent mode of action empagliflozin also has potential for use in the treatment of patients with T1DM. [redacted], this Phase III trial is planned to confirm the efficacy and safety of empagliflozin in patients with T1DM and to further investigate tolerability and PK.

2.2 TRIAL OBJECTIVES

The objective of this study is to assess the efficacy, safety, tolerability and PK of once daily oral doses of empagliflozin 2.5 mg, 10 mg and 25 mg compared to placebo in patients with T1DM as adjunctive to insulin therapy.

2.3 BENEFIT - RISK ASSESSMENT

A pharmacologic rationale for the use of empagliflozin in T1DM can be found in Section 1.1. The overall tolerability and safety profile outlined in Section 1.2, and the current IB, supports chronic administration of empagliflozin 2.5 mg, 10 mg and 25 mg in human studies.

According to the medication assignment planned in this trial, 75% of the patients will receive empagliflozin, and 25% of patients will be assigned to placebo. For those assigned to empagliflozin, patients may benefit from positive glycaemic effects. In addition to achieving better glycaemic control, patients receiving empagliflozin are expected to benefit from a reduced number and intensity of hypoglycaemic events due to a reduced need for insulin/reduced glucose excursions (since when using insulin only, its subcutaneous administration often leads to over-insulination ultimately causing hypoglycaemia). Nevertheless, patients will be closely monitored for hypoglycaemic episodes throughout the trial, and the frequency of this monitoring will be adjusted in accordance with the anticipated risk (including night-time glucose measurements during the first days after initiation of the study medication). Patients assigned to both empagliflozin and placebo may also derive general medical benefit from careful and close monitoring by medical personnel during the study. Placebo patients may benefit from optimising the therapy for T1DM as part of the T1DM therapy optimisation period.

As part of the preparation for entry into the randomised treatment period, therapy for T1DM will be optimised (e.g. review of blood glucose values, insulin dose and its adjustment for meals, ability to carbohydrate count etc.) over a 6 week period (T1DM therapy optimisation period) to ensure that, in the Investigator's opinion, a patient is achieving the best standard of care in accordance with local guidelines before entering the randomised treatment period of the trial. This optimal therapy will then be continued, and at randomisation, Investigators are

advised to reduce the patient's total insulin dose based on need/ by 10% to minimise the risk for hypoglycaemia. Since glomerular filtration is physiologically decreased during episodes of severe hypoglycaemia (due to reduced renal blood flow hence leading to lowering of urine glucose excretion and therefore efficacy of empagliflozin), hypoglycaemia induced by insulin is not expected to be significantly aggravated by empagliflozin [R12-4766].

Special attention will be paid to prevent T1DM-inherent DKA. Due to the mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA. Patients receiving empagliflozin may be at risk to underestimate their need for insulin if blood sugar levels are within individual target ranges or only slightly elevated. Insulin deficiency might lead to ketoacidosis which could be life-threatening if not recognised and appropriately treated. All patients will be made aware of this risk and be instructed not to reduce their insulin dose below Investigator recommendations. In addition to blood glucose monitoring, the frequency of which will be increased after starting the study medication (for further details see Section 5.3.2.1), in the same way as during routine clinical care, patients will be reminded how to determine ketones in case of any symptoms of DKA, e.g. nausea, vomiting, abdominal pain etc. They will be instructed to do this irrespective of the glucose value in the event of DKA symptoms occurring. More frequent ketone testing (e.g. once daily) will be recommended during the run-in period and during the first 4 weeks of the treatment period; this will allow patients and Investigators to understand baseline ketosis rates and compare them, as appropriate, to the incidence of ketosis following the initiation of study medication. A meter will be provided to the patient for this purpose; as an additional safeguard, the meter will also be used to check ketone levels at most clinic visits (see Flow Chart). Patients will be reminded of the interpretation of ketone values measured by the meter, and on appropriate action to be taken in the event of increased ketone levels (see Section 5.3.2.2). In addition, patients will be reminded about insulin adjustment during "sick days" and about the importance of keeping themselves hydrated.

Investigators should also differentiate deteriorating ketosis/DKA from any mild to moderate increase of ketones which may be seen due to the mechanism of action of empagliflozin, especially in the fasted state (e.g. in the morning). See also Section 1.2.3.2.

Patients will be carefully selected for the trial in line with the eligibility criteria, to ensure, in the Investigator's judgement, that they 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. This means, for example, that patients should be able to lead the optimisation of their T1DM therapy since they are judged to have sound self-management skills and approaches to insulin dose adjustment, and are reliable in terms of performing frequent home testing of both glucose and ketones when required.

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 investigational medicinal product used in a clinical trial setting, such as unexpected adverse clinical or laboratory events.

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

To continue the assessment of the long-term safety of empagliflozin, an adjudication of certain hepatic events will be performed in this trial. Furthermore, adjudication of cardiovascular events, severe hypoglycaemia and DKA will be performed. The progress of the trial will also be assessed at regular intervals by an independent Data Monitoring Committee (DMC). For further details please refer to Section 3.1.1.1.

Based on the findings in non-clinical studies conducted to date, and in accordance with international regulatory guidelines, the inclusion of women of child-bearing potential in this trial is justified. To minimise the risk of unintentional exposure of an embryo or foetus to the investigational drug, women of child-bearing potential must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol (for further details see Section 3.3.3).

Safety will be carefully assessed by monitoring the patients for AEs clinically, by laboratory testing and by blood glucose and ketone monitoring. The Investigator will have the discretion to remove patients from the study should there be any safety concerns or if the patient's wellbeing is at jeopardy.

The potency, selectivity, and efficacy in various animal models and the PD data from studies in healthy volunteers and patients with diabetes suggest that empagliflozin may be able to provide a valuable benefit to patients with T1DM.

Given the positive risk-benefit ratio for empagliflozin to date, the careful selection of patients and their monitoring during the study, the blood glucose and ketone monitoring performed by the patients at home and the option to adjust a patient's insulin treatment, the Sponsor considers the benefit-risk assessment for the use of empagliflozin in T1DM patients in this trial to be favourable.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This multi-national, randomised, placebo-controlled, double-blind, parallel group study compares 3 doses of empagliflozin (2.5 mg, 10 mg and 25 mg) to placebo in patients with T1DM as adjunctive to insulin therapy. In total, 960 patients with T1DM who meet the entry criteria will be entered (randomised) in the trial. The randomised treatment will be double-blind. A triple-dummy design will be used for masking the treatment assignment, i.e. each patient will take 3 tablets a day, receiving 1 active treatment and 2 placebo matching the alternative active treatments, or 3 placebos matching the alternative treatments.

Patients will be enrolled (screened) in the trial once they have signed the informed consent. All patients who are suitable after screening will undergo a 6 week T1DM therapy optimisation period, followed by a 2 week open-label placebo run-in period before randomisation. Patients who successfully complete both of these periods and who still meet the inclusion/exclusion criteria will be randomised into the 26 week double-blind treatment period in which they will receive either one of the 3 doses of empagliflozin or placebo in addition to their regular insulin therapy.

About 30% of the patients will take part in a CGM substudy. In addition to the regular trial assessments, these patients will have 4 CGM period of 2 weeks each (Week -2 to Week -1, Week 1 to 2, Week 3 to 4 and Week 25 to 26). This substudy will be conducted at selected trial sites which are experienced with CGM. Participation in the substudy will be optional for patients at these sites.

After the 26 week treatment period, all patients will enter a 3 week follow-up period during which they will not be treated with study medication. During this period all AEs need to be collected, documented and reported. The patient's participation is concluded when they have undergone the last planned visit (i.e. Trial Completion/Visit 12); last-patient-last-visit-primary-endpoint will occur when all patients have completed 26 weeks of treatment. The end of the trial is defined as "last patient out" (i.e. last Visit 12 completed by the last patient in the trial). For further details regarding the definition of the end of the trial, please see Section 8.6.

For a graphical representation of the trial, see Figure 3.1: 1.

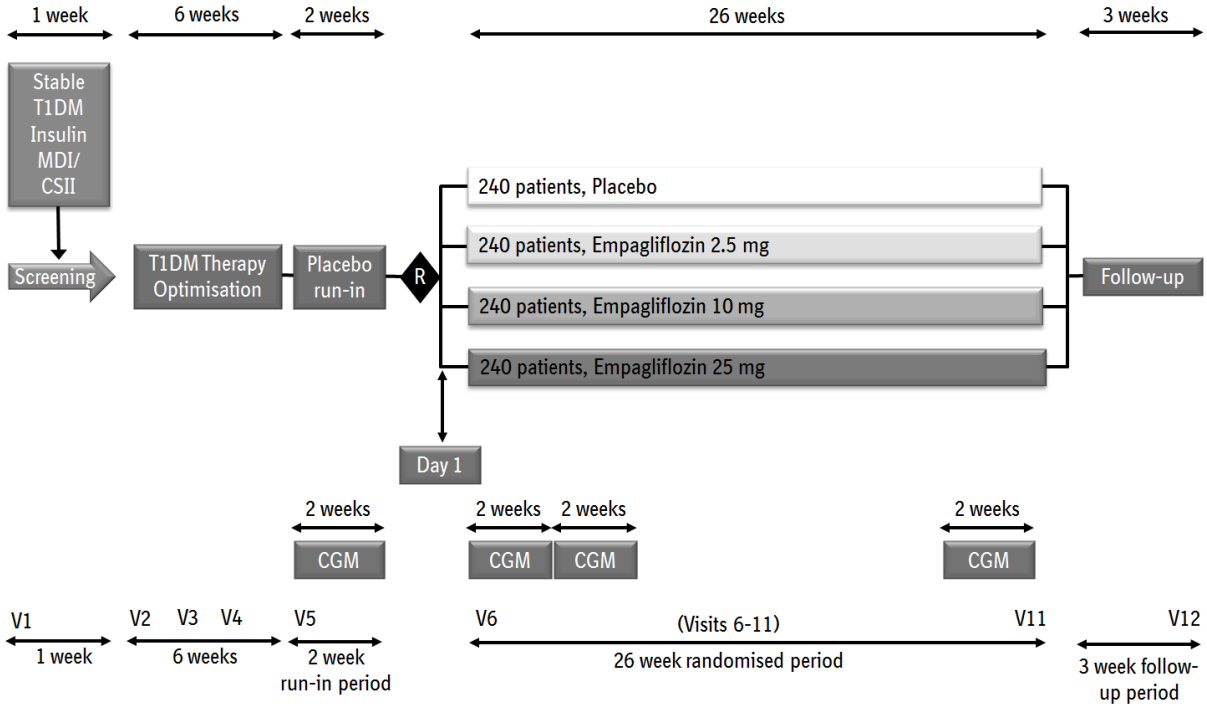


Figure 3.1: 1 Trial Design

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

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

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (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 of participating countries

Data Management and Statistical Evaluation will be done by BI according to BI SOPs. For these activities, a Trial Data Manager (TDM) and a Trial Statistician (TSTAT) will be appointed. Central laboratory services will be provided via [redacted] will be provided by [redacted]

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

An independent external committee (Clinical Event Committee, [CEC]) will be established to adjudicate centrally and in a blinded fashion events suspect of stroke, myocardial ischaemia (including myocardial infarction), cardiovascular death and other relevant events (e.g. hospitalisation for unstable angina, hospitalisation for heart failure) based on the FDA guideline [R09-2151]. The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as electrocardiograms (ECGs), laboratory values, angiography, echocardiography reports, CT and/or MRI scans, discharge summaries, and autopsy reports 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 Clinical Event Committee – severe hypoglycaemia, DKA

An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspect of severe hypoglycaemia (for further details see Section 5.3.5.2) and DKA (for further details see Section 5.3.6.1). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

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

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

3.1.1.4 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 will be defined in a charter. Events may either be defined by abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for events of hepatic injury, 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

This trial will investigate the efficacy, safety and tolerability of empagliflozin in patients with T1DM, as adjunctive to insulin therapy, and will further characterise the PK.

The trial design was chosen according to the FDA's "Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention" [R08-2669]. According to this guideline, insulin is the essential glucose-lowering therapy for patients with T1DM. All experimental T1DM treatments that are not insulin analogues or other insulin receptor ligands should be studied as add-on therapies to insulin. Consequently, in this trial empagliflozin and matching placebo will be administered as add-on to an existing insulin therapy. Treatment with MDI of insulin or CSII (i.e. insulin pump therapy) are held as the practical gold standard for the treatment of T1DM [P13-05979].

A 6 week T1DM therapy optimisation period, followed by a 2 week placebo run-in period is deemed appropriate to screen out non-compliant patients, and to capture a "true" baseline incidence rate of hypoglycaemia, together with optimal insulin use.

HbA_{1c} as the primary endpoint has been demonstrated to be a reflection of the glycaemic control over the preceding 12 weeks and maintenance data over a period of approximately 6 months are requested by the different regulatory agencies. Therefore the primary endpoint is the change from baseline in HbA_{1c} after 26 weeks of randomised treatment.

The 3 week follow-up period is considered to be sufficient, as previous studies with empagliflozin have shown that its' PD effect only extends to about three days after the last dose. Furthermore, it will allow for the assessment of reversibility of unexpected long-term side effects.

Use of a placebo group is deemed acceptable since it is expected that the insulin therapy requirement of patients receiving placebo will remain unchanged compared to their treatment before randomisation.

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

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of male and female patients with T1DM will be screened to ensure the randomisation of 960 patients from around 180 trial sites.

It is expected that around 5 patients will be randomised at each trial site. If enrolment is delayed, additional sites may be recruited. Permission to enrol more than 36 patients per site must be obtained from the TCM at BI. This will only be allowed after a careful review of the enrolment status and of the site.

Screening of patients for this trial is competitive across all countries within the trial, i.e. screening for the trial will stop at all sites when it is anticipated that a sufficient number of patients have been screened to yield the desired number of patients randomised to trial treatment. Investigators will be notified when sufficient patients have been screened and when screening is complete, and will not be allowed to recruit additional patients for the study. Patients who have completed Visit 1 procedures prior to notification of the termination of recruitment will be allowed to continue in the study, if they meet all entry criteria and they are able to follow the visit schedule specified in this Clinical Trial Protocol (CTP).

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.

3.3.1 Main diagnosis for trial entry

Only patients with confirmed, insulin-dependent T1DM for at least a year will be screened for suitability for the study. Inclusion will be based upon a complete medical history, including physical examination, vital signs, 12-lead ECG and clinical laboratory tests.

Please refer to section 8.3.1 for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

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

2. Male or female patient receiving insulin for the treatment of documented diagnosis of T1DM for at least 1 year at the time of Visit 1

3. Fasting C-peptide value of < 0.7 ng/mL (0.23 nmol/L) at Visit 2 measured by the central laboratory

4. Use of, and be willing, based on the Investigator's judgement, to continue throughout the duration of the trial, either:

   - MDI of insulin consisting of at least one basal insulin injection and at least three daily bolus injections OR
   - CSII of any insulin type, with at least 5 months experience of using CSII prior to Visit 1

   For both MDI and CSII, the total daily insulin dose must be ≥ 0.3 U/kg and ≤ 1.5 U/kg at Visit 1

5. HbA_{1c} ≥ 7.5% and ≤ 10.0% at Visit 5 measured by the central laboratory, and provided that the patient's HbA_{1c} does not increase by > 0.5% between Visit 1 and Visit 5

6. Based on the Investigator's judgement patient must have a good understanding of his/her disease and how to manage it, and be willing and capable of performing the following study assessments (assessed at Visits 1-5 and just before randomisation):

   - patient-led management and adjustment of insulin therapy
   - reliable approach to insulin dose adjustment for meals, such as carbohydrate counting
   - reliable and regular home-based blood glucose monitoring
   - recognise the symptoms of DKA, and reliably monitor for ketones
   - implementation of an established "sick day" management regimen

7. Age ≥ 18 years at Visit 1

8. Body Mass Index (BMI) of ≥ 18.5 kg/m^2 at Visit 1

9. eGFR ≥ 30 mL/min/1.73 m² as calculated by the CKD-EPI formula, based on creatinine measured by the central laboratory at Visit 1

10. Women of child-bearing potential* must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Such methods should be used throughout the study and the patient must agree to periodic pregnancy testing during participation in the trial. A list of contraceptive methods meeting these criteria will be provided in the patient information

    *Women of child-bearing potential are defined as follows:
    Any female who has experienced menarche and is not post-menopausal (defined as at least 12 months with no menses without an alternative medical cause) or who is not permanently sterilised (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy)

11. Compliance with trial medication administration must be between 80% and 120% during the open-label placebo run-in period (see Section 4.1.8.1 for calculation of compliance), to be judged before randomisation

12. To participate in the optional CGM substudy: Patient is willing to participate in that substudy and eligible based on Investigator's judgement to perform CGM. CGM substudy is conducted at the trial site

13. To participate in the optional CGM substudy: Patient is willing, based on the Investigator's judgement, not to take any paracetamol (acetaminophen) containing drugs throughout the CGM monitoring periods, since this may falsely raise CGM glucose readings

3.3.3 Exclusion criteria

1. History of T2DM, maturity onset diabetes of the young (MODY), pancreatic surgery or chronic pancreatitis

2. Pancreas, pancreatic islet cells or renal transplant recipient

3. T1DM treatment with any other antihyperglycaemic drug (e.g. metformin, alpha-glucosidase inhibitors, glucagon-like-peptide 1 [GLP-1] analogues, SGLT-2 inhibitors, pramlintide, inhaled insulin, pre-mixed insulins etc.) except subcutaneous basal and bolus insulin within 3 months prior to Visit 1 or any history of clinically relevant hypersensitivity according to Investigator's judgement

4. Occurrence of severe hypoglycaemia involving coma/unconsciousness and/or seizure that required hospitalisation or hypoglycaemia-related treatment by an emergency physician or paramedic within 3 months prior to Visit 1 and until randomisation

5. Occurrence of DKA within 3 months prior to Visit 1 and until randomisation at Visit 6

6. Irregular sleep/wake cycle (e.g. patients who habitually sleep during the day and work during the night) based on Investigator's judgement

7. Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or transient ischaemic attack (TIA) within 3 months prior to Visit 1

8. Diagnosis of severe gastroparesis (based on Investigator's judgement)

9. Diagnosis of brittle diabetes based on Investigator judgement

10. Indication of liver disease, defined by serum levels of either alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase above 3 x upper limit of normal (ULN) at Visit 1 or Visit 5 as measured by the central laboratory

11. Eating disorders such as bulimia or anorexia nervosa

12. Treatment with anti-obesity drugs, weight-loss surgery or aggressive diet regimen leading to unstable body weight (based on Investigator's judgement) 3 months prior to Visit 1 and until randomisation

13. Treatment with systemic corticosteroids or planned initiation of such therapy at Visit 1 and until randomisation. Inhaled or topical use of corticosteroids (e.g. for asthma/chronic obstructive pulmonary disease) is acceptable

14. Change in dose of thyroid hormones within 6 weeks prior to Visit 1 or planned change or initiation of such a therapy at Visit 1 and until randomisation

15. Medical history of cancer or treatment for cancer in the last five years prior to Visit 1. Resected basal cell carcinoma considered cured is exempted

16. Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells (e.g. malaria, babesiosis, haemolytic anaemia) at Visit 1

17. Women who are pregnant, nursing, or who plan to become pregnant whilst in the trial

18. Alcohol or drug abuse within the 3 months prior to Visit 1 that would interfere with trial participation based on Investigator's judgement

19. Intake of an investigational drug in another trial within 30 days prior to Visit 1

20. Patient not able to understand and comply with study requirements, including the use of an e-diary, based on Investigator's judgement

21. Any other clinical condition that, based on Investigator's judgement, would jeopardise patient safety during trial participation or would affect the study outcome (e.g. immunocompromised patients who might be at higher risk of developing genital or mycotic infections, patients with chronic viral infections etc.)

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 start a restricted concomitant therapy (as listed in Section 4.2) that, in the Investigator's opinion, poses a safety risk if taken as add-on to the trial medication
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy)

- The patient experiences severe hypoglycaemia (for further details see Section 5.3.5.2) or repeated hypoglycaemic episodes or DKA that, in the Investigator's opinion, may put the patient at risk with continued participation

If a patient becomes pregnant during the trial the study medication will be stopped, the patient will be discontinued from the trial and the patient will be followed up until birth or otherwise termination of the pregnancy.

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

Patients who drop out during the screening, T1DM therapy optimisation, or run-in periods prior to randomisation will be considered screening failures. They will be recorded as screening failures in the Electronic Case Report Form (eCRF) and no further follow-up is required. The data will be included in the trial database and will be reported.

Patients who discontinue the trial treatment or withdraw from the study after randomisation will be considered as "early discontinuations" and the reason for this premature discontinuation of trial treatment or withdrawal from the study must be recorded in the eCRF. The data will be included in the trial database and will be reported.

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

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

3.3.4.2 Discontinuation of the trial by the Sponsor

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

- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
- Violation of GCP, the 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 BI.

Existing insulin therapy is not considered part of the clinical trial supplies, and therefore will not be provided.

4.1.1 Identity of BI investigational products and comparator product

The characteristics of the test products are as shown below.

Substance:	empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	2.5 mg
Posology:	once daily
Route of administration:	oral

Substance:	empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	10 mg
Posology:	once daily
Route of administration:	oral

Substance:	empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	25 mg
Posology:	once daily
Route of administration:	oral

The characteristics of the reference products are as shown below.

Substance:	placebo matching empagliflozin 2.5 mg
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	-
Posology:	once daily
Route of administration:	oral

Substance:	placebo matching empagliflozin 10 mg
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	-
Posology:	once daily
Route of administration:	oral

Substance:	placebo matching empagliflozin 25 mg
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	-
Posology:	once daily
Route of administration:	oral

4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into the randomised double-blind treatment period, treatment assignment will be by means of a third-party randomisation system at Visit 6, Day 1. This will involve the use of IRT, which will take into consideration the relevant stratification factors. To facilitate the use of IRT, the Investigator will receive all necessary instructions and/or documents for using the IRT.

Patients will be randomly assigned, in a 1:1:1:1 ratio, to either:

(i) empagliflozin 2.5 mg
(ii) empagliflozin 10 mg
(iii) empagliflozin 25 mg
(iv) placebo

For further details refer to Section 7.6.

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

The kit(s) corresponding to the assigned medication number(s) should be given to the patient and the number of the kit(s) that was/were dispensed will be entered in the eCRF. Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.3 Selection of doses in the trial

The exposure response relationship between empagliflozin and UGE was evaluated for patients with T1DM (for further details please refer to Section 1.2.2). Results indicate that near maximal effects are achieved with empagliflozin 10 mg and 25 mg once daily; these findings are comparable to those observed in patients with T2DM. It is concluded that there are no clinically relevant differences in PK/PD between the T1DM and T2DM populations and that the approved doses for T2DM patients are appropriate for use in studies assessing

the safety and efficacy of empagliflozin in adult patients with T1DM. A detailed comparison of empagliflozin PK/PD in patients with T1DM versus T2DM is provided in Section 1.2.2.3.

In addition, an empagliflozin 2.5 mg dose group is included into this trial to establish a minimal safe and effective dose for the treatment of patients with T1DM.

For further details with respect to T2DM PK/PD, please refer to Section 1.2.2.1 and to the current version of the IB for empagliflozin [c01678844].

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 qualify will be randomised to one of the dosage and treatment schedules described. Except for the open-label run-in period, trial medication will be dispensed in a double-blind manner.

All patients will be assigned placebo at the beginning of the placebo run-in period (Visit 5) and dispensing will occur once within this period. Dispensing of kits for the double-blind treatment will begin at Visit 6. Dispensing will occur on 4 occasions as indicated in the Flow Chart, covering a period of 26 weeks. For further details regarding packaging please refer to Section 4.1.6.

The dose of empagliflozin is fixed as shown in Table 4.1.4: 1 below. Double doses and dose reductions are not permitted. On the other hand, adjustment of a patients' existing insulin therapy is permitted (for further details see Section 4.2.1).

From the start of the run-in period, patients will be instructed to take their trial medication once daily in the morning with a glass of water. To ensure a dose interval of about 24 hours, the medication should be taken each day at approximately the same time in the morning.

Table 4.1.4: 1 Empagliflozin and matching placebo, daily oral administration per dose group

		Empagliflozin 2.5 mg	Empagliflozin 10 mg	Empagliflozin 25 mg	Total # units per dose	Timing
Placebo run-in period (open-label):						
All patients		Matching placebo	Matching placebo	Matching placebo	3 tablets	Once daily, morning
Treatment period (double-blind):						
Dose group	2.5 mg	Empagliflozin 2.5 mg	Matching placebo	Matching placebo	3 tablets	Once daily, morning
	10 mg	Matching placebo	Empagliflozin 10 mg	Matching placebo	3 tablets	Once daily, morning
	25 mg	Matching placebo	Matching placebo	Empagliflozin 25 mg	3 tablets	Once daily, morning
	Placebo	Matching placebo	Matching placebo	Matching placebo	3 tablets	Once daily, morning

If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. On days prior to a visit, the dose should be taken approximately 24 hours before the planned dose at the visit. Empagliflozin can be taken with or without food.

Patients should be instructed not to take their trial medication in the morning before visits as they will be dosed at the site. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day. Insulin administration (basal and/or bolus) on the morning of clinic visits will be left to the discretion of the patient and/or Investigator and may be dependent on planned meal intake etc. Visits should be routinely scheduled in the morning, at approximately the same time of day (e.g. 7am to 11am) for each visit. The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

After randomisation at Visit 6, patients, Investigators and everyone involved in analysing or with an interest in this double-blind study will remain blinded with regard to the randomised treatment assignments until after database lock. However, due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomisation code for individual patients during study conduct. In such cases, access to the code will only be permitted by authorised drug safety representatives. Access to the code will be via the IRT system.

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

The randomisation codes will be provided to bioanalytics prior to last patient out to allow them to exclude PK samples taken from placebo-treated patients from the bioanalytical analyses. Bioanalytics will not disclose the randomisation code or the results of their measurements until the study is officially unblinded.

4.1.5.2 Unblinding and breaking the code

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

4.1.6 Packaging, labelling, and re-supply

Trial medication will be labelled with the trial identification and medication code number. It will be dispensed as indicated in the Flow Chart. At each dispensing, an appropriate number of tablets (empagliflozin and/or placebo-to-match empagliflozin) plus some reserve will be given to the patient.

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

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

4.1.7 Storage conditions

The trial medication must be kept in its tightly closed original packaging under the recommended storage conditions indicated on the label. A temperature log must be maintained by the Investigator/Pharmacist/investigational drug storage manager to make certain that the medication is stored at the correct temperature. If storage conditions are found to be outside the specified range, the process outlined in the ISF should be followed.

Trial medication must be stored securely at the study sites, out of reach of children and be protected from moisture and direct sunlight, e.g. in a locked cupboard or at a Pharmacy. It may only be dispensed to trial patients fulfilling the inclusion and exclusion criteria by authorised study personnel as documented in the ISF. Receipt, usage and return of the trial medication must also be documented on the respective forms in the ISF.

All unused medication including all packaging, empty or filled, must be either returned to the Sponsor, or, following written authorisation from the Sponsor, may be destroyed at site. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.8 Drug accountability

The Investigator and/or Pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- approval of the CTP by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
- availability of a signed and dated clinical trial contract between the Sponsor and the Head of Trial Centre
- approval/notification of the regulatory authority, e.g. Competent Authority
- availability of the curriculum vitae of the Principal Investigator
- availability of a signed and dated CTP
- availability of the proof of a medical licence for the Principal Investigator (if applicable)
- for USA: availability of the Form 1572

The Investigator and/or Pharmacist and/or 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 (see Section 4.1.8.1 below), and the return to the Sponsor or alternative disposition of unused product(s).

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

4.1.8.1 Patient treatment compliance

Patients will be asked to bring all trial medication kits (with or without any remaining tablets) with them to each trial visit. The tablets will be counted by the Investigator or a qualified designee and compliance will be calculated according to the following formula unless there are reasons to use a different calculation (e.g. to account for periods during which a patient was genuinely unable to take any trial medication):

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

Compliance during the open-label placebo run-in period must be between 80% and 120%. If compliance is outside this range, the patient should not be randomised.

Compliance during the randomised period should also be between 80% and 120%. Patients who are non-compliant according to this definition will be treated as protocol violators. The significance of protocol violations will be determined individually for the purposes of the per-protocol analysis.

Patients who are not compliant with their medication should again be carefully interviewed and again informed about the purpose and the conduct of the trial. This discussion should be documented.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Details of all concomitant therapy used during the trial will be recorded on the appropriate pages of the eCRF. Where appropriate, dedicated eCRF pages may also be developed to record information and any changes relating to certain classes of concomitant therapy (e.g. anti-hypertensive concomitant therapy).

4.2.1 Rescue medication, emergency procedures, and additional treatments

There are no rescue medications in this trial.

All patients will be required to keep their existing insulin therapy as stable as possible from screening at Visit 1 until the beginning of the T1DM therapy optimisation period at Visit 2. From Visit 2, therapy for T1DM should be optimised (e.g. review of blood glucose values and insulin dose and its adjustment for meals, improve the patients' ability to carbohydrate count etc.) over a 6 week period to ensure that, in the Investigator's opinion, a patient is achieving the best standard of care in accordance with local guidelines. In CSII patients, and where considered appropriate, adjustments in T1DM therapy might be supported by basal rate testing.

Optimisation of the T1DM therapy should be complete by the end of the 6 week T1DM therapy optimisation period (i.e. by Visit 5), so that a patient's insulin regimen is as stable as possible as they enter the placebo run-in period and for 2 weeks prior to randomisation at Visit 6.

During periods of stability, in case of hypoglycaemia (e.g. with measured glucose concentration ≤ 70 mg/dL [≤ 3.9 mmol/L]), patients should preferably ingest additional carbohydrates according to standard practice in the management of T1DM. However, a patient's existing insulin regimen should be adjusted any time for safety reasons if deemed necessary by the Investigator, e.g. in case of persisting hyperglycaemia or hypoglycaemia despite adequate carbohydrate intake.

Based on the mode of action of empagliflozin and the results of previous trials in T1DM (for further details see Section 1), at randomisation on Day 1 (Visit 6) and the initiation of randomised study medication, for patients with an HbA_{1c} of 7.5 to < 8% at Visit 5, Investigators are advised to reduce the patient's total insulin dose by 10% to avoid hypoglycaemia. For patients with an HbA_{1c} of ≥ 8% at Visit 5, Investigators are advised to adjust the patient's total insulin dose based on need as assessed by frequent SBGM and close patient follow-up upon initiation of randomised study medication. In all cases, the actual reduction will be dependent upon individual glucose values. Thereafter and until the end of the trial (Visit 12), further adjustments to insulin therapy (both basal and bolus insulin) may be implemented as necessary to avoid hypoglycaemia and also hyperglycaemia to keep ensuring that, in the Investigator's opinion, the patient is achieving the best standard of care in accordance with local guidelines.

Apart from the recommendation for an initial insulin reduction as mentioned above at the start of randomised treatment, there will be no protocol-defined algorithm towards insulin adjustment in this trial. However, the Sponsor will provide additional support to the Investigator with respect to insulin adjustment via training documentation that will be presented at Investigator Meetings and made available in the ISF. Throughout the trial, adjustment needs to balance a patient's individual risk for hypoglycaemia on the one hand and the risk for hyperglycaemia and DKA on the other hand with special caution at the beginning of the treatment period, and in the Follow-up period, when empagliflozin treatment

is started and stopped respectively. Any insulin dose change or adjustment must be based on laboratory tests or SBGM. However, there are no blood glucose targets defined throughout this trial to allow Investigators to follow their local standard of care guidelines for the management of blood glucose. Whenever possible, patients should keep to the same trademark and application device for their existing insulin with no intention to change this during the trial; for medical/safety reasons however (e.g. malfunction of a pump in a CSII patient), switches in mode of insulin delivery are permitted. There should also be no planned major changes of the injection sites/areas.

In accordance with Section 3.3.2, Investigator's must ensure that patients selected for the trial are capable of leading the management and adjustment of their insulin therapy when at home, including a "sick day" management plan, and at the same time, can be relied upon to contact the Investigator for advice at the appropriate point in time, as this is an outpatient trial. Investigator oversight will also be an important element of the insulin adjustment process.

Special attention must be paid to the prevention of DKA. Due to the mechanism of action, 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 recognised and appropriately treated. All patients must be made aware of this risk and be instructed not to reduce their insulin intake below Investigator recommendations. For further details see Section 2.3.

In addition to performing glucose monitoring, the frequency of which will be increased after starting the study medication (for further details see Section 5.3.2.1), in the same way as during routine clinical care, patients will be reminded to determine ketones in case of any symptoms of DKA, e.g. nausea, vomiting, abdominal pain etc (see Section 5.3.2.2). They will be instructed to do this irrespective of the glucose value in the event of DKA symptoms occurring. A meter will be provided to the patient for this purpose. Patients will also be reminded about the interpretation of ketone values measured via the meter, and on appropriate action to take in the event of increased ketone levels (see Section 5.3.2.2). Ketones should also be determined in case of repeatedly elevated blood glucose levels (e.g. > 200 - 240 mg/dL [> 11.1 - 13.3 mmol/L]) which cannot be explained. Regular (e.g. 2-3 times a week) measurements before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements before breakfast are recommended during the run-in period and during the first 4 weeks of the treatment period and might also be agreed upon with the patient afterwards if deemed necessary by the Investigator. In case of a suspected DKA the Investigator should ensure that appropriate tests are performed at the earliest opportunity according to local guidelines, such as a blood gas test (i.e. pH, bicarbonate; the results will be collected on the relevant page of the eCRF) and that the patient is appropriately treated (i.e. hospitalized or referred to emergency treatment) according to local treatment guidelines.

Other concomitant therapies should be kept as stable as possible over the course of the trial but might be changed in case of medical need. New anti-diabetic therapy should not be initiated during the randomised treatment period and the Follow-up period.

Insulin will not be provided as part of the clinical trial supplies.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Treatment with anti-obesity drugs or systemic corticosteroids will be prohibited due to their influence on glucose metabolism. There are no restrictions on treatment with non-systemic corticosteroids such as inhaled or local corticosteroids.

For patients taking thyroid hormones, any change in the dose should be avoided. If dose changes do occur, then they should be recorded in the source documents and in the eCRF.

Patients participating in the CGM substudy must not take any paracetamol (acetaminophen) containing drugs – provided there is no medical necessity – throughout the CGM monitoring periods, since this may falsely raise CGM glucose readings.

4.2.2.2 Restrictions on diet and life style

Throughout the trial, patients must follow a reliable approach to insulin dose adjustment for meals, such as carbohydrate counting, and based on Investigator recommendations. This method will be discussed with the patient at Visit 1 as part of the eligibility checks.

Patients who participate in the CGM substudy and who already use real-time CGM as part of their therapy for T1DM may continue their own CGM but would also need to wear the (blinded) trial CGM in addition during the trial CGM periods.

At the beginning of the T1DM therapy optimisation period (Visit 2), patients will be reminded about the appropriate management of their diet and physical activity by the Investigator or qualified site personnel. This must include a reminder to maintain adequate daily fluid intake to avoid dehydration. They will also be reminded about the importance of following a “sick day” management plan and corresponding insulin adjustments, should they become unwell during the trial. This discussion will be based on local recommendations for individuals with T1DM and should be evident from source documents (see Section 8.3.1). Site-specific tools may be used where necessary. Patients will be reminded to follow the recommended dietary and physical activity plan during the study. Extreme diets (e.g. ketogenic diets such as the Atkins diet) should be avoided.

Patients must not take any other investigational drug within 30 days before Visit 1 until the last visit (Visit 12) of this trial.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of child-bearing potential must continue to practice a highly effective method of birth control (in accordance with the trial inclusion criteria Section 3.3.2) throughout the duration of the study including the Follow-up period.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

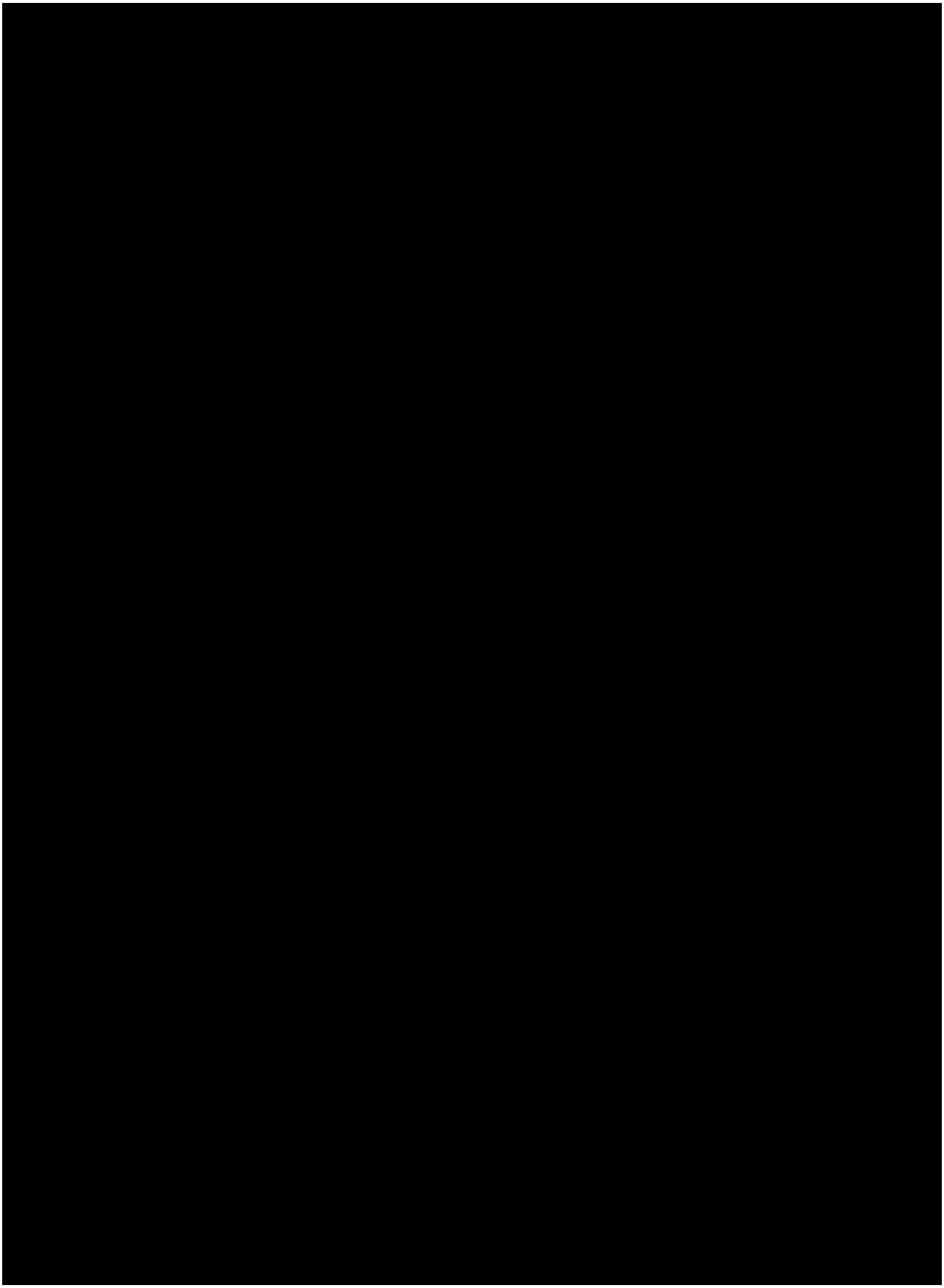
5.1.1 Primary endpoint

In this trial, the primary endpoint to assess efficacy is the change from baseline in HbA_{1c} (%) after 26 weeks. Throughout this CTP, the term "baseline" for HbA_{1c} refers to the last observation prior to the first intake of randomised trial medication.

5.1.2 Secondary endpoints

The key secondary endpoints to assess efficacy are as shown below. Throughout this CTP, the term "baseline" refers to the 4 week period prior to randomisation for the rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs and the 2 week placebo run-in period for the mean daily insulin requirement.

- Incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 5 to Week 26
    - severe hypoglycaemia is defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (see Section 5.3.5.2)
    - The rate will be calculated from Day 29 (start of Week 5) up to Day 183 (end of Week 26 + 1 day) or date of last study medication intake + 1 day inclusive, whichever occurs first
- Incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs (see Section 5.3.5.2) per patient-year from Week 1 to Week 26
    - the rate will be calculated from the date of first study medication intake up to Day 183 (end of Week 26 + 1 day) or date of last study medication intake + 1 day inclusive, whichever occurs first
- Change from baseline in body weight (kg) after 26 weeks
- Change from baseline in total daily insulin dose (TDID), U/kg, after 26 weeks
- Change from baseline in systolic blood pressure (SBP) after 26 weeks
- Change from baseline in diastolic blood pressure (DBP) after 26 weeks



5.2 ASSESSMENT OF EFFICACY

5.2.1 HbA_{1c} and fasting plasma glucose

FPG and HbA_{1c} will be analysed by the central laboratory at the timepoints indicated in the Flow Chart.

The samples will be analysed at a central laboratory or its affiliates having a National Glycohemoglobin Standardisation Program (NGSP) Level I certificate. HbA_{1c} results will be reported in both NGSP (%) and International Federation of Clinical Chemistry, IFCC (mmol/mol) units. The relationship between HbA_{1c} results from the NGSP network (% HbA_{1c}) and the IFCC network (mmol/mol) has been evaluated and a master equation has been developed (NGSP = [0.09148*IFCC] + 2.152). This relationship is continuously monitored and any changes are investigated. The NGSP certification process and test results for NGSP-certified methods do not change as a result of the IFCC standardisation of HbA_{1c}, and will continue to be directly traceable to the Diabetes Control and Complications Trial (DCCT) reference and now also the IFCC reference.

Further details about HbA_{1c} sample handling, shipment, and assay procedures can be found in the laboratory manual in the ISF.

Blood samples for the determination of FPG at the central laboratory will be taken after an overnight fast (no food or drinks except for water for at least 10 hours). The samples should be taken before trial medication administration. The samples will be measured at a central laboratory using validated assays. Further details about FPG sample handling and shipment can be found in the laboratory manual in the ISF.

5.2.2 Weight

Weight measurements should always be done on the same approved scales for an individual patient at the timepoints indicated in the Flow Chart.

In order to get comparable body weight values, it should ideally be performed in the following way:

- fasting (at visits to which a patient has to come fasted, see Flowchart)
- after bladder voiding
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc.)

5.2.3 Electronic diary

From the beginning of the T1DM therapy optimisation period (Visit 2) until the end of the Follow-up period (Visit 12), all patients will be provided with an electronic (e)-diary for daily use during these periods of the study. Prior to its first use, instructions on the proper use of the e-diary will be provided by the site staff. Refresher training should be provided at subsequent timepoints as deemed appropriate by the Investigator or designated site-personnel.

Daily entries into the e-diary will include at least:

- glucose values from SBGM (see Section 5.3.2.1)
- any hypoglycaemic events that have occurred
    - for criteria for hypoglycaemic events, see Section 5.3.5.2
- insulin requirement

Any ketone measurements performed should also be entered into the e-diary if and when any data becomes available (see Section 5.3.2.2).

During the T1DM therapy optimisation period, and daily for 5 days following clinic Visit 6, data from the e-diary should be reviewed remotely by designated site personnel, paying particular attention to adjustments in the insulin regimen, glucose values, and if available, ketone measurements. In addition, the patient should be contacted by telephone (e.g. weekly during the T1DM therapy optimisation period) if e-diary data, including glucose data, is not available and/or if the data suggest closer monitoring of the patient is required. Additional clinic visits can also be arranged if necessary (for further details see Section 6.2.2); assessments at such visits would be defined according to Investigator judgement.

Throughout the trial, the Investigator and/or designated site personnel should review the patient's glucose and e-diary results to determine if treatment adjustments need to be implemented. As a minimum, this review must take place at the timepoints indicated in the Flow Chart.

The e-diary data will be transferred to a vendor server for data collection and transfer to the Sponsor.

5.2.4 Systolic/diastolic blood pressure and pulse rate (vital signs)

SBP and DBP as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured at the timepoints indicated in the Flow Chart with a calibrated electronic sphygmomanometer. The BP measurement should be performed three times at each timepoint and the mean value of the measurements will be analysed.

Initially, BP should be taken 3 times in both arms. The arm with the higher average pressure (systolic or – if equal – diastolic) should be used for subsequent measurements; if measurements for both arms are equal, the non-dominant arm should be chosen.

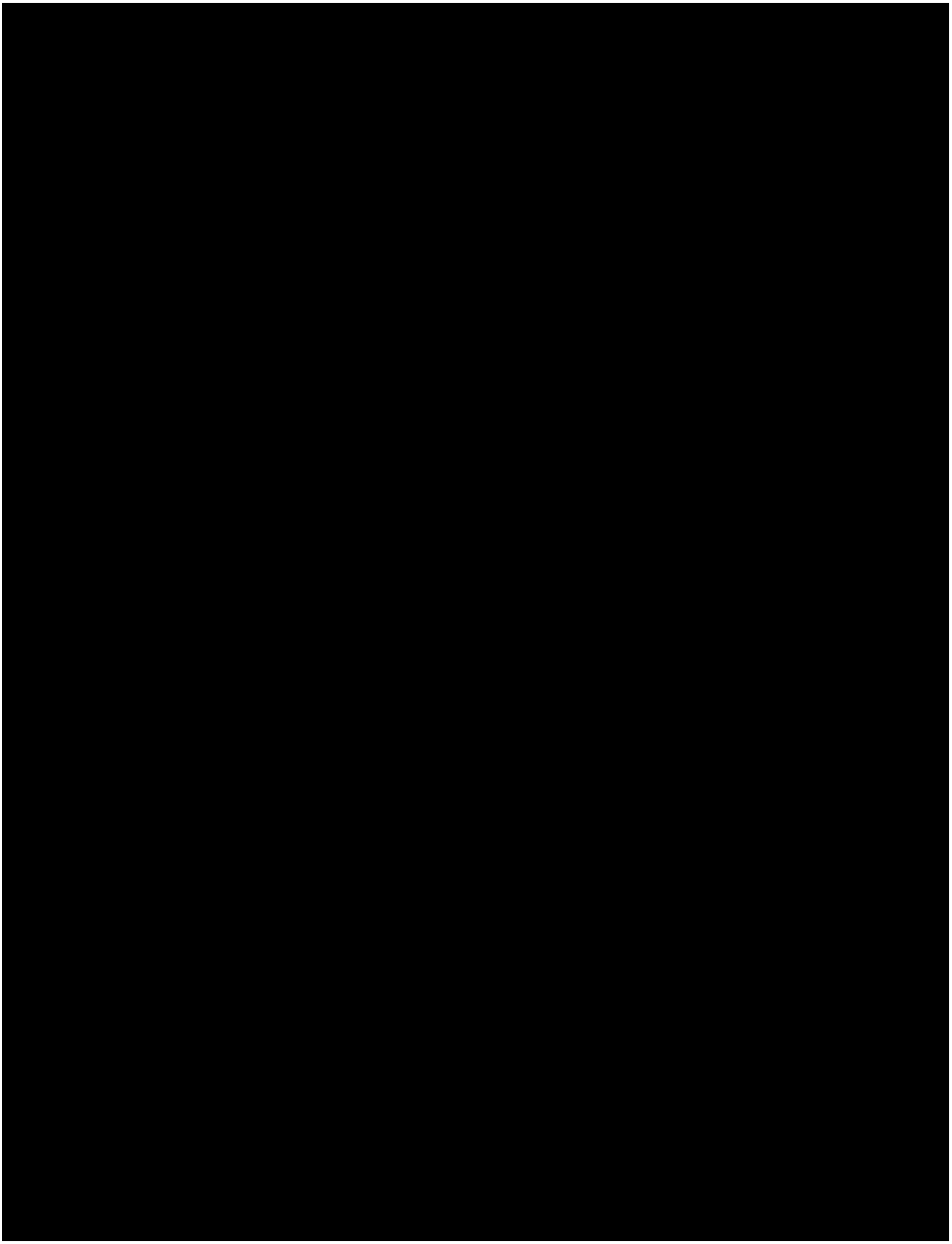
BP measurements should always be performed on the same arm and, if possible, by the same person and using the same device. The same method must be used throughout the trial for a given patient i.e. if a patient receives the first BP measurement for example with an electronic device, the same method and device should be used throughout the study for this patient.

After patients have rested quietly, in the seated position for at least 5 minutes, 3 BP measurements will be taken approximately 2 minutes apart. The seated pulse rate should be from the second BP reading.

BP measurements should be recorded to the nearest 1 mmHg.

BP should always be measured before any blood samples are taken.

[redacted]



5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

Physical examinations will be performed by the Investigator or designated site-personnel at the timepoints indicated 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 Home monitoring

5.3.2.1 Self-blood glucose monitoring

From the beginning of the T1DM therapy optimisation period (Visit 2) until the end of the Follow-up period (Visit 12), all patients will be provided with SBGM equipment (i.e. a glucose monitoring device/meter) and supplies for use at home during the study for self-measurement of blood glucose. Instructions on the proper use of the SBGM equipment will be provided by the site staff. The patient will be asked to enter data from the glucose meter to the e-diary on a daily basis.

Routinely, SBGM testing should be performed 4 times a day as a minimum (e.g. at least before breakfast, lunch, dinner and at bedtime); furthermore, for 5 days from the day of randomisation (i.e. Days 1-5), SBGM testing frequency should be increased to 8-10 times a

day and include at least one overnight measurement (i.e. a measurement taken at night, between the patient going to bed and getting up). On one of these 5 days, the daytime timepoints of the SBGM testing should mirror the timepoints for a 9-point plasma glucose profile (for further details see Section 5.2.5). Additional tests should be done as recommended by the Investigator (e.g. up to 7 days post randomisation) or at any time the patient is symptomatic, i.e. experiences signs/symptoms of hyper- or hypoglycaemia. In patients prone to nocturnal hypoglycaemic events, a bedtime snack consisting of long-acting carbohydrates should be considered. Alternatively, minimum glucose levels of e.g. > 110-130 mg/dL (> 6.1-7.2 mmol/L) should be targeted at bedtime to avoid nocturnal hypoglycaemia. The Sponsor will also provide guidance on this topic via documentation in the ISF.

If, after an overnight fast, an SBGM test result reveals blood glucose of > 200 – 240 mg/dL (> 11.1 – 13.3 mmol/L) or ≤ 70 mg/dL (≤ 3.9 mmol/L), the patient should be asked to contact the site for advice. The Investigator should then instruct the patient on appropriate measures in order to adequately control their hyperglycaemia or hypoglycaemia. All insulin treatment decisions should be based on blood glucose values measured using SBGM or based on laboratory values obtained through the central laboratory (or, if applicable, the local laboratory).

A comparable SBGM system will be supplied to all patients and must be used by them throughout the study. In accordance with Section 3.3.2, Investigator's should carefully select patients for the study in terms of their ability to comply with the SBGM requirements. Patients not adhering to the SBGM instructions given by the Investigator should be retrained at the earliest possible opportunity.

5.3.2.2 Ketone measurement

Patients will be equipped with an electronic device to determine their ketone concentration (i.e. a blood glucose monitoring device/meter that is also capable of measuring blood ketones).

Patients should be reminded to test their ketones in case of any symptoms of DKA, e.g. nausea, vomiting, abdominal pain, etc., irrespective of the glucose value. Patients must be reminded about the signs and symptoms of DKA, on the interpretation of ketone values measured via the meter, and on appropriate action to take in the event of increased ketone levels (see below). In the same way as during routine clinical care, patients should also be reminded to test for ketones in case of repeatedly elevated blood glucose levels (e.g. > 200 - 240 mg/dL [> 11.1 - 13.3 mmol/L]) which cannot be explained. Regular (e.g. 2-3 times a week) measurements before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements before breakfast are recommended during the run-in period and during the first 4 weeks of the treatment period and might also be agreed upon with the patient afterwards if deemed necessary by the Investigator.

In the event of increased ketones, patients should either follow the rules given by their Investigator (e.g. increased fluid intake and/or insulin bolus; food intake and insulin bolus in case of near-normal blood glucose) or contact their trial site. In case of deteriorating ketosis,

blood glucose and ketone levels should be checked every 1-2 hours until they are back in a range considered to be normal for the patient. Patients should be instructed to immediately refer themselves to hospital and/or the Investigator, or to contact an emergency physician in case of a blood ketone concentration > 1.5 mmol/L (as indicated in the meter manual). In case of a suspected DKA the Investigator should ensure that appropriate tests are performed at the earliest opportunity according to local guidelines, such as a blood gas test (pH, bicarbonate). The results will be collected on the relevant page of the eCRF.

Investigators should also differentiate deteriorating ketosis/DKA from any mild to moderate increase of ketones which may be seen due to the mechanism of action of empagliflozin, especially in the fasted state (e.g. in the morning). For further details, see also Sections 1.2.3.2 and 2.3.

In accordance with Section 3.3.2, Investigator's should carefully select patients for the study in terms of their ability to comply with ketone measurement requirements. Patients not adhering to the instructions given by the Investigator should be retrained at the earliest possible opportunity.

5.3.3 Safety laboratory parameters

At the following visits, laboratory samples will be collected from the patient after a full overnight fast (i.e. nothing to eat or drink except water for at least 10 hours): Visits 2, 6, 9, 11 EOT, eEOT (if applicable), and 12. At all other visits, the patient does not have to be in a fasted state when laboratory samples are taken.

When applicable, laboratory samples, as described in the Flow Chart, should be collected before trial medication is taken.

All parameters that will be determined during the trial conduct are listed in Table 5.3.3: 1 and Table 5.3.3: 2. The analysis will be performed by a central laboratory. The respective reference ranges and details about sample handling and shipment will be provided in the laboratory manual in the ISF.

UACR in spot urine will be calculated at the central laboratory.

The central laboratory will derive the eGFR from (and report it together with) serum creatinine values based on the CKD-EPI formula which is considered more accurate in the normal range than the Modification of Diet in Renal Disease (MDRD) formula. The CKD-EPI formula will be defined in central laboratory documentation due to regional/racial variations in the formula that is applied.

The eGFR (cystatin C, serum) will also be derived, at the visits where cystatin C levels are measured.

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

Haematology

- Haematocrit
- Haemoglobin
  - reticulocyte count (reflex test if haemoglobin is outside normal range)
- Red blood cells (RBC)/erythrocytes
- White blood cells (WBC)/leukocytes
- Platelet count/thrombocytes
- Differential automatic (relative and absolute count):
  - neutrophils, eosinophils, basophils, monocytes, lymphocytes

Clinical chemistry

- Albumin
- Alkaline phosphatase[1]
  - gamma-glutamyl transferase (γ-GT, reflex test triggered by elevated alkaline phosphatase on two sequential measures)
- ALT (alanine aminotransferase, SGPT)[1]
- AST (aspartate aminotransferase, SGOT)[1]
- Beta-hydroxy-butyrate
- Bicarbonate
- Bilirubin total, fractionated if elevated
- Calcium
- Chloride
- C-peptide[2]
- Creatinine[1]
- Creatine kinase (CK)
  - troponin I (reflex test if CK is elevated)
- Cystatin C[3]
- Lactate dehydrogenase
- Lipase
- Magnesium
- Phosphate
- Potassium
- Protein total
- iPTH (intact parathyroid hormone)[4]
- Sodium
- TSH[1,5]
- Blood urea nitrogen (BUN)
- Uric acid

Lipids[6]

- Cholesterol (total)
- HDL cholesterol
- LDL cholesterol (calculated)
- Free fatty acids
- Apo A-1
- Apo B
- Triglycerides
  - direct measurement of LDL cholesterol (reflex test if triglycerides are > 400 mg/dL or 4.52 mmol/L)

[1] At the screening visit (Visit 1), only the following parameters are part of the profile: liver transaminases, alkaline phosphatase, creatinine, and TSH
[2] C-peptide will only be assessed at Visit 2
[3] Cystatin C will only be assessed at Visits 6, 11 EOT, eEOT (if applicable) and 12
[4] iPTH will be only be assessed at Visits 6, 8, 11 EOT and eEOT (if applicable)
[5] TSH will only be assessed at Visit 1
[6] Lipids will only be assessed at Visits 6, 11 EOT, eEOT (if applicable), and 12

Table 5.3.3: 2 Laboratory parameters – urine

Semi-quantitative (dipstick) urinalysis	**Quantitative urinalysis**
• Nitrite[1] • Protein • Ketones[3] • Urine pH • Leukocyte esterase (for WBC)[1]	• Albumin • Creatinine • Human chorionic gonadotrophin (hCG)[2]
Microscopic urinalysis Microscopic analysis will be performed as a reflex test if any of the above semi-quantitative (dipstick) tests except for ketones are abnormal: • Urine RBC/erythrocyte • Urine WBC/leukocytes[1] • Urine sediment microscopic examination	
Urine culture Urine culture will be triggered by positive leukocyte esterase (for WBC) and/or nitrite in the semi-quantitative test/dipstick. The culture will include an antibiogram	

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

[2] Urine pregnancy testing will be performed locally in female patients of child-bearing potential only according to the timepoints indicated in the Flow Chart

[3] At clinic visits where centralized safety laboratory tests are not planned, urine ketones will be determined only locally at the site.

5.3.3.1 Follow-up on suspicion for urinary tract infections

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

Throughout the trial, patients should be closely observed for symptoms of UTI or genital infection. In case these symptoms occur, symptomatic relief and anti-infectives should be provided as appropriate [c01678844].

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

- In any case of suspected UTI (symptomatic or asymptomatic) a urine culture sample has to be taken and sent to the central laboratory for confirmation of the diagnosis and to obtain an antibiogram
- To be able to identify asymptomatic UTIs immediately, a dipstick test (leukocyte esterase [for WBC] and nitrite) will be performed at the site at the timepoints indicated in the Flow Chart. In case of a positive result at site, a urine culture sample must be obtained and sent to the central laboratory for confirmation of the diagnosis and to obtain an antibiogram

5.3.4 Electrocardiogram

Printed paper traces from 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected at the timepoints indicated in the Flow Chart. In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischaemia), an additional ECG will be recorded. All ECGs will be evaluated, signed, dated and commented upon by the treating physician/Investigator and stored locally. Any clinically relevant changes in the ECG will be reported as AEs and followed up and/or treated locally until normal or stable condition.

5.3.5 Other safety parameters

5.3.5.1 Assessment of hypoglycaemia rate

Hypoglycaemia rates will be assessed based on AE data, which in turn rely on the criteria for hypoglycaemic events (see Section 5.3.5.2 below). Glucose values used within the criteria for hypoglycaemic events will originate in the SBGM device and from central laboratory measurements. All glucose values originating in the SGBM device will subsequently be entered into the e-diary (for further details please see Sections 5.2.3 and 5.3.2.1).

5.3.5.2 Criteria for hypoglycaemic events

Every episode of blood/plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L) should be documented with the respective time and date of occurrence. This includes hypoglycaemia with glucose values < 54 mg/dL (< 3.0 mmol/L) and all symptomatic and all severe hypoglycaemic events.

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 hypoglycaemia: event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following

the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration [R14-0982]

If a patient is provided with an emergency glucagon injection device as part of their local, routine T1DM care, it is advisable for the patient to carry this throughout the trial.

5.3.5.3 Assessment of cardiovascular events (CEC adjudication)

Please refer to Section 3.1.1.2.

5.3.5.4 Assessment of severe hypoglycaemia and DKA (CEC adjudication)

Please refer to Sections 3.1.1.3 and 5.3.5.2.

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 medicinal product and which does not necessarily have to have a causal relationship with this treatment.

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

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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, BI 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 5.3.6.1

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. AESIs need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

Patients with AESIs need to be followed up appropriately, regardless of the origin of the laboratory data (e.g. central, local etc.). The Investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per Investigator discretion.

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation (Visit 6):

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

These laboratory findings constitute a hepatic injury alert and the patients showing these 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 laboratory 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

Decreased renal function is defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN.

For the AESI "decreased renal function" the Investigator shall collect an unscheduled laboratory sample for creatinine as soon as possible and initiate follow-up laboratory tests of creatinine according to medical judgement.

Diabetic ketoacidosis (DKA)

DKA is defined by the diagnostic criteria in Table 5.3.6.1: 1 below, and as defined by the American Diabetes Association (ADA) [R14-5435].

Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgement should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in Table 5.3.6.1: 1 below (see Sections 1.2.3.2 and 2.3 for further details).

Table 5.3.6.1: 1 Diagnostic criteria for DKA

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

* Nitroprusside reaction method
** Calculation: 2[measured Na (mEq/L) + glucose (mg/dL)/18
*** Calculation: $(Na+) – (Cl^- + HCO3^-)$ (mEq/L)

Severe hypoglycaemic episodes

Severe hypoglycaemic episodes are events requiring the assistance of another person to actively administer carbohydrate, glucagon or other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

This includes fatal hypoglycaemic events.

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 judgement 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.

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.

The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (such as any active comparator or placebo and for trial procedure).

5.3.7 Adverse event collection and reporting

AE collection

The following must be collected and documented on the appropriate eCRF and/or other designated data collection repository by the Investigator (see also Figure 5.3.7: 1 below):

- From signing the informed consent onwards through the Residual Effect period (REP), until trial completion, all AEs (serious and non-serious), and AESIs
- If in an individual patient only vital status information is collected from a certain time point on, no further AEs or AESIs will be reported for this patient

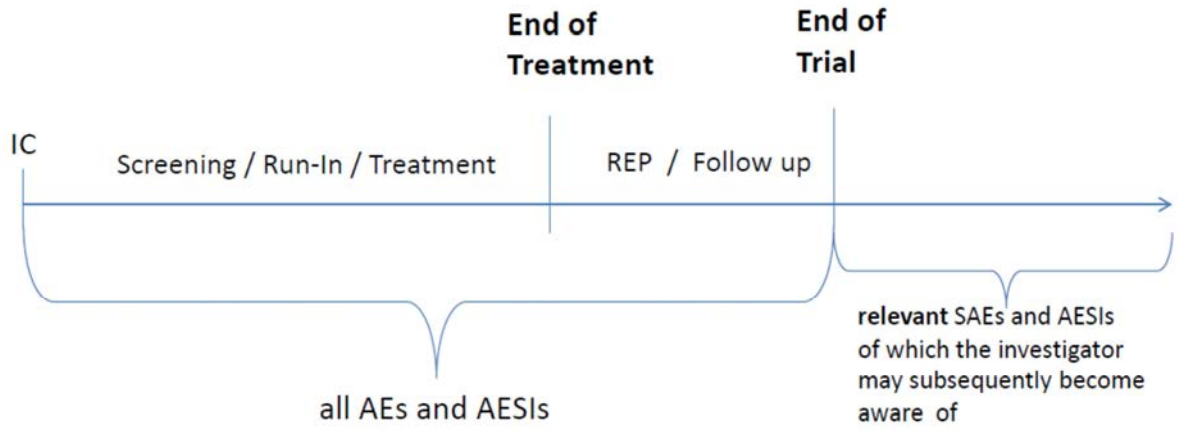


Figure 5.3.7: 1 Trial periods for collection of AEs

The REP is defined as 7 days after the last trial medication application, except for hypoglycaemia, where the REP is 1 day. All AEs which occurred through the treatment period and throughout the REP will be considered as on treatment (please see Section 7.3.4). Events which occurred after the REP will be considered as post-treatment events.

After the last per protocol contact the Investigator does not need to actively monitor patients for AEs. However, if the Investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the Investigator to the Sponsor if considered relevant by the Investigator.

AE reporting to Sponsor and timelines

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

The same timeline applies if follow-up information becomes available. On specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and/or other designated data collection repository and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication and the trial procedures outlined under Section 6.2.

The following should also be recorded as an (S)AE in the eCRF and/or other designated data collection repository 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 to trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Screening failures

SAEs occurring in patients after having discontinued in the trial due to screening failures, i.e. after the screening period and who did not receive any trial medication, are to be reported if the Investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedures.

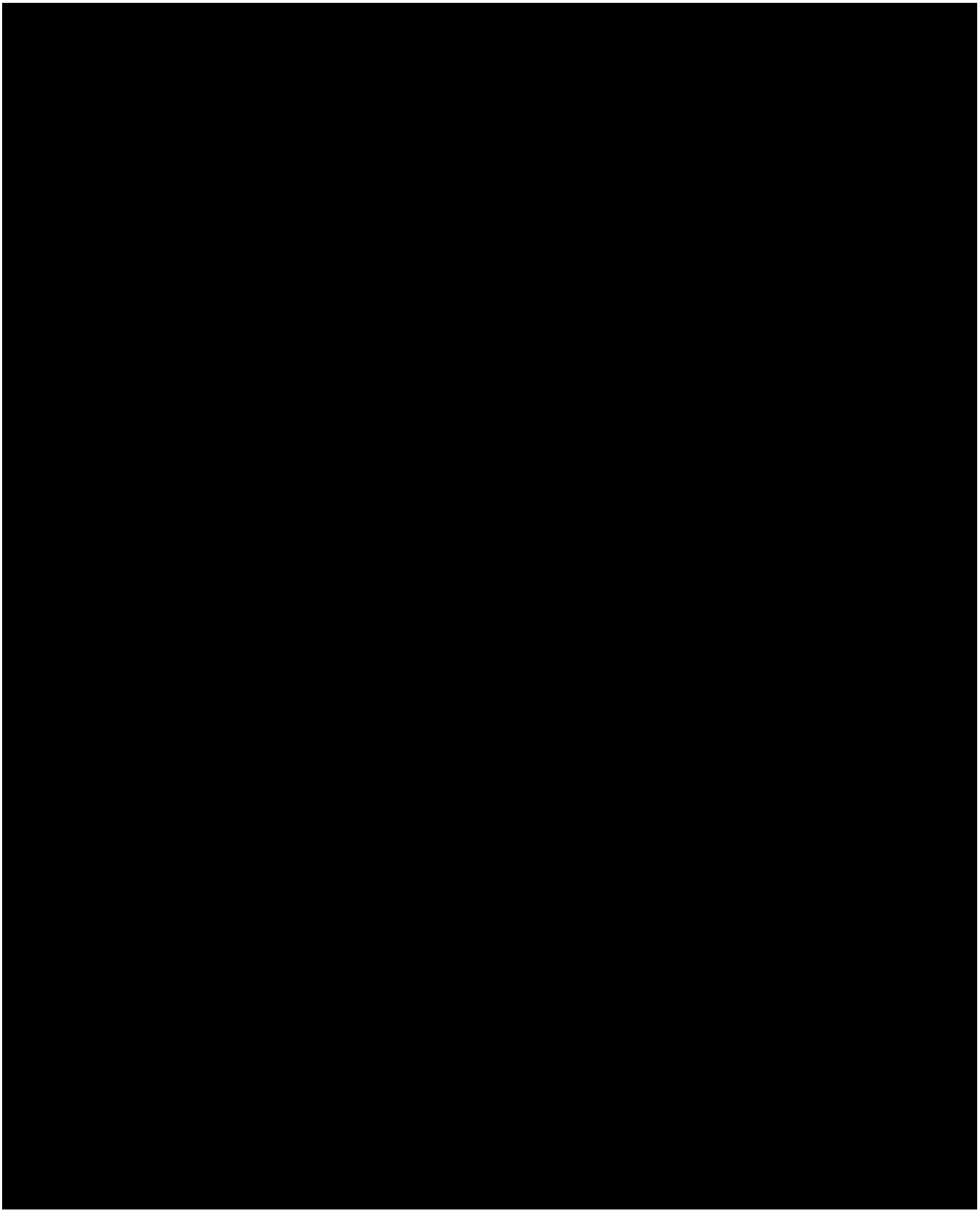
Pregnancy

In the rare case that a female patient 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 Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the DEDP 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).



[redacted]

[redacted]

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are considered standard measurements in the clinical development of a non-insulin product such as empagliflozin, and/or standard as part of routine care for T1DM [R08-2669, R14-0344]. All defined measurements will be performed in order to monitor safety and tolerability aspects and to determine efficacy and PK in an appropriate way.

A surrogate endpoint (i.e. the laboratory parameter HbA_{1c}) is used as the primary efficacy endpoint, since for the purposes of drug approval and labeling, which will support an indication of glycaemic control, regulatory authorities state that this endpoint, albeit surrogate, is the primary endpoint of choice [R08-2669].

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits should take place in the morning (e.g. between 7am and 11am). All patients must adhere to the visit schedule as specified in the Flow Chart. [redacted]

If any visit has to be re-scheduled, subsequent visits should follow the original visit schedule. The trial medication kits will contain sufficient medication to allow for the protocol-permitted visit windows.

If a patient mistakenly takes trial medication on the morning of a visit before attending the clinic (excluding visits prior to randomisation) or comes in non-fasted where a fasting condition is required, the visit should be re-scheduled to the next day reminding the patient about the expected conditions. [redacted]

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

At each visit, assessments should be performed as indicated in the Flow Chart and as detailed in the respective protocol sections.

6.2.1 Screening, T1DM therapy optimisation and placebo run-in periods

6.2.1.1 Screening visit (Visit 1)

- The screening visit does not need to be done with the patient in a fasted state (see Section 5.3.3)
- 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 to have started screening. The patient should be recorded on the enrolment log and be registered in the IRT system as a screened patient
- BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see Section 5.2.4
- Patients who are not eligible to proceed to Visit 2 should be registered as a screen failure in the IRT system and the eCRF and no further follow-up is required

6.2.1.2 T1DM therapy optimisation period (Visits 2, 3 and 4T)

- Visit 2 should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours) (see Section 5.3.3)

- [redacted]
- Visit 3T, if performed as a telephone visit, does not require attendance at the clinic. If performed as a clinic visit, Visit 3 does not need to be done with the patient in a fasted state (see Section 5.3.3)
- Visit 4T is a telephone visit and does not require attendance at the clinic
- Each visit should only be performed once it has been confirmed that the patient is eligible to progress to the next visit; ineligible patients should be registered in the IRT system and the eCRF as a screen failure and no further follow-up is required
- BP should always be measured before any blood samples are taken (relevant for Visit 2 only). For details regarding the correct method for measuring BP, see Section 5.2.4
- At the end of each visit, patients should be reminded about the importance of entering data into their e-diary on a daily basis, including data from the glucose/ketone meter, so that optimisation of the T1DM therapy can be monitored remotely by designated site-personnel, and an assessment made of the need for weekly telephone discussions and/or additional visits

6.2.1.3 Placebo run-in period (Visit 5)

- Visit 5 does not need to be done with the patient in a fasted state (see Section 5.3.3)
- Visit 5 should only be performed once it has been confirmed that the patient is eligible to progress to this visit, based on an assessment of results from Visits 2 to 4T
- As for Visit 1, BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see Section 5.2.4
- Following completion of the Visit 5 procedures, eligible patients will be dispensed a placebo run-in kit for the 2 week run-in period which will be assigned via the IRT system. Ineligible patients should be registered in the IRT system and the eCRF as a screen failure and no further follow-up is required
- [redacted]

6.2.2 Randomised treatment period

The randomised treatment period is from Visit 6 to Visit 11 EOT.

Throughout the treatment period, BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see Section 5.2.4. Laboratory samples should also be taken prior to the intake of trial medication at clinic visits throughout the treatment period.

All patients, including those who discontinue treatment early, must be followed up until the end of the study. Patients must continue to be followed up according to the visit schedule (unless they withdraw consent for further follow-up) in order to collect data at the end of the planned observation period. For further details see Section 6.2.3.

6.2.2.1 Randomisation visit (Visit 6)

- Visit 6 should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours), and only once it has been confirmed that the patient is eligible to progress to randomisation. This includes a check of the data from the patient e-diary, and [redacted]
- Eligible patients will be randomised on Day 1 by using the IRT system; all visit assessments should have been completed prior to this, and before the first intake of study medication
- At Visit 6 (Day 1) the patient should also be reminded to contact the site without delay if he/she has any questions or concerns with respect to insulin adjustments. The patient should also be reminded to increase the frequency of SBGM testing for 5 days from the day of randomisation (i.e. on Days 1-5), [redacted]
  Where considered necessary, the patient should be called daily for 5 days following Day 1 to discuss further adjustment of their insulin therapy; additional clinic visits should be scheduled if closer monitoring of the patient is warranted

6.2.2.2 Interim visits (Visits 7-10)

- Visit 9 should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours); Visits 7, 8 and 10 do not require fasting
- [redacted]
- Prior to each clinic visit, patients should be reminded to attend without having taken their trial medication in the morning, and to bring all used/unused medication with them to the visit
- [redacted] using their SBGM device, starting directly before a dose of study medication is administered, and to continue this until directly before administering study medication on the following day
- [redacted]

[redacted]

6.2.3 End of treatment and follow-up period

6.2.3.1 End of treatment – completers (Visit 11 EOT)

Patients who successfully complete the 26 week treatment period should have the assessments for Visit 11 EOT performed, as indicated in the Flow Chart. Patients who complete the full 26 week treatment period should be registered as completed in the IRT system.

- Visit 11 EOT should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours), and patients should be reminded to attend without having taken their trial medication in the morning as they will take the last dose at the site, and to bring all used/unused medication with them to the visit. The patient should be reminded not to start any new anti-diabetic therapy until after Visit 12
- [redacted]
- Patients should be reminded to continue with e-diary entries, checks of glucose and ketones using the glucose and ketone monitoring device for another 3 weeks until Visit 12

6.2.3.2 End of treatment - early discontinuations (eEOT) and withdrawals

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

Patients who discontinue study medication early should have the assessments for eEOT (Early Discontinuations Only) performed, as indicated in the Flow Chart. For such patients, the eEOT Visit should be done as soon as possible after the decision to discontinue has been made. If the eEOT Visit occurs within the time window of a scheduled visit and the patient continues to be followed up, the eEOT Visit will replace that scheduled visit. For example:

- if a patient discontinues study medication 16 weeks after randomisation (i.e. between Visits 9 and 10), the eEOT Visit could be scheduled one week later, and it would occur within the time window of the next scheduled visit (i.e. Visit 10 at Week 18 +/-7 days). When returning to the visit schedule, after completing the 3 week Follow-up Visit (see Section 6.2.3.3 below), the patient would return for Visit 11 EOT at Week 26

If a patient intends to immediately discontinue (withdraw) from the study, an eEOT Visit should be performed as soon as possible after the decision to withdraw has been made.

Patients who discontinue treatment prematurely (prior to 26 weeks) but continue to be followed up should be registered as "withdrawn from treatment" in the IRT system, whereas patients who withdraw from the trial should be registered as "withdrawn from study".

- eEOT should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours), and patients should be reminded to bring all used/unused medication with them to the visit. The patient should be reminded not to start any new anti-diabetic therapy until after Visit 12
- [redacted]
- Patients should be reminded to continue with e-diary entries, checks of glucose and ketones using the glucose and ketone monitoring device for the remainder of the observation period

6.2.3.3 Follow-up visit (Visit 12) - completers

Patients who successfully complete the 26 week treatment period should have the assessments for Visit 12 performed, as indicated in the Flow Chart. For these patients:

- Visit 12 should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours)
- The patient e-diary will be checked after which it should be removed from the patient, together with all other study-related devices and equipment, once Visit 12 is complete

6.2.3.4 Follow-up visit (Visit 12) – early discontinuations (eEOT) and withdrawals

For patients who discontinue treatment prematurely prior to completion of 26 weeks the following should be performed whenever possible once an eEOT Visit has been completed (see Section 6.2.3.2):

- 3 weeks after the date of the eEOT Visit, patients should complete Visit 12. Visit 12 should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours), and all assessments indicated in the Flow Chart for Visit 12 should be performed
- Thereafter, patients should be followed up according to the visit schedule (e.g. a patient who discontinued study medication a week after Visit 8 (Week 4) – i.e. at Week 5 - would next be followed up for Visit 9 (Week 12) after having completed an eEOT visit as soon as possible after Week 5, and a Visit 12 at Week 8.
- The Investigator may negotiate a revised visit schedule should the patient be unwilling or unable to adhere to the regular schedule according to the Flow Chart. These follow-up visits may occur by telephone or in the clinic but Visit 11 EOT (Week 26) must be performed as a clinic visit in order to complete all scheduled assessments
- When being followed up according to the visit schedule, only assessments relating to the primary and secondary endpoints and general safety have to be completed (i.e. weight, vital signs, physical examination, ECG, safety laboratory, pregnancy test, HbA_{1c}, e-diary completion, [redacted] and the

collection of AEs and changes in concomitant therapy). All other assessments [redacted] are optional

- Visit 11 EOT at 26 weeks will be the last visit for these patients, since Visit 12 will already have been completed 3 weeks after the eEOT Visit as explained above. At Visit 11 EOT therefore, the patient e-diary will be checked after which it should be removed from the patient, together with all other study-related devices and equipment, once the visit is completed

For patients who discontinue treatment prematurely and do not wish to follow the visit schedule, at least a contact should be planned, at the timepoint of the primary endpoint at 26 weeks to collect data about the vital status as a minimum.

If study treatment is stopped prior to completion of 26 weeks and the patient intends to immediately discontinue (withdraw) from the study, an eEOT Visit should be performed as soon as possible after the decision to withdraw has been made. The patient should return for a Visit 12 (3 weeks after the eEOT). At this visit all assessments should be performed according to the Flow Chart.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, double blind, multi-centre, placebo-controlled, parallel group, 26 week study to assess the efficacy, safety, tolerability, and PK of once daily oral doses of empagliflozin 2.5 mg, 10 mg and 25 mg compared to placebo in patients with T1DM as adjunctive to insulin therapy.

The superiority of the 3 doses of empagliflozin will be tested against placebo. A Bonferroni adjustment will first correct for the parallel testing of the 2 higher doses (empagliflozin 25 mg and 10 mg) in order to maintain a type I error rate of 0.05. Each of these 2 doses will therefore be tested at the level of α=0.025 (two-sided).

Following the efficacy analysis (on-treatment data only) of the primary endpoint, change from baseline in HbA_{1c} after 26 weeks, for the 2 higher doses, an effectiveness analysis (on- and off-treatment data) will be performed in a hierarchical manner. If the null hypothesis is rejected for both the efficacy and effectiveness analysis the error rate will be unequally split and transferred between the testing of the lowest dose empagliflozin 2.5 mg (with an allocated alpha weight of 1/5) and the testing of key secondary endpoints (with an allocated alpha weight of 4/5) in a gatekeeping strategy. If the null-hypothesis of "equal HbA_{1c} change after 26 weeks between placebo and empagliflozin 2.5 mg" can be rejected using on-treatment data only, alpha of this test will be equally split and added to the alpha level for the test of the key secondary endpoints of the two higher doses.

Superiority of empagliflozin 10 mg versus placebo in key secondary endpoints will be sequentially tested with an unequal alpha split. The same approach will be followed to test superiority of empagliflozin 25 mg versus placebo on these endpoints.

See Section 7.2 for further details on the endpoint testing strategy.

With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to administration of any randomised study medication, the 4 week period prior to randomisation for the rate of hypoglycaemia and the run-in period from Visit 5 to Visit 6 for the mean daily insulin requirement.

Patients who prematurely discontinue trial medication will continue to attend all visits and be followed up until the end of the trial when possible.

The randomisation will be stratified by the Visit 5 eGFR value (< 60 mL/min/1.73 m^2 versus ≥ 60 mL/min/1.73 m^2), the Visit 5 HbA_{1c} value (< 8.5% versus ≥ 8.5%), by the patients' pre-existing insulin therapy (MDI versus CSII), and by the patient's participation in the CGM substudy (CGM participation versus non-CGM participation). If necessary, and depending upon global distribution, entry of patients into a particular HbA_{1c} stratum may be capped.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following testing procedure will be used to evaluate the superiority for the primary endpoint for empagliflozin 25 and 10 mg doses against placebo at the level of α=0.025. The overall probability of type I error is therefore maintained at α=0.05 (two-sided).

The superiority of treatment with empagliflozin to placebo will be tested for HbA_{1c} change from baseline at Week 26, via the pairwise comparison of the two higher empagliflozin doses against placebo, at α=0.025 level. Both doses will be tested in parallel on the Full Analysis Set (FAS) for the efficacy analysis and on the modified Intention-to-Treat (mITT) set for the effectiveness analysis; see Section 7.3 for the analysis set definitions. Both analyses will test the same null hypothesis:

$H_{0,0,1}$: Mean change from baseline in HbA_{1c} (%) after 26 weeks in the empagliflozin 10 mg group = Mean change from baseline in HbA_{1c} (%) after 26 weeks in the placebo group

$H_{0,0,2}$: Mean change from baseline in HbA_{1c} (%) after 26 weeks in the empagliflozin 25 mg group = Mean change from baseline in HbA_{1c} (%) after 26 weeks in the placebo group

Following testing of the null hypotheses $H_{0,0,1}$ and $H_{0,0,2}$ for both efficacy and effectiveness for HbA_{1c}, within each dose group (empagliflozin 10 and 25 mg) the remaining alpha will be unequally split for testing the superiority of empagliflozin 2.5 mg to placebo on the primary endpoint and for testing the superiority of the key secondary endpoints for the higher doses as detailed below.

- One-fifth of the remaining alpha will be used for testing the superiority of empagliflozin 2.5 mg to placebo on the primary endpoint. The test will be done two-sided. The null hypothesis is as follows:

$H_{0,0,3}$: Mean change from baseline in HbA_{1c} (%) after 26 weeks in the empagliflozin 2.5 mg group= Mean change from baseline in HbA_{1c} (%) after 26 weeks in the placebo group

Depending on the success of the testing of $H_{0,0,1}$ and $H_{0,0,2}$, $H_{0,0,3}$ will be tested at the following alpha level $\alpha_{0,3}$:

- If either $H_{0,0,1}$ or $H_{0,0,2}$ is rejected at 0.025 level, then
  - $\alpha_{0,3} = 1/5 \times 0.025 = 0.005$.
- If $H_{0,0,1}$ and $H_{0,0,2}$ are both rejected at 0.025 level, then
  - $\alpha_{0,3} = 1/5 \times 0.025 + 1/5 \times 0.025 = 0.01$.

- Four-fifth of the remaining alpha will be transferred for testing the superiority of the key secondary endpoints for empagliflozin 10 and 25 mg. Additionally, if $H_{0,0,3}$ is rejected, the alpha $\alpha_{0,3}$ of the testing of $H_{0,0,3}$ will be equally split and added to the alpha level for testing the superiority of the key secondary endpoints. For further details, see Step 2 in Table 7.2: 1. The null hypotheses for the key secondary endpoints are as follows:

$H_{0,1,1}$: Mean change from baseline in body weight (kg) after 26 weeks in the empagliflozin 10 mg group = Mean change from baseline in body weight (kg) after 26 weeks in the placebo group

$H_{0,2,1}$: Mean change from baseline in TDID (U/kg) after 26 weeks in the empagliflozin 10 mg group = Mean change from baseline in TDID (U/kg) after 26 weeks in the placebo group

$H_{0,3,1}$: Incidence rate of hypoglycaemia from Week 5 to Week 26 in the empagliflozin 10 mg group = Incidence rate of hypoglycaemia from Week 5 to Week 26 in the placebo group

$H_{0,4,1}$: Incidence rate of hypoglycaemia from Week 1 to Week 26 in the empagliflozin 10 mg group = Incidence rate of hypoglycaemia from Week 1 to Week 26 in the placebo group

$H_{0,5,1}$: Mean change from baseline in SBP after 26 weeks in the empagliflozin 10 mg group = Mean change from baseline in SBP after 26 weeks in the placebo group

$H_{0,6,1}$: Mean change from baseline in DBP after 26 weeks in the empagliflozin 10 mg group = Mean change from baseline in DBP after 26 weeks in the placebo group

All tests will be done two-sided.

Similarly, we note $H_{0,1,2}$ to $H_{0,6,2}$ the null hypotheses for the test of superiority of empagliflozin 25 mg versus placebo on the key secondary endpoints.

Within each dose group (empagliflozin 10 mg and 25 mg), the key secondary endpoints will be tested sequentially with an unequal alpha split. One-tenth of the alpha level for the key secondary endpoints will be used to sequentially test $H_{0,1,1}$ and $H_{0,2,1}$. Nine-tenths of the alpha level for the key secondary endpoints will be used to sequentially test $H_{0,3,1}$ and $H_{0,4,1}$ as follows.

Depending on the success of the testing of $H_{0,0,1}$ and $H_{0,0,2}$ and $H_{0,0,3}$, $H_{0,1,1}$ will be tested at the following alpha level $\alpha_{1,1}$:

- If $H_{0,0,1}$ is rejected at 0.025 level, but $H_{0,0,3}$ is not rejected then
  - $\alpha 1,1 = 1/10 \times (4/5 \times 0.025) = 0.002$

- If $H_{0,0,1}$ is rejected at 0.025 level, as well as $H_{0,0,3,}$ then
  - $\alpha_{1,1} = 1/10 \times [4/5 \times (0.025) + 1/2 \times (0.005)] = 0.00225$, if $H_{0,0,2}$ is not rejected
  - $\alpha_{1,1} = 1/10 \times [4/5 \times (0.025) + 1/2 \times (0.01)] = 0.0025$, if $H_{0,0,2}$ is rejected at 0.025

- If $H_{0,0,2}$ is rejected at 0.025 level, as well as $H_{0,0,3,}$ but $H_{0,0,1}$ is not rejected then
  - $\alpha_{1,1} = 1/10 \times [4/5 \times (0) + 1/2 \times (0.005)] = 0.00025$

- Otherwise $H_{0,1,1}$ will not be tested

The same will apply for $H_{0,2,1}$, provided $H_{0,1,1}$ is rejected.

Depending on the success of the testing of $H_{0,0,1}$ and $H_{0,0,2}$ and $H_{0,0,3}$, $H_{0,3,1}$ will be tested at the following alpha level $\alpha_{3,1}$:

- If $H_{0,0,1}$ is rejected at 0.025 level, but $H_{0,0,3}$ is not rejected then
  - $\alpha 3,1 = 9/10 \times(4/5\times 0.025)=0.018$

- If $H_{0,0,1}$ is $_{\text{rejected}}$ at 0.025 level, as well as $H_{0,0,3,}$ then
  - $\alpha_{3,1} = 9/10 \times[4/5\times (0.025) + 1/2\times(0.005)]=0.02025$, if $H_{0,0,2}$ is not rejected
  - $\alpha_{3,1} = 9/10 \times[4/5\times (0.025) + 1/2\times(0.01)]=0.0225$, if $H_{0,0,2}$ is rejected at 0.025

- If $H_{0,0,2}$ is $_{\text{rejected}}$ at 0.025 level, as well as $H_{0,0,3,}$ but $H_{0,0,1}$ is not rejected then
  - $\alpha 3,1 = 9/10 \times[4/5\times (0) + 1/2\times(0.005)]=0.00225$

- Otherwise $H_{0,3,1}$ will not be tested

The same will apply for $H_{0,4,1}$, provided $H_{0,3,1}$ is rejected.

Depending on the success of each sequential testing, the alpha will contribute towards the significance level for the sequential testing of $H_{0,5,1}$ and $H_{0,6,1}$.

- If $H_{0,1,1}$ and $H_{0,1,2}$ are rejected, but $H_{0,3,1}$ or $H_{0,4,1}$ are not rejected then $\alpha= \alpha_{1,1}$ will contribute towards the testing of $H_{0,5,1}$, and $H_{0,6,1}$.
- If $H_{0,3,1}$ and $H_{0,4,1}$ are both rejected, but $H_{0,1,1}$, or $H_{0,1,2}$ are not rejected then $\alpha= \alpha_{3,1}$ will contribute towards the testing of $H_{0,5,1}$, and $H_{0,6,1}$.
- If all null hypotheses ($H_{0,1,1}$ to $H_{0,4,1}$) are rejected, $H_{0,5,1}$ and $H_{0,6,1}$ will be tested at the level $\alpha = \alpha_{1,1} + \alpha_{3,1}$

The same approach will apply for the testing of key secondary endpoints for Empagliflozin 25 mg.

If at any stage a null hypothesis cannot be rejected, all subsequent tests in the same branch according to the diagram in Table 7.2: 1 will be performed in an exploratory manner only.

Table 7.2: 1 Summary of endpoint testing strategy

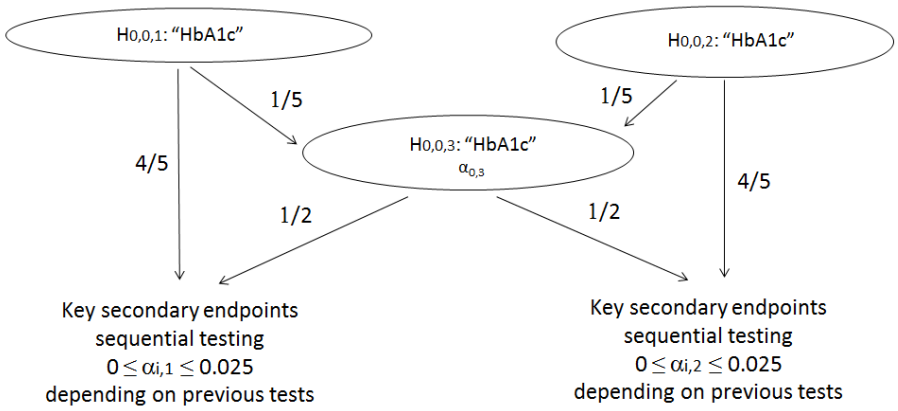
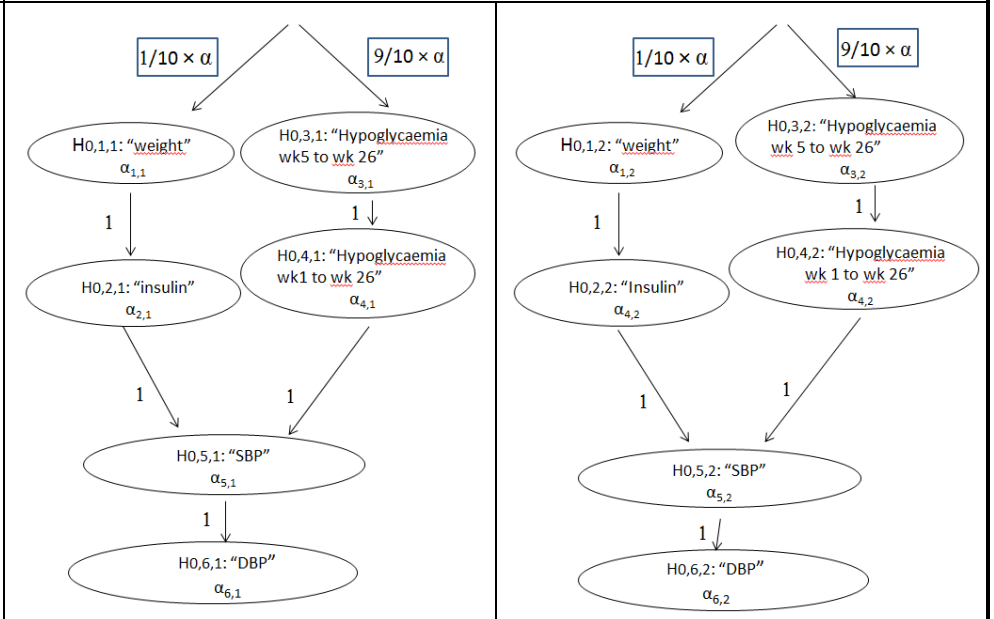
	Empagliflozin 10 mg	Empagliflozin 2.5 mg	Empagliflozin 25 mg
Step 1: Primary endpoint (efficacy) **Bonferroni,** two-sided (alpha=0.025)	If $H_{0,0,1}$ for primary endpoint is rejected at alpha=0.025 level using on-treatment data only then go to step 2, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.		If $H_{0,0,2}$ for primary endpoint is rejected at alpha=0.025 level using on-treatment data only then go to step 2, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.
Step 2: Primary endpoint (effectiveness)	If $H_{0,0,1}$ is rejected at alpha=0.025 level using all on- and off-treatment data then go to step 3, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes		If $H_{0,02}$ is rejected at alpha=0.025 level using all on- and off-treatment data then go to step 3, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes
Step 3: Primary endpoint **Gatekeeping**			

Table 7.2: 1 Summary of endpoint testing strategy (continued)

Step 4: Key secondary endpoints **Sequential testing, Gatekeeping** with alpha based on the outcome of primary endpoint testing	

7.3 PLANNED ANALYSES

To account for the testing of 2 doses of empagliflozin 25 and 10 mg, a Bonferroni adjustment will be applied to the type I error rate and tests for the primary endpoint (efficacy and effectiveness sequentially) will be conducted at the level of α=0.025 (two-sided). A gatekeeping strategy will then be employed for the test of the primary endpoint for empagliflozin 2.5 mg against placebo. Gatekeeping and sequential testing strategy will follow for tests of the key secondary endpoints for empagliflozin 25 and 10 mg to maintain the type I error rate at the level of α=0.025 (two-sided) within each dose (see Section 7.2 for details).

Safety analyses will be performed on the treated set (TS). The TS is defined as all patients treated with at least one dose of study medication.

The primary efficacy analysis for all empagliflozin doses will be performed on the FAS. The FAS is defined as all randomised patients who are treated with at least one dose of study medication, have a baseline HbA_{1c} and at least one on-treatment HbA_{1c} measurement. The effectiveness analysis of the primary endpoint for empagliflozin 10 mg and 25 mg will be performed on the mITT set. The mITT set is defined as all randomised patients who have a baseline HbA_{1c} and at least one post randomisation HbA_{1c} measurement.

A per protocol set (PPS) of patients following the trial protocol in essential criteria will be created for sensitivity analyses. Patients included in the FAS who have important protocol violations (IPVs) that can be expected to have a distorting influence on the assessment of the

primary endpoint will be excluded from the PPS. Details regarding the definitions of IPVs will be provided in the Trial Statistical Analysis Plan (TSAP).

Further sensitivity analyses will be based on the randomised set (RS). The RS includes all randomised patients regardless of treatment with study medication.

All analyses will be conducted in SAS® version 9.2 or later.

7.3.1 Primary endpoint analyses

7.3.1.1 Primary analysis of the primary endpoint

The primary endpoint in this trial is the change from baseline in HbA_{1c} (%) after 26 weeks.

The primary efficacy analysis will be performed on the FAS; patients will be assigned to the treatment they were randomised to and analysed according to the stratum to which they belong (regardless of any mis-assignment based on identification of the wrong stratum). Only on-treatment HbA_{1c} values will be included in the primary analysis for efficacy.

Mean changes from baseline in HbA_{1c} after 26 weeks will be analysed using a restricted maximum likelihood-based repeated measures approach (MMRM analysis). Analyses will include the fixed categorical effects of treatment, pre-existing insulin therapy, week and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA_{1c}, baseline eGFR and baseline HbA_{1c} by week interaction. An unstructured (co)variance structure will be used to model the within patient measurements.

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

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.025$ (two-sided 97.5% confidence intervals). The residuals are assumed to have a multivariate normal distribution with zero means and covariance matrix as specified above. The primary treatment comparisons will be the contrast between treatments at Week 26.

The statistical model will be:

HbA_{1c} change from baseline = overall mean + continuous baseline HbA_{1c} + pre-existing insulin therapy + continuous baseline eGFR + treatment + week + baseline HbA_{1c} by week interaction + treatment by week interaction + random error

For empagliflozin 10 mg and 25 mg, following the analysis of the efficacy estimand, an effectiveness analysis will be performed on the mITT set. This will use the same model as described for the efficacy analysis, but include all available on- and off- treatment values.

[redacted]

[redacted]

7.3.2 Secondary endpoint analyses

For empagliflozin 10 and 25 mg the key secondary endpoints will be tested in a confirmatory way.

7.3.2.1 Key secondary endpoints – confirmatory analyses

The analysis of change from baseline in body weight after 26 weeks will follow the strategy for the primary endpoint, MMRM, with the addition of terms for baseline body weight and baseline body weight by week interaction into the model. This analysis will be performed on the FAS, including all available on-treatment data.

The analysis of change from baseline in TDID after 26 weeks will follow the strategy for the primary endpoint MMRM, with the addition of terms for baseline TDID and baseline TDID by week interaction into the model. This analysis will be performed on the FAS, including all available on-treatment data. The baseline TDID will be calculated based on the mean daily insulin requirement during the 2 week run-in period. The TDID after 26 weeks will be calculated based on the mean daily insulin requirement over the previous 7 days (i.e. during Week 26).

The analysis of the incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (<3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 5 to Week 26 will utilise a negative binomial model, with terms for treatment, baseline rate, baseline $HbA_{1c,}$ baseline eGFR and pre-existing insulin therapy as fixed effects, and log(days of follow-up) as an offset. This analysis will include patients from the FAS, including all available on-treatment events from the start of Week 5 (Day 29) up to one day after treatment stop. The baseline rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (<3.0 mmol/L) and/or severe hypoglycaemic AEs will be calculated based on the event rate during the 4 weeks prior to randomisation.

The analysis of the incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (<3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 1 to Week 26 will follow the same strategy as the analysis from Week 5 to Week 26. This analysis will include all patients from the FAS, including all available on-treatment events from date of first study medication intake up to one day after treatment stop.

The analysis of change from baseline in SBP after 26 weeks will follow the strategy for the primary endpoint MMRM, with the addition of terms for baseline SBP and baseline SBP by week interaction into the model. This analysis will be performed on the FAS, including all available on-treatment data.

The analysis of change from baseline in DBP after 26 weeks will follow the strategy for the primary endpoint MMRM, with the addition of terms for baseline DBP and baseline DBP by week interaction into the model. This analysis will be performed on the FAS, including all available on-treatment data.

[redacted]

[redacted]

7.3.4 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.1.3.2. All treated patients will be included in the safety evaluation (i.e. in the TS). Safety analyses will assign patients to the treatment group as randomised. Safety analyses will be mostly descriptive in nature and will be based on BI standards. In addition, statistical analysis for selected endpoints (to be defined in the TSAP) may be performed, if appropriate. No hypothesis testing is planned.

The active empagliflozin treatment groups will be compared with the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to summarise continuous (quantitative) data.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). The analysis of AEs will be based on the concept of treatment emergent adverse events. That means that all AEs occurring from first study medication intake until 7 days after last study medication intake will be assigned to the randomised treatment. This includes AEs that start before first study medication intake and deteriorate under treatment. All AEs occurring before first study medication intake will be assigned to ‘pre-treatment’ and all AEs occurring after last study medication intake + 7 days will be assigned to ‘post-treatment’. Additional listings based on actual treatment at onset of AE will be produced for patients who receive incorrect treatment at any point during the trial. Specific analyses of hypoglycaemia will assign events only up to the end of the last study medication intake + 1 day to the randomised treatment, later hypoglycaemia events will be assigned to ‘post-treatment’.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

Independent of this rule, the relationship of an AE to the study medication will be assessed by the Investigator.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

[redacted]

[redacted]

7.4 INTERIM ANALYSES

There is no interim analysis planned for this trial but the conduct of the trial will be monitored by a DMC. For further details please refer to Section 3.1.1.1.

7.5 HANDLING OF MISSING DATA

For the primary analysis of the primary endpoint, if a patient misses a visit, the missing data will not be imputed and only on-treatment data will be included. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption". Every randomised patient with at least baseline and one on-treatment measurement will be included in the analysis. This approach will also be used for the confirmatory analysis of the key secondary endpoints investigating change from baseline in body weight, TDID, SBP and DBP.

An analysis including off-treatment data and multiple imputation will be used as a sensitivity analysis for the primary endpoint to handle missing data. A detailed description of multiple imputation will be included in the TSAP. This approach will also be applied to the key secondary endpoints of change from baseline in body weight, TDID, SBP and DBP.

For the key secondary endpoint of incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (<3.0 mmol/L) and/or severe hypoglycaemia, available on-treatment data will be analysed and no imputation performed. A sensitivity analysis including post treatment events will also be performed.

Details regarding the imputation rule for further endpoints will be specified in the TSAP. No imputation is planned for any analysis of AEs, laboratory data, and vital signs.

7.6 RANDOMISATION

The trial will be performed as a double-blind design with respect to placebo and the 3 active dose groups of empagliflozin. Patients will be randomised in blocks to the 4 study treatments in a 1:1:1:1 ratio at Visit 6. The randomisation will be stratified by the baseline eGFR value as calculated by the CKD-EPI formula (< 60 mL/min/1.73 m^2 versus ≥ 60 mL/min/1.73 m^2), baseline HbA_{1c} (< 8.5% versus ≥ 8.5%), the patients' pre-existing insulin therapy (MDI

versus CSII), and by the patient's participation in the CGM substudy (CGM participation versus non-CGM participation). If necessary, and depending upon global distribution, entry of patients into a particular HbA_{1c} stratum may be capped.

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

7.7 DETERMINATION OF SAMPLE SIZE

Based on previous experience with empagliflozin [redacted] it is estimated that the change in HbA_{1c} from baseline after 26 weeks of treatment is 0.3% in empagliflozin (2.5 mg, 10 mg and 25 mg) and 0% in placebo and that the standard deviation of this difference is 0.9%.

As this trial investigates primarily the 2 higher dose levels of empagliflozin, 10 mg and 25 mg, the alpha (Type I error) is assumed to be 2.5%. Assuming that the change from baseline in HbA_{1c} follows a normal distribution (Student's t-test) and that a two-sided test will be employed, with equal standard deviations, then a sample size of 225 patients per arm will show superiority with a power of 90%.

Based on the results of these 2 tests (see Section 7.2 for further details), when comparing empagliflozin 2.5 mg (n=225) to placebo (n=225) on the primary endpoint, there is 82% power, respectively 76%, to detect a significant difference (alpha=1%, respectively alpha=0.5%) of 0.3% with a common standard deviation of 0.9%.

Software package nQuery version 7.0 was used to derive the sample size.

Given that there are 4 treatment groups, a total sample size of 960 patients (240 per group) will be randomised to allow for an estimated 6% of patients who do not qualify for the FAS.

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 Harmonised Tripartite Guideline for GCP,relevant BI SOPs and relevant regulations.

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.

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

As applicable locally, the certificate of insurance cover will be made available to the Investigator and the patients, and will be stored in the ISF.

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 IRB /IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

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 or Sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

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

8.3.1 Source documents

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For empagliflozin this is the current version of the Investigator's Brochure [c01678844], which will be provided in the ISF.

No AEs are classified as listed for matching placebo, trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IECs/IRBs, will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 END OF TRIAL

The end of the trial is defined as defined in Section 6.2.3.

The IEC/CA in each participating EU member state will be notified about the end (i.e. last patient last trial visit) or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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[redacted]

[redacted]

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		21-Oct-2016
EudraCT number		2014-005256-26
BI Trial number		1245.72
BI Investigational Product(s)		Empagliflozin
Title of protocol		A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of **E**mpagliflozin as **A**djunctive to in**S**ulin th**E**rapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3)
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		Endpoints: "Secondary endpoints which will be assessed in an exploratory fashion in a subset of about 30% of the patients are: • Change from baseline in the percentage of time spent in target glucose range of 70-180 mg/dL (3.9-10.0 mmol/L) as determined by CGM in Week 25 to 26 • Change from baseline in interstitial glucose variability (inter quartile range, IQR) as determined by CGM in Week 25 to 26 • Change from baseline in AUC for interstitial glucose (mmol/24 hour, average from evaluable data from CGM period, minimum

		of 1 week required) in Week 25 to 26” Has been removed
Rationale for change		Exploratory secondary endpoints were moved from secondary endpoints to further endpoints to align with project standards
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		Safety criteria: “Incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 1 to Week 4 Frequency of patients with adverse events of special interest (AESIs): • diabetic ketoacidosis (DKA) • hepatic injury • decreased renal function • severe hypoglycaemic episodes Frequency of patients with hypoglycaemia Frequency of patients with adjudicated events: • cardiovascular events • severe hypoglycaemia • DKA” Has been changed to: “Incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 1 to Week 4 Frequency of patients with adverse events of special interest (AESIs): • diabetic ketoacidosis (DKA) • hepatic injury • decreased renal function • severe hypoglycaemic episodes Frequency of patients with hypoglycaemia **Hypoglycaemia rate** Frequency of patients with adjudicated events: • cardiovascular events • severe hypoglycaemia • DKA”
Rationale for change		Addition of “Hypoglycaemia rate” to correct omitted text in the original protocol

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		Statistical methods: "The subsequent test will be the confirmatory testing of the primary endpoint between empagliflozin 2.5 mg and placebo and will follow a gatekeeping strategy. For empagliflozin 10 mg and 25 mg the key secondary endpoints will be tested in a confirmatory way, following the test of the primary endpoint. The key secondary endpoints will be analysed using a gatekeeping approach, with unequal splitting of the alpha, and sequential testing." Has been changed to: "**The primary analysis will be an efficacy analysis, including on-treatment data only. Following the efficacy analysis, an effectiveness analysis (on-and off-treatment data) of empagliflozin 10 mg and 25 mg versus placebo will be performed in a hierarchical manner. If the null hypothesis is rejected for both the efficacy and effectiveness analysis then the primary endpoint (between empagliflozin 2.5 mg and placebo, on-treatment data only) and the key secondary endpoints will be tested in a confirmatory way** using a gatekeeping approach, with unequal splitting of the alpha, and sequential testing."
Rationale for change		Adjustments of the primary analysis based on regulatory feedback
Section to be changed		FLOW CHART
Description of change		"Visit 3" Has been changed to: "Visit 3/**3T^{D}**"
Rationale for change		To increase flexibility for visit scheduling
Section to be changed		FLOW CHART
Description of change		Rows "Vital signs" and "Blood ketone measurement at the site with home monitoring device, urine ketone measurement":

		Brackets have been added around the assessment at Visit 3/3T
Rationale for change		If Visit 3 is performed as a telephone visit these assessments are not required
Section to be changed		FLOW CHART
Description of change		Footnote B: "The patient's therapy for T1DM (e.g. skills for carbohydrate estimation and insulin adjustment) should be optimised from Visit 2 for a period of 6 weeks (i.e. until the patient reaches Visit 5 and the placebo run-in period) to achieve the best standard of care in accordance with local guidelines." Has been changed to: "The patient's therapy for T1DM (e.g. **ability to review blood glucose values,** skills for carbohydrate estimation and insulin adjustment) should be optimised from Visit 2 for a period of 6 weeks (i.e. until the patient reaches Visit 5 and the placebo run-in period) to achieve the best standard of care in accordance with local guidelines."
Rationale for change		To align with section 4.2.1
Section to be changed		FLOW CHART
Description of change		Footnote D: "Visit 4T is a telephone visit" Has been changed to: "Visit 4T is a telephone visit**. Visit 3 can be a telephone visit (3T), if deemed sufficient based on Investigator judgement, or a clinic visit; if performed as a telephone visit, assessments in brackets in the Flow Chart do not have to be performed**"
Rationale for change		To increase flexibility for visit scheduling
Section to be changed		FLOW CHART
Description of change		Footnote F: "Following randomisation and prior to the initiation of study medication, Investigators are advised to reduce the patient's total insulin dose by 10% to avoid hypoglycaemia; thereafter further insulin adjustments may be implemented as necessary."

		Has been changed to: "Following randomisation and prior to the initiation of study medication, Investigators are advised to reduce the patient's total insulin dose **based on need/** by 10% to avoid hypoglycaemia; thereafter further insulin adjustments may be implemented as necessary."
Rationale for change		Clarification and optimisation of suggested insulin titration
Section to be changed		FLOW CHART
Description of change		Footnote Y: "At visits with safety laboratory, ketone measurements should be done directly before or after the collection of laboratory samples and also in a fasted state. At visits without safety laboratory, ketones could be measured in a non-fasted state. Regular (e.g. 2-3 weekly) measurements at home before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements are recommended during the run-in phase and during the first 4 weeks of the treatment phase." Has been changed to: "At visits with safety laboratory, ketone measurements should be done directly before or after the collection of laboratory samples**. At visits which require fasting, ketone measurements should be done** in a fasted state. Regular (e.g. 2-3 **times a week**) measurements at home before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements are recommended during the run-in **period** and during the first 4 weeks of the treatment **period**."
Rationale for change		Clarification
Section to be changed		ABBREVIATIONS
Description of change		The following abbreviations have been added: CV Coefficient of Variation MAGE Mean Amplitude of Glycaemic Excursions mITT Modified Intention-to-Treat
Rationale for change		New abbreviation required due to modified text in

		the revised protocol
Section to be changed		Multiple Sections
Description of change		1.1 MEDICAL BACKGROUND 1.2.1 Non-clinical assessment of safety 1.2.2.1 Clinical pharmacokinetics – Type 2 diabetes mellitus 1.2.3.1 Clinical efficacy and safety – Type 2 diabetes mellitus 4.1.3 Selection of doses in the trial 5.3.3.1 Follow-up on suspicion for urinary tract infections 8.4.1 Listedness 9.2 UNPUBLISHED REFERENCES In all of the above sections reference "c01838761" has been changed to "c01678844"
Rationale for change		Administrative change. The referenced document, "Investigator Brochure, Empagliflozin (BI 10773)" has remained the same
Section to be changed		1.2.3.1 Clinical efficacy and safety – Type 2 diabetes mellitus
Description of change		"Approximately 550 healthy volunteers were exposed to empagliflozin (up to 800 mg single dose and up to 50 mg multiple dosing). In addition, approximately 250 patients with T2DM included in Phase I trials received multiple dosing with empagliflozin up to 100 mg. Approximately 8500 patients with T2DM have been treated with empagliflozin in research studies, of which approximately 4400 have been treated for more than 52 weeks. As of May 2014 approximately 8000 patients are still participating in ongoing long-term studies with empagliflozin." Has been changed to: "**Empagliflozin has been studied as part of a global development program with 15582 patients with T2DM treated in clinical studies of which 10004 were treated with empagliflozin, either alone or in combination with metformin, a sulfonylurea, a PPARγ agonist, dipeptidyl peptidase-4 inhibitors, or insulin.**"
Rationale for change		Alignment of protocol with latest edition of

		Investigator's brochure for empagliflozin
Section to be changed		2.3 BENEFIT - RISK ASSESSMENT
Description of change		"As part of the preparation for entry into the randomised treatment period, therapy for T1DM will be optimised (e.g. review of insulin dose and its adjustment for meals, ability to carbohydrate count etc.) over a 6 week period (T1DM therapy optimisation period) to ensure that, in the Investigator's opinion, a patient is achieving the best standard of care in accordance with local guidelines before entering the randomised treatment period of the trial. This optimal therapy will then be continued, and at randomisation, Investigators are advised to reduce the patient's total insulin dose by 10% to minimise the risk for hypoglycaemia. Since glomerular filtration is physiologically decreased during episodes of severe hypoglycaemia (due to reduced renal blood flow hence leading to lowering of urine glucose excretion and therefore efficacy of empagliflozin), hypoglycaemia induced by insulin is not expected to be significantly aggravated by empagliflozin [R12-4766]." And "In addition to blood glucose monitoring, the frequency of which will be increased after starting the study medication (for further details see Section 5.3.2.1), in the same way as during routine clinical care, patients will be reminded how to determine ketones in case of any symptoms of DKA, e.g. nausea, vomiting, abdominal pain etc. They will be instructed to do this irrespective of the glucose value in the event of DKA symptoms occurring. A meter will be provided to the patient for this purpose. " Has been changed to: "As part of the preparation for entry into the randomised treatment period, therapy for T1DM will be optimised (e.g. review of **blood glucose values,** insulin dose and its adjustment for meals, ability to carbohydrate count etc.) over a 6 week period (T1DM therapy optimisation period) to ensure that, in the Investigator's opinion, a patient is achieving

		the best standard of care in accordance with local guidelines before entering the randomised treatment period of the trial. This optimal therapy will then be continued, and at randomisation, Investigators are advised to reduce the patient's total insulin dose **based on need/** by 10% to minimise the risk for hypoglycaemia. Since glomerular filtration is physiologically decreased during episodes of severe hypoglycaemia (due to reduced renal blood flow hence leading to lowering of urine glucose excretion and therefore efficacy of empagliflozin), hypoglycaemia induced by insulin is not expected to be significantly aggravated by empagliflozin [R12-4766]." And "In addition to blood glucose monitoring, the frequency of which will be increased after starting the study medication (for further details see Section 5.3.2.1), in the same way as during routine clinical care, patients will be reminded how to determine ketones in case of any symptoms of DKA, e.g. nausea, vomiting, abdominal pain etc. They will be instructed to do this irrespective of the glucose value in the event of DKA symptoms occurring. **More frequent ketone testing (e.g. once daily) will be recommended during the run-in period and during the first 4 weeks of the treatment period; this will allow patients and Investigators to understand baseline ketosis rates and compare them, as appropriate, to the incidence of ketosis following the initiation of study medication.** A meter will be provided to the patient for this purpose**; as an additional safeguard, the meter will also be used to check ketone levels at most clinic visits (see Flow Chart)**."
Rationale for change		Clarification and optimisation of suggested insulin titration; clarification of additional safety monitoring
Section to be changed		2.3 BENEFIT - RISK ASSESSMENT
Description of change		"To continue the assessment of the long-term safety of empagliflozin, an adjudication of certain hepatic events, and an external assessment of cancer events will be performed in this trial."

		Has been changed to: "To continue the assessment of the long-term safety of empagliflozin, an adjudication of certain hepatic events will be performed in this trial."
Rationale for change		Removal of the requirement for external assessment of cancer events based on cumulative safety data obtained to date
Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		"The patient's participation is concluded when they have undergone the last planned visit (i.e. Trial Completion/Visit 11 EOT); last-patient-last-visit-primary-endpoint will occur when all patients have completed 26 weeks of treatment." Has been changed to: "The patient's participation is concluded when they have undergone the last planned visit (i.e. Trial Completion/Visit **12**); last-patient-last-visit-primary-endpoint will occur when all patients have completed 26 weeks of treatment."
Rationale for change		Correction of a typo
Section to be changed		3.1.1.4 Hepatic external adjudication and cancer assessments
Description of change		Section title has been changed to: "Hepatic external adjudication" And "Certain events of cancer will be assessed for causal relationship with the trial medication, and certain hepatic events will be adjudicated by external independent experts for severity and causal relationship with the trial medication; both in a blinded fashion. The events which will be reviewed will be defined in two charters, one for hepatic events and one for malignancies. Events may either be defined by abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for events of malignancies and hepatic injury events, including liver enzyme elevations."

		Has been changed to: "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 will be defined in **a** charter. Events may either be defined by abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for events of hepatic injury, including liver enzyme elevations."
Rationale for change		Removal of the requirement for external assessment of cancer events based on cumulative safety data obtained to date
Section to be changed		3.3 SELECTION OF TRIAL POPULATION
Description of change		"A sufficient number of male and female patients with T1DM will be screened to ensure the randomisation of 960 patients from around 170 trial sites." Has been changed to: "A sufficient number of male and female patients with T1DM will be screened to ensure the randomisation of 960 patients from around **180** trial sites."
Rationale for change		Adjustment
Section to be changed		3.3.2 Inclusion criteria
Description of change		"Women of child-bearing potential are defined as follows: Any female who has experienced menarche and is not post-menopausal (defined as at least 12 months with no menses without an alternative medical cause) or who is not permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy)" Has been changed to: "Women of child-bearing potential are defined as follows: Any female who has experienced menarche and is

		not post-menopausal (defined as at least 12 months with no menses without an alternative medical cause) or who is not permanently sterilised (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy)"
Rationale for change		Tubal occlusion is not accepted as a method of permanent sterilisation any longer. (Though it is considered as a method of highly effective birth control)
Section to be changed		3.3.3 Exclusion criteria
Description of change		"4. Occurrence of severe hypoglycaemia involving coma and/or seizure that required hospitalisation or hypoglycaemia-related treatment by an emergency physician or paramedic within 3 months prior to Visit 1" And "13. Treatment with systemic corticosteroids or planned initiation of such therapy at Visit 1. Inhaled or topical use of corticosteroids (e.g. for asthma/chronic obstructive pulmonary disease) is acceptable" And "14. Change in dose of thyroid hormones within 6 weeks prior to Visit 1 or planned change or initiation of such a therapy at Visit 1" Has been changed to: "4. Occurrence of severe hypoglycaemia involving coma/**unconsciousness** and/or seizure that required hospitalisation or hypoglycaemia-related treatment by an emergency physician or paramedic within 3 months prior to Visit 1 **and until randomisation**" And "13. Treatment with systemic corticosteroids or planned initiation of such therapy at Visit 1 **and until randomisation**. Inhaled or topical use of corticosteroids (e.g. for asthma/chronic obstructive pulmonary disease) is acceptable"

		And "14. Change in dose of thyroid hormones within 6 weeks prior to Visit 1 or planned change or initiation of such a therapy at Visit 1 **and until randomisation**"
Rationale for change		Adjustment of eligibility for safety reasons, and clarification
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		"An individual patient is to be withdrawn from trial treatment if: […] • The patient needs to take forbidden concomitant therapy (as listed in Section 3.3.3 and Section 4.2)" Has been changed to: "An individual patient is to be withdrawn from trial treatment if: […] • The patient needs to **start a restricted** concomitant therapy (as listed in Section 4.2) **that, in the Investigator's opinion, poses a safety risk if taken as add-on to the trial medication**"
Rationale for change		Concomitant therapies that require to screen-fail a patient might not always pose a safety risk. It should therefore be left to investigator's discretion if a patient should discontinue the trial medication if such concomitant therapies need to be initiated after randomization
Section to be changed		4.1.8.1 Patient treatment compliance
Description of change		"The tablets will be counted by the Investigator or a qualified designee and compliance will be calculated according to the formula: […] Compliance during the open-label placebo run-in period must be between 80% and 120%. If compliance is outside this range, the patient should be carefully interviewed and, if necessary, re-informed about the purpose and the conduct of the trial. Unreliable patients should not be randomised at the discretion of the Investigator."

		And "The tablets will be counted by the Investigator or a qualified designee and compliance will be calculated according to the **following** formula **unless there are reasons to use a different calculation (e.g. to account for periods during which a patient was genuinely unable to take any trial medication)**: […] Compliance during the open-label placebo run-in period must be between 80% and 120%. If compliance is outside this range, the patient should not be randomised."
Rationale for change		Clarification
Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatments
Description of change		"Based on the mode of action of empagliflozin and the results of previous trials in T1DM (for further details see Section 1), at randomisation on Day 1 (Visit 6) and the initiation of study medication, Investigators are advised to reduce the patient's total insulin dose by 10% to avoid hypoglycaemia. The actual reduction will be dependent upon individual glucose values." And "Apart from the recommendation for an initial insulin reduction of 10% at the start of randomised treatment, there will be no protocol-defined algorithm towards insulin adjustment in this trial." And "Ketones should also be determined in case of repeatedly elevated blood glucose levels (e.g. > 200 - 240 mg/dL [> 11.1 - 13.3 mmol/L]) which cannot be explained. Regular (e.g. 2-3 weekly) measurements before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements before breakfast are recommended during the run-in phase and during the first 4 weeks of the treatment phase and might also be agreed upon with the patient afterwards if deemed necessary by the Investigator."

		And "Other concomitant therapies should be kept as stable as possible over the course of the trial but might be changed in case of medical need. New anti-diabetic therapy should not be initiated during the Follow-up period." Has been changed to: "Based on the mode of action of empagliflozin and the results of previous trials in T1DM (for further details see Section 1), at randomisation on Day 1 (Visit 6) and the initiation of study **randomised** medication, **for patients with an HbA_{1c} of 7.5 to < 8% at Visit 5,** Investigators are advised to reduce the patient's total insulin dose by 10% to avoid hypoglycaemia. **For patients with an HbA_{1c} of ≥ 8% at Visit 5, Investigators are advised to adjust the patient's total insulin dose based on need as assessed by frequent SBGM and close patient follow-up upon initiation of randomised study medication. In all cases, t**he actual reduction will be dependent upon individual glucose values." And "Apart from the recommendation for an initial insulin reduction **as mentioned above** at the start of randomised treatment, there will be no protocol-defined algorithm towards insulin adjustment in this trial." And "Ketones should also be determined in case of repeatedly elevated blood glucose levels (e.g. > 200 - 240 mg/dL [> 11.1 - 13.3 mmol/L]) which cannot be explained. Regular (e.g. 2-3 **times a week**) measurements before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements before breakfast are recommended during the run-in **period** and during the first 4 weeks of the treatment **period** and might also be agreed upon with the patient afterwards if deemed necessary by the Investigator."

		And "Other concomitant therapies should be kept as stable as possible over the course of the trial but might be changed in case of medical need. New anti-diabetic therapy should not be initiated during **the randomised treatment period and** the Follow-up period."
Rationale for change		Clarification and optimisation of suggested insulin titration
Section to be changed		4.2.2.2 Restrictions on diet and life style
Description of change		"Extreme diets (e.g. ketogenic diets) should be avoided." Has been changed to: "Extreme diets (e.g. ketogenic diets **such as the Atkins diet**) should be avoided."
Rationale for change		Alignment project level patient information sheet text for Type 1 diabetes trials
Section to be changed		5.1.2 Secondary endpoints
Description of change		"Throughout this CTP, the term "baseline" refers to the 4 week period prior to randomisation for the rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs and the 2 week placebo run-in period for the mean daily insulin requirement (1 week of evaluable data required)." Has been changed to "Throughout this CTP, the term "baseline" refers to the 4 week period prior to randomisation for the rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs and the 2 week placebo run-in period for the mean daily insulin requirement."
Rationale for change		Clarification
Section to be changed		5.1.2 Secondary endpoints
Description of change		"The following secondary endpoints will be assessed in an exploratory fashion. For CGM the term

		"baseline" refers to the 2 week placebo run-in period throughout this protocol (1 week of evaluable data required). • Change from baseline in the percentage of time spent in target glucose range of 70-180 mg/dL (3.9-10.0 mmol/L) as determined by CGM in Week 25 to 26 • Change from baseline in interstitial glucose variability (inter quartile range, IQR) as determined by CGM in Week 25 to 26 Change from baseline in AUC for interstitial glucose (mmol/24 hour, average from evaluable data from CGM period, minimum of 1 week required) in Week 25 to 26" Has been removed
Rationale for change		Exploratory secondary endpoints moved from secondary endpoints to further endpoints to align with project standards
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		5.3.2.2 Ketone measurement
Description of change		"Regular (e.g. 2-3 weekly) measurements before breakfast are recommended throughout the trial as from Visit 2. More frequent (e.g. once daily) measurements before breakfast are recommended during the run-in phase and during the first 4 weeks of the treatment phase and might also be agreed upon with the patient afterwards if deemed necessary by the Investigator." Has been changed to: "Regular (e.g. 2-3 **times a week**) measurements before breakfast are recommended throughout the

		trial as from Visit 2. More frequent (e.g. once daily) measurements before breakfast are recommended during the run-in **period** and during the first 4 weeks of the treatment **period** and might also be agreed upon with the patient afterwards if deemed necessary by the Investigator."
Rationale for change		Clarification
Section to be changed		5.3.6.1 Definitions of AEs
Description of change		Added to Adverse events of Special Interest (AESIs): "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."
Rationale for change		To meet new regulatory requirements
Section to be changed		[redacted]
[redacted]		[redacted]

		[redacted]
Rationale for change		Correction of error/omission
Section to be changed		Multiple sections
Description of change		6.2.1.1 Screening visit (Visit 1) 6.2.1.2 T1DM therapy optimisation period (Visits 2, 3 and 4T) 6.2.1.3 Placebo run-in period (Visit 5) References to Section 5.2.3 have been changed to Section 5.**3**.3
Rationale for change		Correction of errors
Section to be changed		6.2.1.2 T1DM therapy optimisation period (Visits 2, 3 and 4T)
Description of change		"Visit 2 should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours) whereas Visits 3 does not need to be done with the patient in a fasted state (see Section 5.2.3)" Has been changed to: "Visit 2 should be done with the patient in a fasted state (i.e. no food or drink except water for 10 hours) (see Section 5.**3.**3)" And the following item has been added: • **Visit 3T, if performed as a telephone visit, does not require attendance at the clinic. If performed as a clinic visit, Visit 3 does not need to be done with the patient in a fasted state (see Section 5.3.3)**
Rationale for change		To increase flexibility for visit scheduling
Section to be changed		7.1 STATISTICAL DESIGN - MODEL
Description of change		"Following the analysis of the primary endpoint, change from baseline in HbA_{1c} after 26 weeks, for the 2 higher doses, the error rate will be unequally split and transferred between the testing of the lowest dose empagliflozin 2.5 mg (with an allocated

		alpha weight of 1/5) and the testing of key secondary endpoints (with an allocated alpha weight of 4/5) in a gatekeeping strategy. If the null-hypothesis of "equal HbA_{1c} change after 26 weeks between placebo and empagliflozin 2.5 mg" can be rejected, alpha of this test will be equally split and added to the alpha level for the test of the key secondary endpoints of the two higher doses." Has been changed to: "Following the **efficacy** analysis **(on-treatment data only)** of the primary endpoint, change from baseline in HbA_{1c} after 26 weeks, for the 2 higher doses, **an effectiveness analysis (on-and off-treatment data) of empagliflozin 10 mg and 25 mg versus placebo will be performed in a hierarchical manner. If the null hypothesis is rejected for both the efficacy and effectiveness analysis** the error rate will be unequally split and transferred between the testing of the lowest dose empagliflozin 2.5 mg (with an allocated alpha weight of 1/5) and the testing of key secondary endpoints (with an allocated alpha weight of 4/5) in a gatekeeping strategy. If the null-hypothesis of "equal HbA_{1c} change after 26 weeks between placebo and empagliflozin 2.5 mg" can be rejected **using on-treatment data only**, alpha of this test will be equally split and added to the alpha level for the test of the key secondary endpoints of the two higher doses."
Rationale for change		Adjustments of the primary analysis based on regulatory feedback
Section to be changed		7.1 STATISTICAL DESIGN - MODEL
Description of change		"With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to administration of any randomised study medication, the 4 week period prior to randomisation (Visit 4T to Visit 6) for the rate of hypoglycaemia and the 2 week run-in period for the mean daily insulin requirement." Has been changed to: "With regard to efficacy and safety endpoints, the

		term "baseline" refers to the last observed measurement prior to administration of any randomised study medication, the 4 week period prior to randomisation for the rate of hypoglycaemia and the run-in period **from Visit 5 to Visit 6** for the mean daily insulin requirement."
Rationale for change		Clarification
Section to be changed		7.1 STATISTICAL DESIGN - MODEL
Description of change		"The randomisation will be stratified by the Visit 5 eGFR value (< 60 mL/min/1.73 m^2 versus ≥ 60 mL/min/1.73 m^2), the Visit 5 HbA_{1c} value (< 8.5% versus ≥ 8.5%), by the patients' pre-existing insulin therapy (MDI versus CSII), and by the patient's participation in the CGM substudy (CGM participation versus non-CGM participation)." Has been changed to: "The randomisation will be stratified by the Visit 5 eGFR value (< 60 mL/min/1.73 m^2 versus ≥ 60 mL/min/1.73 m^2), the Visit 5 HbA_{1c} value (< 8.5% versus ≥ 8.5%), by the patients' pre-existing insulin therapy (MDI versus CSII), and by the patient's participation in the CGM substudy (CGM participation versus non-CGM participation). **If necessary, and depending upon global distribution, entry of patients into a particular HbA_{1c} stratum may be capped.**"
Rationale for change		To ensure an adequate number of patients with an HbA1c > 8.5% are included in the trial
Section to be changed		7.2 NULL AND ALTERNATIVE HYPOTHESES
Description of change		"The superiority of treatment with empagliflozin to placebo will be tested for HbA_{1c} change from baseline at Week 26, via the pairwise comparison of the two higher empagliflozin doses against placebo, at α=0.025 level. Both doses will be tested in parallel on the Full Analysis Set (FAS). […] Following testing of the null hypotheses $H_{0,0,1}$ and $H_{0,0,2}$ for HbA_{1c}, within each dose group (empagliflozin 10 and 25 mg) the remaining alpha will be unequally split for testing the superiority of empagliflozin 2.5 mg to placebo on the primary endpoint and for testing the superiority of the key

		secondary endpoints for the higher doses as detailed below." Has been changed to: "The superiority of treatment with empagliflozin to placebo will be tested for HbA_{1c} change from baseline at Week 26, via the pairwise comparison of the two higher empagliflozin doses against placebo, at α=0.025 level. Both doses will be tested in parallel on the Full Analysis Set (FAS) **for the efficacy analysis and on the modified Intention-to-Treat (mITT) set for the effectiveness analysis; see Section 7.3 for the analysis set definitions. Both analyses will test the same null hypothesis:** […] Following testing of the null hypotheses $H_{0,0,1}$ and $H_{0,0,2}$ for **both efficacy and effectiveness for** HbA_{1c}, within each dose group (empagliflozin 10 and 25 mg) the remaining alpha will be unequally split for testing the superiority of empagliflozin 2.5 mg to placebo on the primary endpoint and for testing the superiority of the key secondary endpoints for the higher doses as detailed below."
Rationale for change		Adjustments of the primary analysis based on regulatory feedback
Section to be changed		Table 7.2: 1 Summary of endpoint testing strategy

Description of change

	Empagliflozin 10 mg	Empagliflozin 2.5 mg	Empagliflozin 25 mg
Step 1: Primary endpoint **Bonferroni,** two-sided (alpha=0.025)	If $H_{0,0,1}$ for primary endpoint is rejected at alpha=2.5% level then go to step 2, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.		If $H_{0,0,2}$ for primary endpoint is rejected at alpha=2.5% level then go to step 2, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.
Step 2: Primary endpoint			

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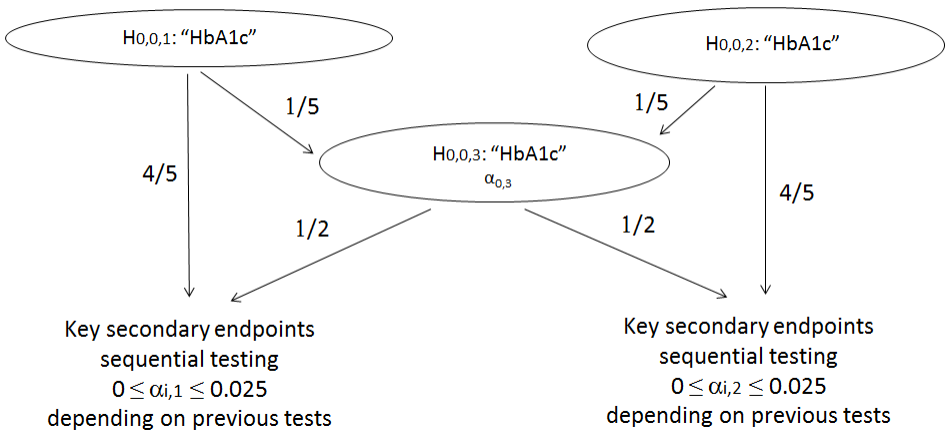
<tr><td>Gatekeeping</td><td colspan="2"> 
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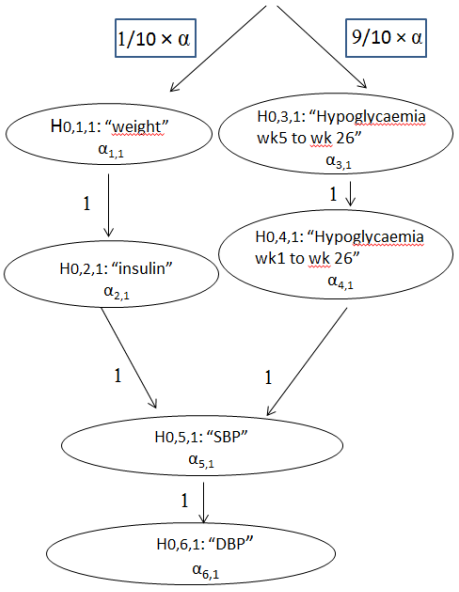
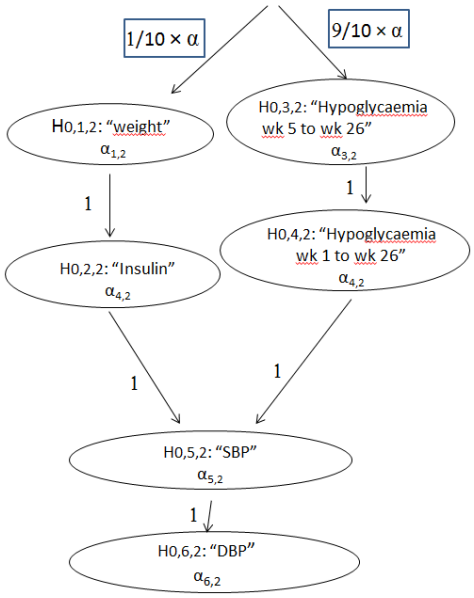
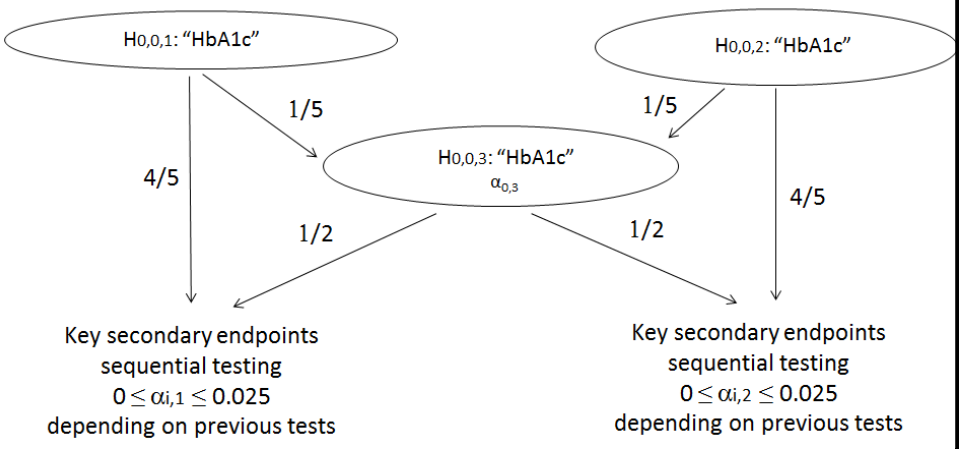
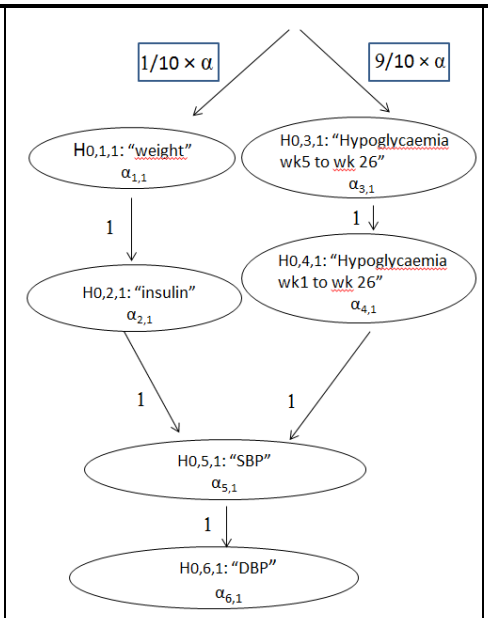
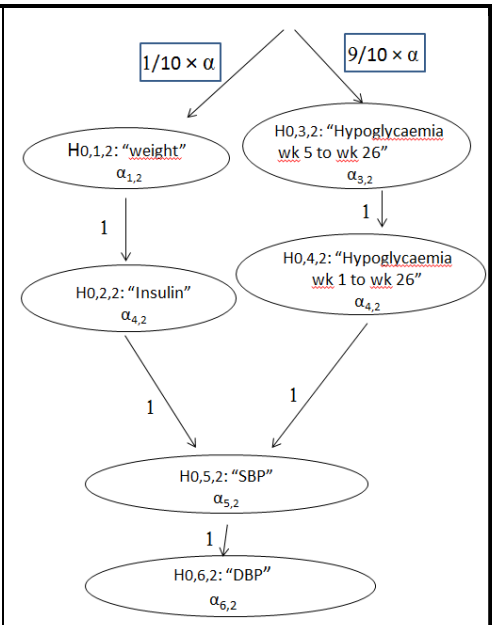
<tr><td><u>Step 3</u>:
Key secondary endpoints

Sequential testing, Gatekeeping with alpha based on the outcome of primary endpoint testing</td><td> 
</td><td> 
</td></tr>
</table>

Has been changed to:

	Empagliflozin 10 mg	Empagliflozin 2.5 mg	Empagliflozin 25 mg
<u>Step 1</u>: Primary endpoint **(efficacy)** **Bonferroni,** two-sided (alpha=0.025)	If $H_{0,0,1}$ for primary endpoint is rejected at alpha=**0.025** level **using on-treatment data only** then go to step 2, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.		If $H_{0,0,2}$ for primary endpoint is rejected at alpha=**0.025** level **using on-treatment data only** then go to step 2, otherwise procedure is stopped and subsequent tests will be done only for

			exploratory purposes.
<u>Step 2</u>: Primary endpoint (effectiveness)	**If $H_{0,0,1}$ is rejected at alpha=0.025 level using all on- and off-treatment data then go to step 3, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes**		**If $H_{0,02}$ is rejected at alpha=0.025 level using all on- and off-treatment data then go to step 3, otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes**
<u>Step **3**</u>: Primary endpoint **Gatekeeping**			

Step **4**: Key secondary endpoints **Sequential testing, Gatekeeping** with alpha based on the outcome of primary endpoint testing		

Rationale for change		Adjustments of the primary analysis based on regulatory feedback; corrections for consistency
Section to be changed		7.3 PLANNED ANALYSES
Description of change		"To account for the testing of 2 doses of empagliflozin 25 and 10 mg, a Bonferroni adjustment will be applied to the type I error rate and tests for the primary endpoint will be conducted at the level of α=0.025 (two-sided). […] The primary analysis will be performed on the FAS. The FAS is defined as all randomised patients who are treated with at least one dose of study medication, have a baseline HbA_{1c} and at least one on-treatment HbA_{1c} measurement." Has been changed to: "To account for the testing of 2 doses of empagliflozin 25 and 10 mg, a Bonferroni adjustment will be applied to the type I error rate and tests for the primary endpoint **(efficacy and effectiveness sequentially)** will be conducted at the level of α=0.025 (two-sided). […] The primary **efficacy** analysis **for all empagliflozin doses** will be performed on the FAS. The FAS is defined as all randomised patients who are treated with at least one dose of study medication, have a baseline HbA_{1c} and at least one on-treatment HbA_{1c} measurement. **The effectiveness analysis of the**

		primary endpoint for empagliflozin 10 mg and 25 mg will be performed on the mITT set. The mITT set is defined as all randomised patients who have a baseline HbA_{1c} and at least one post randomisation HbA_{1c} measurement."
Rationale for change		Adjustments of the primary analysis based on regulatory feedback
Section to be changed		7.3.1.1 Primary analysis of the primary endpoint
Description of change		"The primary analysis will be performed on the FAS; patients will be assigned to the treatment they were randomised to and analysed according to the stratum to which they belong (regardless of any mis-assignment based on identification of the wrong stratum). Only on-treatment HbA_{1c} values will be included in the primary analysis." Has been changed to: "The primary **efficacy** analysis will be performed on the FAS; patients will be assigned to the treatment they were randomised to and analysed according to the stratum to which they belong (regardless of any mis-assignment based on identification of the wrong stratum). Only on-treatment HbA_{1c} values will be included in the primary analysis **for efficacy**." And the following paragraph has been added: "**For empagliflozin 10 mg and 25 mg, following the analysis of the efficacy estimand, an effectiveness analysis will be performed on the mITT set. This will use the same model as described for the efficacy analysis, but include all available on- and off- treatment values.**"
Rationale for change		Adjustments of the primary analysis based on regulatory feedback
Section to be changed		7.3.1.2.1 Sensitivity analyses
Description of change		Handling of missing data – The following sensitivity analyses has been removed: "An MMRM analysis including all available on- and off-treatment data will be performed, using the same model as for the primary analysis. This analysis will be performed on the FAS"

Rationale for change		Adjustments of the primary analysis based on regulatory feedback
Section to be changed		7.3.2.2 Key secondary endpoints – secondary analyses
Description of change		The following analysis has been removed: "A logistic regression will be performed to assess the proportion of patients experiencing symptomatic hypoglycaemic events with confirmed plasma glucose < 54 mg/dL (<3.0 mmol/L) and/or severe hypoglycaemic events confirmed by adjudication during the respective time periods, while on treatment. The model will include terms for treatment, baseline rate, baseline HbA_{1c}, baseline eGFR and pre-existing insulin therapy"
Rationale for change		The logistic regression for proportion of patients experiencing an event will rather be included as a sensitivity analysis in the TSAP, if considered applicable
Section to be changed		7.3.2.3 Secondary endpoints
Description of change		This section has been deleted
Rationale for change		Exploratory secondary endpoints moved from secondary endpoints to further endpoints to align with project standards
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		7.3.4 Safety analyses
Description of change		"All treated patients will be included in the safety evaluation (i.e. in the TS). Safety analyses will assign patients to the treatment group as treated." Has been changed to: "All treated patients will be included in the safety evaluation (i.e. in the TS). Safety analyses will assign patients to the treatment group as **randomised**."
Rationale for change		To match project standards
Section to be changed		[redacted]
Description of change		[redacted] [redacted] [redacted]"
Rationale for change		Correction of error/omission
Section to be changed		7.6 RANDOMISATION
Description of change		The following sentence was added: "**If necessary, and depending upon global distribution, entry of patients into a particular HbA_{1c} stratum may be capped.**"
Rationale for change		To ensure an adequate number of patients with an HbA1c > 8.5% are included in the trial

APPROVAL / SIGNATURE PAGE

Document Number: c02993089 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol

Title: A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of Empagliflozin as Adjunctive to inSulin thErapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	21 Oct 2016 14:26 CEST
Approval-Therapeutic Area [redacted]		21 Oct 2016 14:51 CEST
Approval-Team Member Medicine		21 Oct 2016 15:51 CEST
Approval-Team Member Medicine		24 Oct 2016 13:17 CEST
Author-Trial Clinical Pharmacokineticist		24 Oct 2016 20:12 CEST
Author-Trial Statistician		25 Oct 2016 15:37 CEST
Verification-Paper Signature Completion		26 Oct 2016 17:34 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed